Post-Traumatic Arthritis Following Intra-Articular Fractures: First Hit or Chronic Overload?

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Introduction

Post-traumatic osteoarthritis (PTOA) occurs after traumatic injury to the joint; most commonly following injuries that disrupt the articular surface, or injuries that lead to joint instability[1]. It has been suggested that 12% of the global osteoarthritis burden can be attributed to previous trauma, and that the cost burden in the United States is approximately 3.06 billion dollars annually[2]. The risk of post-traumatic arthritis following significant joint trauma has been reported to be as high as 20-74%, and articular fractures increase the risk of osteoarthritis more than 20-fold[3-5]. Despite changes in surgical treatment, including fracture fixation and management of chondral injuries, the incidence of post-traumatic arthritis following intra-articular fractures is relatively unchanged over the last few decades[6].

The mechanisms and contributing factors to the development of PTOA following intra-articular fractures are not well-understood; hence, the ability to clinically intervene and forestall the progression of PTOA is currently limited. The best current data suggests that factors contributing to PTOA are multiple, including acute mechanical cartilage injury at the time of impact, biologic response including bleeding and inflammation, and chronic cartilage overload from incongruity, instability, and malalignment. Other factors, including patient age[7], and injury severity[8,9], may also contribute to worse clinical outcomes and progressive degeneration after intra-articular fractures.

The purpose of this review is to describe the multifactorial contributors associated with the development of PTOA after intra-articular fracture, to provide insight into possible clinical interventions to forestall or halt the progression of PTOA in traumatically-injured patients.

The "First Hit" Phenomenon—Articular Cartilage: Structure, Function, and Response to Mechanical Injury

Articular cartilage is comprised of 60-85% water, with the dry contents including extracellular matrix (ECM) components of collagens (primarily type II, but also types VI, IX, and XI) and proteoglycans (primarily aggrecan, but also decorin, biglycan, and fibromodulin),

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and a cell population (chondrocytes)[10]. The composition, architecture, and remodeling of articular cartilage are uniquely adapted to function over a lifetime of repetitive use, but are inherently poor responders to traumatic injury. Mechanical loading of articular cartilage, such as during injury, generates a biologic response from the tissue down to the cellular level, activating intracellular signaling cascades, through a process called mechanotransduction. Depending on the nature of the mechanical insult and the post-injury environment, cartilage may either recover or degrade, leading to PTOA[10].

One of the proposed mechanisms of PTOA in intra-articular fractures is a "first-hit phenomenon"—that is, acute insult to the cartilage triggers death or dysfunction of chondrocytes with subsequent dysfunction of cartilage metabolism. This presumably triggers a cascade of whole-joint degeneration. In explanted tissues after intra-articular calcaneal fractures, chondrocyte viability was significantly lower than control specimen (73% versus 95% viability)[11]. In a recent study, Tochigi et al. simulated a whole-joint model of intra-articular tibial plafond injury by delivering an impaction injury to a whole fresh human ankle cadaveric specimen[12]. The authors observed a reproducible pattern of plafond injury and chondrocyte death, with significantly more death adjacent to the fracture lines than distant from the fracture (26% death near fracture vs. 8.6% death remote from fracture). Chondrocyte death progressed over 48 hours after the initial injury[12]. Further, animal models have re-enforced this idea that chondrocyte death occurs at the fracture site following impaction injuries, with more chondrocyte death in fractured specimen, when compared to sub-fracture impaction injuries, likely due to the supraphysiological forces associated with actual fracture of the articular surface[13].

Several *in vitro* studies have sought to examine the pattern of chondrocyte death (apoptosis versus necrosis) and the mechanisms associated with cell death. Martin et al. demonstrated that 65% of chondrocytes necrose within the first 12 hours following injury in a bovine explant impaction injury model[14]. Further, several studies have observed markers of apoptosis in explanted human cartilage specimen following intra-articular fractures[15,16].

One of the proposed mechanisms for chondrocyte death is that release of reactive oxygen species and/or pro-inflammatory mediators following injury lead to progressive chondrocyte damage and matrix degeneration. In several *in vitro* studies of impact injuries on cartilage explants, injury induced the release of oxygen free radicals from chondrocytes, possibly from mitochondrial injury[17], which led to chondrocyte death and matrix degeneration[1,17]. Further, more severe injuries, resulting from higher impact injuries, resulted in greater local tissue damage, as measured by a higher proportion of cells releasing reactive oxygen species, and a higher rate of chondrocyte death and matrix disruption[1,18]. Further, intra-articular fracture has been shown to result in elevated synovial levels of pro-inflammatory cytokines and mediators, including tumor necrosis factor-alpha, interleukin-1, nitrous oxide, matrix metalloproteinases, and fibronectin fragments, which can stimulate cell and matrix degradation[1,19-21].

Finally, recent studies have demonstrated that cellular events related to initial impact injuries are associated with the progression of PTOA in animal models. Furman et al. observed degenerative changes, including loss of bone density and increases in subchondral bone thickness, as early as 8 weeks following untreated closed impaction injuries of the tibial plateau in mice, with severe cartilage loss by 50 weeks[20,21]. Further, these authors showed that the joint changes are accompanied by rapid changes in pro-inflammatory cytokines and cartilage biomarkers in the serum and synovial fluid[22]. In another animal model, the authors compared the injury patterns in standard C57Bl/6 mice with those in a breed of mice (MRL/MpJ) that produce a decreased inflammatory response to injury via decreased production of pro-inflammatory cytokines (interleukin-1) and increased production of anti-inflammatory cytokines (interleukins-4 and 10). This model demonstrated decreased joint inflammatory response to intra-articular injury, with relative radiographic protection from PTOA[23], suggesting that decreasing the inflammatory response clinically may perhaps decrease the severity of PTOA in patients with intra-articular fractures.

The "Second Hit"—Impact of Chronic Joint Incongruity and Instability

The widely accepted clinical recommendation for treating intra-articular fractures involves early surgical intervention to achieve anatomic reduction of the articular surface and absolute fixation of the articular fragments. It is likely that both articular congruity and joint stability have a role in the development or prevention of PTOA, however, their relative contribution to articular stresses and subsequent degeneration are not well characterized. Orthopaedic adage suggests that articular reduction should be within 2 mm of perfect anatomic reduction[24], however, multiple studies suggest that some injuries with much larger incongruities are clinically well-tolerated[24]. Not all patients with anatomic reductions have a perfect clinical outcome, and several long-term studies have revealed good clinical outcomes after non-operative treatment of intra-articular injuries, despite imperfect anatomic reduction and radiographic findings[24]. This section

will present the available experimental and clinical data that examines the impact of articular congruity and stability on the development of PTOA in intra-articular fractures.

In human cadaveric ankles, McKinley et al. observed increases in contact stresses of up to 300% in specimen with articular stepoffs compared to controls[25]. Further, they later noted that instability superimposed on articular surface incongruities caused disproportionate increases in contact stress rates[26]. Further, a cadaveric finite element model showed that instability and articular stepoff yield significant changes in the loading pattern of articular cartilage, resulting in increased stress magnitudes and loading rates[27]. Anderson et al. presented a patient-specific finite element model of an injured human population of tibial plafond fractures[28,29]. In this study, the authors observed that intact ankles had lower peak contact stresses that were more uniform and centrally located than fractured ankles[29]. At 2 years post-injury, the authors correlated the initial finite element model with radiographic outcomes, and observed that 5 different metrics of cartilage stresses were associated with the development of PTOA, and suggested that there may be a contact stress exposure threshold above which incongruously reduced plafond fractures develop PTOA.

On the contrary, many experimental models of joint incongruity demonstrate relatively mild increases in articular surface contact stresses, even in the setting of large incongruities[24,30-33]. In a canine cadaveric model, statically loaded defects of 7mm in the medial femoral condyle showed mean increases in contact stresses of only 10-30%[31]. These results are likely confounded by the fact that the specimen in multiple studies are most frequently statically loaded across a fixed joint position without motion. This testing method cannot detect transiently elevated contact stresses, cumulative stresses that occur during motion, or account for the effects of joint instability[24]. Improved methods of assessing the effects of post-fixation articular incongruity and instability are needed to better elucidate the impact of these factors on the progression of PTOA and outcomes following intra-articular fractures.

In the clinical literature, a recent systematic review examined the effects of articular stepoff on outcomes following treatment of intra-articular fractures, and demonstrated variability depending on the joint involved[24]. In the distal radius literature[34-43], the authors noted that articular stepoffs and gaps were associated with higher incidence of radiographic PTOA, but there was not a definite link between worse long-term clinical outcomes and articular reduction. In the acetabular fracture literature[44-53], they noted that restoration of the superior weightbearing dome of the acetabulum decreased the rate of PTOA and improved clinical outcomes; however, involvement of the posterior wall was a negative prognostic factor, likely independent of articular reduction. Finally, in the tibial plateau literature[30,54-63], articular congruities appeared to be well-tolerated, and other factors, including joint stability, retention of the meniscus, and coronal alignment were proposed to be potentially more important factors. There was no consensus noted in this literature as to the maximal acceptable articular stepoff, and the relative

tolerance of imperfect reduction was suggested to be related to the relative thickness of the tibial plateau cartilage as compared to other anatomic regions.

Conclusions—"First Hit", "Second Hit", or Both?

The development of post-traumatic arthritis after intra-articular fracture is likely multi-factorial, and is associated with both initial cartilage injury via chondrocyte death, matrix disruption, and release of pro-inflammatory cytokines and reactive oxygen species, as well as chronic joint overload via instability, incongruity, and malalignment. Future experimental and clinical studies are needed to better elucidate the relative contributions of these factors on the development of PTOA to permit better treatment algorithms. Based on the best available current clinical data, future interventions will need to consist of both acute biologic interventions, targeted at decreasing the inflammation and cellular death in response to injury, as well as improved surgical methods to better restore stability, congruity, and alignment following intra-articular fractures to reduce the individual and societal burden of PTOA.

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