POST TRAUMATIC ARTHRITIS

Many intra-articular fracture patients eventually experience significant functional deficits, pain, and stiffness from post-traumatic osteoarthritis (PTOA).
Over the last several decades, continued refinement of surgical reconstruction techniques has failed to markedly improve patient outcomes.

New treatment paradigms are needed - ideally, bio/pharmaceutical. Progress in that direction has been impeded because the pathomechanical etiology of PTOA development is poorly understood. In particular, the relative roles and pathomechanisms of acute joint injury (from the initial trauma) versus chronic contact stress elevation (from residual incongruity) are unknown, primarily because there have been no objective methods for reliably quantifying either of these insult entities.

Over the past decade, novel enabling technologies have been developed that provide objective biomechanical indices of injury severity and of chronic contact stress challenge to fractured joint surfaces. The severity of the initial joint injury is indexed primarily on the basis of the energy released in fracture, obtained from validated digital image analysis of CT scans. Chronic contact stress elevations are indexed by patient-specific finite element stress analysis, using models derived from post-reduction CT scans.

These new measures, conceived in the laboratory, have been taken through the stage of validation, and then have been applied in studies of intra-articular fracture patients, to relate these biomechanical indices of cartilage insult to the incidence and severity of PTOA This body of work has provided a novel framework for developing and testing new approaches to forestall PTOA following intra-articular fractures.

For their efforts to delineate the relationship between trauma and osteoarthritis, Drs. Donald Anderson, J. Lawrence Marsh and Thomas Brown were awarded the 2011 OREF Clinical Research Award. “The Pathomechanical Etiology of Post-traumatic Osteoarthritis Following Intra-articular Fractures” .
The authors developed and validated a novel method of measuring the severity of intra-articular fractures; they then applied this method to the study of patients. These measurements are based primarily on the energy released at the time of fracture, and are calculated from digital image analysis of CT scans. The authors also developed and validated a method of measuring

cumulative articular surface contact stress elevation following intra-articular fractures, using computational models derived from post-articular fracture reduction CT scans. They then applied these methods to study patients who suffered intra-articular fractures of the distal tibial articular surface. Subsequent work demonstrated that both of these measures predict the development of osteoarthritis: That is, fracture energies above an identified threshold predictably presaged osteoarthritis within two years; and cumulative contact stress due to intra-articular incongruity above a defined threshold also preceded development of post-traumatic osteoarthritis within two years. This innovative work has stimulated investigations by other research groups and has encouraged new efforts to prevent the development of osteoarthritis following joint injuries.

Relevant Anatomy

Cellular component 3–5%

Extracellular matrix (ECM) 95%

[collagen, glycosaminoglycans (GAGs) and proteoglycans]

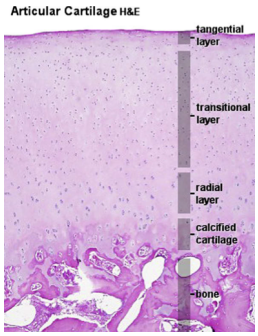
Cells:

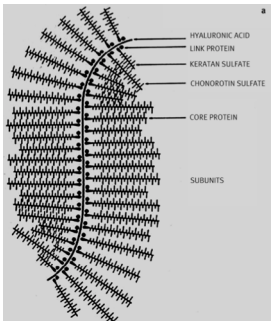
Active chondrocytes: display areas of cytoplasmic basophilia, where protein is synthesised.

Each chondrocyte is surrounded by a thin, pericellular matrix that provides hydrodynamic protection for the chondrocyte; a complex known as the chondron.

3 kinds of GAGs: Hyaluronan, chondroitin sulphate, and keratan sulphate

The most important proteoglycan monomer in the ECM is aggrecan, which is joined by chondroitin sulphate and keratan molecules. Proteoglycans are hydrophilic; this property results in the ability of hyaline cartilage to retain water which is essential to its proper function.





Cut Section of Hyaline cartilage

Pathology

In early OA an increase in matrix molecule synthesis is often recognised. However, once loss of matrix eventually exceeds that which is deposited, a net loss of ECM results.

The chondrocytes are noted to proliferate and form clusters, and cell hypertrophy is often observed.

Loss of chondrocytes in the superficial zone occurs followed by fibrillation, fissuring, erosion, subsequent denudation of bone and finally deformity.

Inflammatory mediators such as cytokines 1 (IL-1); TNF having been implicated.

More than one causative factor will need to be addressed, especially as the severity of the disease progresses.

MRI is the mainstay of diagnostic imaging at present. New techniques such as delayed Gadolinium Enhanced MRI (dGEMRIC) and T2 mapping not only allow morphological detailing of the cartilage surface and subchondral bone.

As glycosaminoglycan (GAG) is one of the first molecules of the ECM to be lost in early degeneration, dGEMRIC is considered the method of choice for detecting proteoglycan depletion in articular cartilage. Following injection of gadolinium, which binds to the negatively charged GAG molecules, T1 images can be used to quantify tissue GAG concentration. T1 signal is high in normal cartilage and low in GAG depleted cartilage.

As these techniques evolve, it is likely that MRI will form the mainstay of diagnosis, and more importantly, the assessment of clinical outcome in correlation with the biomechanical and biochemical characteristics of the repair tissue.

INTRODUCTION: THE CLINICAL PROBLEM

Post-traumatic osteoarthritis occurs following a variety of joint injuries [1]. It ensues most commonly and predictably following injuries that disrupt the articular surface. Data from our institution indicate that roughly 12% of patients presenting with OA of the hip, knee, or ankle have a history of prior joint trauma [2]. Despite the best cur-rent efforts at treatment, OA develops in as many as 25% of patients after fractures of the acetabulum, 35% after intra-articular fractures of the knee, and in more than 50% of patients with fractures of the tibial plafond.

PTOA following an intra-articular fracture has been attributed to the initial joint injury [3] and to elevated cartilage stresses from residual surface incongruity [4]. Neither of these two plausible factors has been amenable to reliable quantification. The severity of the articular injury may well be a primary determinant of outcome, but based on clinical experience, reduction of displaced articular surface fragments has been considered the

most important factor leading to a good outcome. Still, case-specific prognoses remain largely speculative.

Our research group has combined the complementary expertise to address these challenges. Enabling technologies that provide objective mechanical indices of acute cartilage injury and of chronic elevated contact stress have been developed in the laboratory.

Both the fracture severity assessment and the chronic contact stress assessment originate from firm physical foundations. Both are implemented using state-of-the-art computer techniques, both have undergone rigorous physical validation, and both have been successfully applied to prospective patient series.

PART I: THE ROLE OF ACUTE FRACTURE SEVERITY

The difficulty of controlling for the influence of injury severity has been a major confounding factor in clinical studies of intra-articular fracture treatments.
It is a broadly accepted viewpoint within the orthopaedic trauma community that “the extent of bone, cartilage, and soft tissue damage is directly related to the energy imparted to these structures". Yet, the energy involved in producing a given injury has not been measurable, making assessment of the severity of the injury inexact, subjective, and largely empirical.

The joint injury in articular trauma is traditionally assessed using categorical fracture classifications. These classifications at best allow only crude assessments of injury severity, and they have been shown to have very poor inter-observer reliability. Thus, the relationship between fracture severity and eventual outcomes remains very poorly understood.

To address this knowledge gap, in 1998 our group introduced the concept of relating the degree of bony comminution to the amount of energy delivered at the time of injury. CT scans, acquired routinely for many articular fractures, provide the opportunity to directly measure de novo interfragmentary surface area, from which surface energy can be quantified. For studying PTOA in tibial plafond fracture cases, the primary utility of fracture energy is as a metric of the cartilage-injurious energy pulse that must have crossed the articular surface to create the bony fracture.

Laboratory apparatus for controlled comminution energy delivery, In human comminuted fractures, tendency to produce more fragments which are smaller and sharper as energy absorption is increased, order-of-magnitude similarity of intrinsic material mechanical properties, and similarity to natural bone’s radiographic CT

appearance.

Impact tests with the bone fracture surrogate showed a very close linear proportionality between de novo fragment surface area and delivered impact energy, very much as would be expected on theoretical grounds.

Digital image analysis for automated measurement of interfragmentary surface area
Next, special purpose image analysis capabilities were developed to automate the task of interfragmentary surface area measurement in CT images. Accurate segmentation to distinguish bone from its surrounding tissues within CT images poses significant technical challenges, due to similar attenuation characteristics between neighboring tissues. This is especially true where metaphyseal articular fracture fragments that are not cleanly bounded by cortex abut one another, producing barely distinguishable fracture lines.

Multiplication of the bone perimeters (endosteal, periosteal, and subchondral) in a given CT slice by that slice's thickness yields the bone surface area over the slice volume. Summing areas across all slices provides the total amount of bone free surface area. Finally, it is necessary to subtract the pre-existing intact bone surface area from the fractured area to determine the de novo interfragmentary surface area.

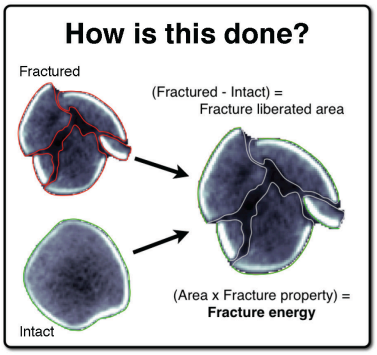


Figure 2. Bone perimeters (matched intact & fractured), plotted along the length of the distal tibia, show how the fracture energy measure is calculated. Inset: CT slice from fracture case, with identified tibia bone fragment edges.

Interfragmentary surface area measurement in a comminuted fracture
Experiments were next performed using bovine cortical bone. We hypothesized that fragment sets resulting from replicate equal-energy impacts would have similar interfragmentary surface areas, whereas fragment sets from impactions at different energy levels would have correspondingly different interfragmentary areas.

The de novo surface area generated in the specimens that absorbed greater energy was significantly higher ($p<0.0001$) than that in the lower energy groups, with energy-proportional linearity.

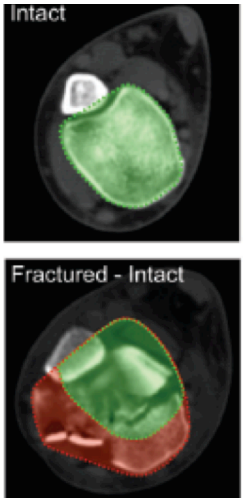
Greater energy absorption produced a greater number of fragments, of correspondingly smaller size.

Incorporation of bone density heterogeneity into the fracture energy determination
The fracture energy assessment technique was then extended for use in human clinical cases. A key difference between the surrogate material and human bone tissue is the latter's heterogeneity. Since the energy-absorbing capacity of bone is both density- and age-dependent bone density.

Energy release rates are then determined by scaling (previously-measured) impact energy/density data to the (patient-specific) bone density values.

Measuring fracture displacement and articular involvement in comminuted fractures

Fragment displacement/dispersion is another factor influencing the outcome of intra-articular fractures. As with fracture energy, this is amenable to quantification from CT studies. When fracture fragments are displaced, the bony regions in given cross-sections are generally translated away from their intact positions, the bone structure is disrupted, and fragments are dispersed relative to one another.



The bone surfaces identified in fracture energy analysis were used to quantify fragment displacement. This required alignment of the intact proximal portion of the fractured tibia with a mirrored image of the uninjured contralateral side.
To determine dispersal volume, for each CT slice, a convex hull (the smallest convex polygon circumscribing a given object) was determined for both the (mirrored) intact bone, and for a composite of the aligned intact and fractured tibias. The difference in these volumes provided a metric of the amount of fragment disperse on, implicitly incorporating limb axial malalignment, as well.

The degree of comminution of the articular surface per se is a key radiographic feature associated with injury severity and with likelihood of PTOA This was quantified in terms of the amount of interfragmentary surface area located within 1. 5 mm of the articular surface, expressed as a percentage of the pre-existing (intact/contralateral) surface area of the distal tibia.

Summarizing, the (objective) CT-derived measures of comminuted fracture severity agreed with the experienced orthopaedic surgeons' (subjective) rankings.

Refinements in fracture severity assessment, toward practical clinical use
Too lengthy for application in the clinical setting.

An expedited fracture severity assessment technique was developed, based upon textural image analysis. This new method quantified “disorder” in a given CT slice, based on a mathematical entity known as the gray level co-occurrence matrix (GLCM). The GLCM indexes the spatial homogeneity of pixel intensities (image texture) within a given image.

Using the GLCM reduced the time required to obtain an objective fracture severity assessment from roughly 8-10 hours to about 10 minutes, while maintaining excellent agreement with the area-based energy metric.

A second step toward use of the CT-based methods in orthopaedic practice is to avoid the need for CT scans of the intact contralateral limb. It was hypothesized that an allometrically scaled tibia model could serve as a surrogate datum capable of accurately measuring interfragmentary surface area.

PART II THE ROLE OF CHRONIC CONTACT STRESS ELEVATION

Attempts have been made to measure residual articular surface incongruity on post-reduction radiographs, as a surrogate for elevated contact stress. Unfortunately, the ability to measure joint incongruity on radiographs has been shown to be poor. Moreover, the measurement of geometric steps or gaps seen on radiographs is a weak surrogate for the actual chronic pathomechanical stimulus of interest at the cellular and molecular level: contact stress abnormality.

In the presence of residual surface incongruity, joint loads that are normally well tolerated generate local areas of elevated contact stress[5]. The degree to which injured articular joints tolerate elevated contact stress is unknown, as is the accuracy of articular reduction required to forestall clinically significant PTOA Finite element (FE) stress analysis techniques, suitably applied and rigorously validated, provide the basis to address this knowledge gap.

Patient-specific FE mesh generation from CT scans

A finite element formulation that automatically generates patient-specific meshes, that overcomes the contact surface stair-stepping difficulty, and that implements whole-duty-cycle analysis. To mesh patient-specific articular surfaces (including those with fracture incongruities), layers of continuum hexahedral ("brick") cartilage elements are zoned outwardly from quadrilateral bone surface meshes (subchondral bone plate).

The accuracy of this pre-processing approach was verified using precisely known analytic geometries (spherical and cylindrical), with the FE solutions showing close correspondence to gold standard (Hertzian) mathematical contact solutions.

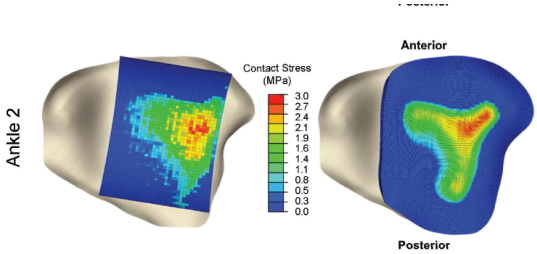


Figure 9. Inferior view of tibia, overlaid with spatially aligned Tekscan pressure results (left) and FE results (right) for each validation ankle. [Reprinted with permission from Anderson DD et al. Physical validation of a patient-specific contact finite element model of the ankle. J Biomech. 40:1662-9, 2007.[54]]

FE Validation: accurate regional reproduction of prevailing contact stress distributions. Next, a validation study was conducted to determine the extent to which Thus-computed ankle contact FE results agreed with experimentally measured tibio-talar contact stress.

Formal site-by-site comparisons between the computed and measured contact stress distributions over the articular surface (1472 locations) also showed strong agreement, with correlations of 90% for one specimen, and 86% for the other. This strong level of agreement between physical measurements and the FE —especially including the spatial distributions—convincingly established the computational formulation's validity.

Contact stress differences in fractured versus intact ankles
Chronic contact stress exposures were then quantified following intra-articular ankle fractures, in the same patient series for which fracture energy analyses had been performed. FE models were generated from CT scans of both the fractured (post surgical reduction) and the intact contralateral ankles. FE solutions were obtained for 11 intact/fractured ankle pairs.

Finite Element-computed contact stress exposure distributions for the 11 paired intact and fractured (post-reduction) ankles, for a single gait cycle.

In general, the intact ankles had lower peak contact stress exposure values and more uniform and centrally positioned exposure regions, than the (reduced) fractured ankles. The peak contact stress and contact area values occurred at the instant in the gait cycle with maximal joint loading, roughly 61% through the stance phase, in a 7. 5° dorsiflexed position.

The fracture cases had several-fold higher amounts of area with high contact stress-time exposures, and correspondingly lesser amounts of area with low exposure values, compared to the intact cases.

PART III: INVESTIGATIONS OF THE ETIOLOGY OF PTOA

We have prospectively followed a series of 36 tibial plafond fracture patients, who have been uniformly treated provisionally with a spanning external fixator, and subsequently with definitive fracture reduction and screw fixation at a time when soft tissue injury had sufficiently resolved.

A goal has been to assess whether these new biomechanical indices of both the acute mechanical insult (from the initial trauma) and chronic contact stress elevation (from residual incongruity) are predictive of OA The tibial plafond fractures ranged in severity from minimally to severely comminuted, with idiosyncratic fragmentation morphologies.

Hypotheses tested have been that functional deficits, symptoms, and the degree of cartilage degeneration in articular fracture patients correlate with metrics of the acute injurious mechanical insult and/or of chronic cartilage contact stress elevations from residual articular incongruity.

The CT-based severity metric successfully discriminated between cases that developed PTOA and those that did not, in a threshold like manner

Fragment displacement/dispersal was not a significant predictor of PTOA in this series of intra-articular tibial plafond fractures.

To investigate the hypothesis that elevated contact stress exposure results in cartilage thinning, a method was needed to measure cartilage thickness in patients with implanted metallic fixation hardware. MRI of cartilage provides an obvious means for this assessment. Unfortunately, the metallic screws and plates normally placed surgically to maintain fracture reduction introduce susceptibility artifacts, which locally distort conventionally acquired MR images, largely precluding reliable cartilage assessment.

Double-contrast CTs were obtained at 6 months and 2 years post injury, for 11 patients.

Localized areas of cartilage thinning generally corresponded to areas exposed to elevated contact stresses. Contact stress exposures of 2. 0 MPa-s or greater were associated with a focal loss of cartilage.

We are currently conducting a multi-center study of plafond fractures using expedited CT-based fracture severity measurements, with novel capabilities for case-by-case comparisons within a large patient population.

REFERENCES

1. Buckwalter JA. Mechanical injuries of articular cartilage.: AAOS; 1992. pp. 83–96.

2. Brown: Posttraumatic osteoarthritis: a first estimate of incidence, prevalence, and

burden of disease. Orthop Trauma. 2006;20(10):739

3. Borrelli J, Ricci WM. Acute effects of cartilage impact. Clin Orthop Relat Res. 2004;(423):33–39.

4. McKinlcy TO, Rudert MJ, Koos DC, Tochigi Y, Baer TE, Brown TD. Pathomechanic determinants of posttraumatic arthritis. Clin Orthop Relat Res. 2004;(427 Suppl):S78–S88.

5. Fitzpatrick DC, Otto JK, McKinley TO, Marsh JL, Brown TD. Kinematic and contact stress analysis of posterior malleolus fractures of the ankle. J Orthop Trauma. 2004;18(5):271–278.