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Intra-articular Traumatic Knee Injuries

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Presented for the Degree of Doctor of Medicine University of Edinburgh 2019
Declaration

This thesis represents research undertaken in the Department of Orthopaedic and Trauma Surgery and the Centre for Integrative Physiology, University of Edinburgh and has been composed by the author. The work is original, and is my own except where specifically stated in the acknowledgments. It has not been submitted elsewhere in candidature for any other degree, diploma or qualification.

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May 2019
Dedication

To my parents and husband for their endless support.

To my wonderful daughter Daisy for my motivation.

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Abstract:

Introduction: Tibial plateau and patellar fractures are common intra-articular fractures. An estimated 44% of patients develop post-traumatic arthritis (PTOA). PTOA is a disabling condition and the precise aetiology is unknown. Research to reduce the burden of PTOA has focussed primarily on operative reduction and rehabilitation protocols. Despite successful treatment of the fractures, clinical outcomes are frequently compromised. Initial chondrocyte death occurring at the time of injury may be the principal prognostic feature of PTOA. Chondrocyte death is irreversible and is followed by irreversible matrix degeneration and therefore cartilage degeneration.

Aim: To investigate the clinical impact of traumatic injury to the knee, specifically tibial plateau and patellar fractures, and study chondrocyte death secondary to traumatic injury.

Studies: Six complementary studies were performed.
1) An epidemiological analysis was carried out to determine the numbers, patient factors and mechanisms of injury of tibial plateau fractures in a large catchment area over 25 years.
2) A clinical study was performed looking at the patient reported outcomes of tibial plateau fractures in the defined population. This included the requirement for total knee replacement following tibial plateau fractures to look at the end stage of post-traumatic osteoarthritis in these patients.
3) An epidemiological analysis was carried out to determine the numbers, patient factors and mechanisms of injury of patellar fractures treated operatively in a large catchment area over 15 years.
4) A clinical study was then performed looking at the patient reported outcomes of these injuries in the defined population. This included the requirement for total knee replacement following patellar fractures to look at the end stage of post-traumatic osteoarthritis in these patients.
5) An in vitro animal model of two blunt trauma mechanisms was developed to investigate the effect on the chondrocytes in various controlled conditions.
6) A human fresh cadaveric whole joint model of blunt trauma was developed to link the animal models findings to the clinical work.

Results: Tibial plateau fractures have an incidence of 11/100,000 per year and are common in elderly women following falls and young men following road traffic accidents. A third of patients suffered complications with 15% requiring further surgery. Symptomatic PTOA was seen in 5% of the population with arthroplasty required in 3%. Outcomes revealed mild to moderate knee problems and a significant decrease in general health following tibial plateau fractures. Patellar fractures that required operative management had an incidence of 3.4/100,000/year and were also common in elderly women and young men with the same mechanisms of injury as tibial plateau fractures. There were complications in 62% of the cases with nearly 50% requiring further surgery. More symptomatic PTOA was seen at
9% but only 1% of patients had arthroplasty surgery. Outcomes despite the higher rates of complications and further surgery were better than for tibial plateau fractures with only mild knee problems and no change in general health compared to the non-fracture population.

Blunt trauma in the form of unintentional iatrogenic trauma during arthroscopy produced cell death with moderate pressure movement of the arthroscopic probe, equivalent to clinical practice. This damage was significantly decreased by the use of hyperosmolar saline in bovine tissue and a reduction trend in human tissue. Increased blunt trauma in the form of an impact injury was also shown to cause chondrocyte death in an energy dependant manner but hyperosmolar solution did not show decreased death in this study.

Conclusion: Chondrocyte death was not limited to sharp trauma; seemingly benign blunt trauma caused measurable cell death in bovine tissue. This cell death was reduced to some extent by increasing the osmolarity of the irrigation fluid. The results in the human cadaveric studies correlated with the bovine model. Further work is required to develop the model to include fracture damage to articular cartilage. Intra-articular injuries including fractures cause chondrocyte death, which can lead to post-traumatic osteoarthritis. The factors influencing the amount of cell death and the progression to arthritis are numerous and some can be modified after injury. The cause of injury, pattern of injury and who it occurs to cannot be modified after the event but prevention of infection, the operative technique and chondroprotection could all be used to reduce the burden of intra-articular injuries leading to post-traumatic osteoarthritis.
Lay Summary:

Introduction: Fractures that extend into the knee joint are common. An estimated 44% of patients go on to develop wear and tear arthritis, called post-traumatic osteoarthritis (PTOA), after these injuries. PTOA is a disabling condition and the cause is unknown. Despite successful treatment of these injuries the patients still suffer compromised outcomes. Studies have shown that irreversible cell death occurring at the time of injury is a feature of PTOA.

Aim: To investigate the impact of a blunt injury to the knee and study the cell death.

Results: Fractures involving the shinbone at the knee joint occur in 11/100,000 per year and are common in elderly women following falls and young men following road traffic accidents. A third of patients suffered compromised outcomes despite appropriate treatment. PTOA was seen in 5% of patients and 3% required knee joint replacement surgery. Outcomes revealed mild to moderate knee problems and a significant decrease in general health following these fractures. Fractures involving the kneecap that required an operation were also common in elderly women after falls and young men after road traffic accidents. Although compromised outcomes were seen in almost two thirds of the cases only 1% of patients needed knee replacement surgery and patients only complained of mild knee problems with no change to their general health.

A small probe, used in keyhole surgery, was shown to cause blunt trauma to the surface of the knee joint and produced cell death. This damage was reduced by increasing the amount of salt in the fluid surrounding the joint surface in cow cartilage experiments. A similar reduction in cell death was seen in human joints when the amount of salt was increased. A higher energy blunt trauma using a mechanical ram also caused cell death but this was not significantly reduced by the higher concentration of salt in the fluid surrounding the joint.

Conclusion: The outcome of fractures involving the knee joint varies depending on the location of the fracture and whether the fracture requires an operation. Fractures involving the shinbone extending into the knee joint had a worse outcome than kneecap fractures and required more knee replacement surgery. Elderly women who sustained high-energy injuries were most likely to require knee replacement surgery.

Cell death was caused by mild blunt trauma to the joint surface. Cell death was reduced by increasing the concentration of salt in the fluid surrounding the joint. The cell death seen after blunt trauma and the outcomes seen after fractures (blunt trauma) to the knee joint, add to our knowledge of the progression of PTOA, and suggest some methods by which we may be able to reduce PTOA, pain and the need for further surgery in the future.
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Abbreviations

ADL  Activities of Daily Living
AO  Arbeitsgemeinschaft für Osteosynthesefragen
ATP  Adenosine Triphosphate
CI  Confidence Interval
CLSM  Confocal Laser Scanning Microscopy
CMFDA  5-chloromethylfluorescein diacetate
CS  Chondroitin Sulphate
CT  Computed Tomography
DVT  Deep Vein Thrombosis
ECM  Extracellular Matrix
EQ5D  EuroQOL 5 Dimensions
FFH  Fall From Height
FFS  Fall From Standing
GS  Glucosamine Sulphate
KOOS  Knee Injury + Osteoarthritis Outcome Score
MDCD  Minimal Detectable Clinical Difference
MCPJ  Metacarpophalangeal Joint
MOI  Mechanism of Injury
MRI  Magnetic Resonance Imaging
MTPJ  Metatarsophalangeal Joint
MUA  Manipulation under Anaesthetic
OA  Osteoarthritis
OKS  Oxford Knee Score
ORIF  Open Reduction and Internal Fixation
PBS  Phosphate Buffered Saline
PI  Propidium Iodide
PROM  Patient Reported Outcome Measure
PTOA  Post-Traumatic Osteoarthritis
QOL  Quality of Life
RA  Rheumatoid Arthritis
REC  Regional Ethics Committee
ROMW  Removal of Metalwork
RTA  Road Traffic Accident
SIMD  Scottish Index of Multiple Deprivation
SNBTS  Scottish National Blood Transfusion Service
St Dev  Standard Deviation
TBW  Tension Band Wiring
TKR  Total Knee Replacement
TUNEL  Terminal Deoxynucleotidyl Transferase End Labelling
Section 1  Introduction:

1.1 Intra-articular fractures of the knee

Proximal tibial fractures have an incidence of 13.3/100,000 in the adult population\(^1\). They are slightly more common in men than women, with a ratio of 54:46, and 24% occur in patients over 65 years old. Multiple papers have been written in the last century documenting the classification, management, complications and outcomes of these fractures. Despite the large literature base, the latest edition of Rockwood and Green, an internationally recognised orthopaedic reference text, describes the treatment of this diverse group of fractures as controversial, presenting many different criteria for operative intervention\(^2\). Outcomes have been described as disabling, despite treatment since 1914\(^3\).

Patellar fractures are another common intra-articular fracture of the knee, with an incidence of 10.7/100,000\(^1\) representing approximately 1% of all skeletal fractures\(^4\). The patella is the largest sesamoid bone in the body and has the thickest articular cartilage measuring up to 1cm\(^5\). The management of patellar fractures depends on the clinical findings, particularly whether the extensor mechanism is functional. If operative management is required, the most widely used technique is tension band wiring (TBW), a technique pioneered in the 1950s by the Arbeitsgemeinschaft für Osteosynthesefragen (AO) group\(^2\).

Surgeons have been aware of these common injuries for a long time, with the first description of tibial plateau fractures published in 1913\(^6\) and the first description of open reduction and internal fixation (ORIF) of a patellar fracture in 1878\(^7\). These fractures affect patients during their most productive years of life\(^8\) and have potentially devastating consequences, including immobility and severe pain\(^9\).
1.2 Post-traumatic osteoarthritis

1.2.1 Epidemiology of post-traumatic osteoarthritis

Acute traumatic joint injury is known to increase the risk for subsequent development of osteoarthritis (OA)\(^{(10-13)}\). Post-traumatic osteoarthritis (PTOA) or secondary osteoarthritis is due to synovial joint degeneration initiated by mechanical joint injury such as intra-articular fractures\(^{(14)}\). Despite successful treatment of intra-articular fractures the clinical outcomes are frequently compromised by PTOA\(^{(15)}\). Rasmussen quoted a 60% rate of incapacitating pain in patients with PTOA after tibial plateau fracture\(^{(16)}\).

The prevalence of symptomatic OA attributable to PTOA is 10-13% overall\(^{(17-19)}\). Buckwalter et al. studied 607 consecutive patients referred to orthopaedic services for treatment of severe OA and found 73% of ankle osteoarthritis, 9% of hip arthritis and 13% of knee arthritis was due to PTOA\(^{(19)}\). PTOA predominantly affects a younger population than primary OA\(^{(17)}\). Furman et al. stated PTOA is one of the most frequent causes of disability following trauma involving weight-bearing joints\(^{(17)}\). The first clear mention of arthritis secondary to tibial plateau fractures was in 1934, when Cubbins et al.\(^{(20)}\) discussed the link between tibial plateau fracture and chronic osteoarthritis. The development of chronic arthritis led to a limp, deformity and therefore disability\(^{(20)}\). The reported prevalence of PTOA after tibial plateau fractures varies greatly in the literature. It has been described as rare, by many authors\(^{(21-24)}\) and occasional, by several others\(^{(25-27)}\), however rates up to 44%-55% have been described\(^{(28, 29)}\). This disparity may be explained by the lack of consistent radiological or functional diagnostic criteria for PTOA, and whether a diagnosis of PTOA should include only symptomatic cases. There is less research on the outcomes following patellar fractures, particularly regarding PTOA, with up to 76% of patients having radiographic arthritic changes post injury\(^{(30)}\).
1.2.2 Aetiology of PTOA

1.2.2.1 Biomechanical Theory of PTOA

The aetiology of PTOA is unknown and research has focussed primarily on operative reduction and rehabilitation protocols to improve the poor outcomes seen after tibial plateau fracture, however, several studies have suggested that PTOA is caused by the initial cartilage damage at the time of injury(31-34).

In 1929, when Cotton and Berg described tibial plateau fractures as ‘Fender Fractures’ they believed the poor outcomes were due to the irregular weight-bearing surface created at the time of injury. Despite attempted surgical reduction to restore the weight-bearing surface, Cotton and others were unable to improve outcomes, with many patients complaining of postoperative stiffness(35, 36). Several other biomechanical reasons for poor prognosis were speculated, including malalignment, loose bodies in the joint cavity and fragmentation of the menisci(20). Haldeman, in 1938, considered a more biological aetiology for the development of PTOA and poor outcomes. He thought of fractures as ‘living tissue that has been crushed and deranged and not blocks of cement that have been chipped off’, suggesting that a further understanding of cartilage would contribute to the management of intra-articular fractures, thereby avoiding poor outcomes(37). The surgical literature however, generally ignored the more complex biological factors(17) and continued to debate the methods of treatment of the fracture, stating PTOA could be prevented by accurate reduction and stable fixation(38-40).

Barr went as far as stating that failure to achieve anatomical reduction of the joint surface failed the patient(41) and Jakobsen et al. predicted arthritis would develop in every malreduced joint surface in proportion to its incongruity(39).

By 2004, damage to the articular surface as a possible mechanism for developing PTOA was more widely accepted but residual joint incongruity and instability were also considered(19). The difficulty for the biomechanical theory enthusiasts was accurate reduction of the joint surface did not
correlate with outcomes\(^{42}\) and functional outcomes were found to be better than anatomical outcome\(^{25, 42}\). Honkonen found a step-off of <3mm or a condylar widening of <5mm had no adverse effect\(^{43}\), whereas Weigel and Marsh showed the articular surface tolerated a degree of residual incongruity, approximately 3mm residual displacement, without progression to arthritis\(^{44}\). Dovey and Heerfordt showed the clinical acceptability reduced from 94\% if <3mm to 50\% if > 10mm depression\(^{45}\), suggesting that a higher degree of incongruity had some part to play in PTOA. Research into step-off deformities was developed in other joints, with any residual incongruity at the articular surface said to contribute to progressive cartilage degeneration\(^{46, 47}\). Wright et al. added to the debate on intra-articular fracture outcomes, showing 83\% of poor outcomes from acetabular surgery had satisfactory postoperative radiographs\(^{48}\). Catalano et al. showed that despite a strong association in distal radial fractures between the development of osteoarthritis of the radiocarpal joint and residual displacement of articular fragments measured on CT scans, the functional status did not correlate. All patients in this series had an acceptable outcome irrespective of radiographic evidence of PTOA\(^{49}\). Marsh et al. also showed a correlation between arthritis and injury severity as well as arthritis and fracture reduction in the tibial plafond, but again no correlation with ankle outcome score\(^{50}\). The research into step-off deformity is compromised due to inaccuracies in measuring the displacement\(^{51}\). The validity of the studies into the effect of articular reduction relies on highly accurate and reproducible measurements\(^{52}\) but the interobserver variability\(^{53}\) for articular incongruity in tibial plateau fractures was poor with a range of 12mm reported. In operatively reduced distal radius fractures, where the range of measurements was only 4mm, the tolerance limits were 3mm\(^{54}\), indicating significant inaccuracy in measuring incongruity consistently. Imaging modalities like computed tomography (CT) also show the unreliability of plain radiographs for measuring displacement\(^{55}\), calling into question the results of any studies that used plain radiographs for measuring incongruity.
In 2011, Anderson et al. followed up a series of 36 patients for two years. The results indicated fracture energy and articular comminution explained 70% of the variation in PTOA severity and that fragment displacement was correlated much less strongly\textsuperscript{[56]}. Martin et al. believed PTOA was likely to be related to both the energy delivered to the articular surface at the time of injury and the repetitive mechanical stresses applied to the altered articular surfaces\textsuperscript{[52, 57]}. Moderate to severe PTOA developed more often if there was greater than 5 degrees malalignment; 9.2% of those with a normal knee axis developed secondary arthritis compared to 27% of those with malalignment of >5 degrees\textsuperscript{[15]}. Instability has also been linked to PTOA in tibial plateau fractures\textsuperscript{[28, 29, 58, 60]}. In a classic study, by Rasmussen et al.\textsuperscript{[60]}, of 204 tibial plateau fractures in patients followed up for at least 5 years, 87% had good outcomes regardless of articular surface reduction, provided that coronal plane stability was maintained. Twenty-year follow-up of 102 knees from that same set of patients revealed continued good results in 90% of patients with as much as 1 cm articular surface depression, provided that their knees were stable\textsuperscript{[59]}. In contrast, patients with residual instability had poor outcomes regardless of the articular reduction. In a series of 46 patients with tibial plateau fractures, the outcomes, in stable knees, were not affected by incongruity, however, residual instability after intra-articular fractures of the knee was poorly tolerated\textsuperscript{[60]}. The aetiology of PTOA is made more complex by the fact the joints of the lower limb, hip, knee and ankle, are affected differently by intra-articular fractures. Incongruity is poorly tolerated in the hip, yet as described, well tolerated in the knee provided that alignment and stability are preserved\textsuperscript{[58, 59]}. Instability is poorly tolerated in all three joints\textsuperscript{[61]}. The published studies, as above, concentrate on accurate reduction and fixation to help improve outcomes, as this is something that surgeons can improve upon, yet despite improved modern surgical techniques the prevalence of PTOA remains high\textsuperscript{[62]}. This suggests that factors other than post-traumatic incongruity and instability, such as cellular and tissue alterations in response to injury, play a crucial role in the progression of PTOA.
PTOA\(^{(63)}\). This led to a change in focus to articular cartilage and its role in the process with discussion of the injury to cartilage resulting in irreversible damage and common residual symptoms developing, despite accurate reduction and fixation\(^{(64)}\).

1.2.2.2 Biological Theory of PTOA

1.2.2.2.1 What is articular cartilage?

Articular cartilage is a complex material that functions to reduce friction and distribute load across the joint surface\(^{(65)}\). It transfers load by matrix deformation and hydrostatic pressurization of the interstitial fluid\(^{(66)}\). Articular cartilage is avascular and its cells, chondrocytes, synthesize and degrade the components of its extracellular matrix (ECM). The ECM is made up principally of type II collagen, proteoglycans and non-collagenous proteins. The ECM acts as a signal transducer, detecting changes to the macromolecular concentration, contributing to the biological and mechanical properties of articular cartilage\(^{(67)}\). These properties can vary depending on load and the physiochemical environment allowing the cartilage to adapt to the altered mechanical forces\(^{(68)}\).

The typical thickness of articular cartilage is between 0.5 and 6mm, varying between joints\(^{(65)}\). Articular cartilage has a very low density of chondrocytes, approximately 1-5% of the volume in adult human tissue\(^{(69)}\). The cell density is inversely proportional to the cartilage thickness and the size of the joint\(^{(68)}\). This means the number of cells is limited by how many can be sustained by nutritional diffusion from the synovial fluid\(^{(68)}\).

Some of the earliest investigators stated that articular cartilage could not regenerate, for example in 1743, Hunter\(^{(70)}\) said:

"From Hippocrates to the present age it is universally allowed that ulcerated cartilage is a troublesome thing and that when once destroyed it is not repaired"
In immature cartilage, Tew et al. (71) found within areas of cell death, chondrocytes that had not died could undergo proliferation but that there was minimal, if any, cell division in skeletally mature normal cartilage (69, 71). It is generally agreed that articular cartilage has very poor reparative potential (46, 67, 72-78). Partial thickness wounds, that do not involve the subchondral bone, do not heal (79), leaving the remaining chondrocytes with a greater burden for maintaining the ECM (80). Full thickness defects repair with inferior fibrocartilage formation (46, 74-76, 79, 81, 82). Fibrocartilage is the only type of cartilage that contains type I collagen, it is tough and has a high tensile strength but lacks flexibility and the ability to load bear (78). In mature articular cartilage, with a limited source of chondrocytes, maintaining cell viability substantially impacts upon the ability of cartilage to repair and the subsequent maintenance of the ECM. Chondrocyte death may therefore be one of the critical factors determining the response of cartilage to injury (83). The specialised properties of articular cartilage allow joints to function under changing loading patterns and also mean that when damaged, the cells die and the tissue cannot regenerate.

1.2.2.2 How do chondrocytes die?

Attempts to classify cell death have been based on morphology and mechanism. Apoptosis and necrosis have been shown as two mechanistically and morphologically distinct types of cell death and while sharing common features, are potentially at the two ends of a continuous spectrum of cell death (84). Although several reports, some as early as 1962, have shown chondrocyte death in response to mechanical injury, the method of cell death, whether by apoptosis or necrosis or an alternative mode is not fully known (85, 86). Most methods of studying apoptosis lack the specificity to discriminate between apoptosis and necrosis e.g. terminal deoxynucleotidyl transferase end labelling (TUNEL) so additional markers e.g. caspases are needed (87). Morphological evidence of cell death is provided by imaging
where cells can be seen to round up and ‘bud’ in apoptosis, with nuclear and cytoplasmic shrinkage. In necrosis, the morphologic appearance is the result of denaturation of intracellular proteins and enzymatic digestion of the cell.

Apoptosis is a highly regulated active process of programmed cell death, requiring energy (adenosine triphosphate (ATP)) that plays an important role under normal physiological conditions in cell turnover for tissue homeostasis. Apoptosis can be found in non-physiological states due to toxic injury or disease processes. The cells shrink and are absorbed by surrounding tissue, preventing inflammation. Necrosis is a passive, catabolic and pathological process in response to cell injury, where cells lose control of ion flow, swell and the cell membrane leaks and ruptures, causing inflammation. Both apoptosis and necrosis may be seen due to the same initial insult. The unusual characteristics of chondrocytes suggest that their apoptotic processes may differ from those observed in other cell types.

Roach et al. proposed the term chondroptosis after reviewing the morphological differences between dying chondrocytes and classical apoptotic cells. Chondroptosis does not depend on phagocytosis but the cells do shrink and the nucleus, like in classical apoptosis, contains condensed chromatin. The end products of cell death are more akin to necrotic cell death as there is extrusion of the cellular material rather than budding of apoptotic bodies. Although there is no consensus on the mechanism of chondrocyte death following injury, a variation on the classical apoptosis specific to chondrocytes on the spectrum between necrosis and apoptosis seems the most likely due to the specialized nature of these cells. Chondrocytes are not the only cells in which a variation of classical apoptosis has been documented. In neuronal cells, apoptotic cell death occurs without nuclear fragmentation ‘paraptosis’ and lipoapoptosis has recently been identified as occurring in obesity and aging (Table 1.1).
**Table 1.1: Mechanisms of cell death. (Adapted from Roach et al. (93))**

<table>
<thead>
<tr>
<th></th>
<th>Physiological cell death</th>
<th>Pathological cell death</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Classical Apoptosis</td>
<td>Chondroptosis</td>
</tr>
<tr>
<td><strong>Nucleus</strong></td>
<td>Condensations of chromatin at perimeter</td>
<td>Patchy condensations of chromatin throughout</td>
</tr>
<tr>
<td><strong>Golgi Apparatus</strong></td>
<td>No Increase</td>
<td>Increase at early stage</td>
</tr>
<tr>
<td><strong>Endoplasmic Reticulum</strong></td>
<td>No changes</td>
<td>Increase in amount and expansion of lumen</td>
</tr>
<tr>
<td><strong>Autophagic vacuoles</strong></td>
<td>Not present</td>
<td>Frequently present</td>
</tr>
<tr>
<td><strong>Blebbing vs. Budding</strong></td>
<td>Budding into apoptotic bodies</td>
<td>Blebbing of cytoplasmic material</td>
</tr>
<tr>
<td><strong>Final elimination</strong></td>
<td>Phagocytosis of apoptotic bodies</td>
<td>Autodigestion of most cellular material</td>
</tr>
<tr>
<td><strong>Release of lysosomal enzymes</strong></td>
<td>Nil remain within intact apoptotic bodies</td>
<td>Nil remain within cytoplasmic islands or autophagic vacuoles</td>
</tr>
<tr>
<td><strong>Function</strong></td>
<td>Elimination of cells without inflammation</td>
<td>Autolysis in absence of phagocytes</td>
</tr>
</tbody>
</table>

Increased chondrocyte death has been shown to occur in osteoarthritic cartilage from humans(94-96) and to correlate with the severity of osteoarthritic changes in human and experimentally induced osteoarthritis(95, 97, 98). Chondrocyte death is also an important event following mechanical injury(61). It has been shown to occur in vitro following acute injury(94, 99), in vivo with a blunt articular impact load model(71), in vivo following intra-articular fracture in humans(100) and in the absence of detectable mechanical damage following mechanical injury(61).

Hashimoto et al.(95) proposed that matrix degradation occurs due to the release of active enzymes from apoptotic bodies. As cartilage does not contain macrophages, there is no mechanism for removing dead cells. This means that chondrocyte death not only disrupts the balanced synthesis and degradation of ECM and reduces the potential of the cartilage to respond to...
changing loads, the actual products of the cell death could cause additional tissue damage. Roach et al. (87) however, felt that the most crucial difference of ‘chondroptosis’ compared to classical apoptosis, related to the elimination of cellular remnants without inflammation as the tissue was not dependent on phagocytosis. Chondrocyte death has been inhibited in various settings (101) with a reduction of proteoglycan loss in the matrix, supporting the notion that cell death is linked to matrix degradation in cartilage. Cell death and proteoglycan release have been shown to correlate with load intensity and with each other, strengthening the link between chondrocyte death and matrix degradation after mechanical injury (83).

1.2.2.2.3 Why is cell death a problem?

The decreased viability of chondrocytes following injury and the association with matrix degeneration is a potential factor in post-traumatic osteoarthritis. Although cartilage has an extraordinary capacity to withstand physiological mechanical loads, its ability to bear mechanical injury is poor. Pathologic levels of static or impact loading cause cartilage deterioration and lead to osteoarthritic changes (34, 85, 102-104). The exact mechanisms leading to development of osteoarthritic changes after trauma have not been clearly identified, but decreased viability of the articular chondrocytes is a potential key factor (105). Death and dysfunction of chondrocytes may be a trigger for the pathological cascade that eventually leads to joint degeneration (106). The clinical importance of microscopic damage to the matrix is dependent on the number of viable cells that can restore the normal tissue composition (107). Cartilage, when devoid of living chondrocytes, results in cartilage defects that progress to more extensive degeneration of the joint (‘secondary’ osteoarthritis) (47, 76).

PTOA is one of the most frequent causes of disability following joint trauma. Trauma occurs more often in younger patients in the prime income earning years of their life (107, 108). To develop strategies to reduce the risk of PTOA, a further understanding of the pathogenesis of progressive joint
degeneration following injury is needed. There are several factors that are likely to contribute to cartilage degeneration after trauma, including acute mechanical damage to the cartilage at the time of injury and biological stimuli secondary to haemarthrosis (joint bleeding) and inflammatory responses\(^\text{106}\) causing immediate or subsequent death of the chondrocytes, altered cartilage metabolism or changes in the structural integrity of the cartilage\(^\text{85}\). Other factors affecting cartilage degeneration occur if the trauma has caused an intra-articular fracture, include whether the fracture extends to the subchondral bone layer, how comminuted the fracture is and the extent of articular cartilage fragmentation. Surgical trauma that may occur managing the fracture and later cartilage overloading due to any incongruity, instability and malalignment as discussed previously\(^\text{106, 109}\) are also factors. All of these factors are difficult to differentiate clinically and make research into the development of PTOA challenging.

Higher energy injuries are presumed to have a greater degree of blunt impact injury, greater displacement of fracture fragments and more comminution, leading to a less accurate surgical restoration of the articular surfaces. All of these may result in more extensive chondrocyte death increasing the risk of joint degeneration and resulting in a higher incidence of post-traumatic arthritis\(^\text{19, 109}\). The three main theories of causality for PTOA\(^\text{61}\) are:

1) direct acute damage to the cartilage or bone\(^\text{31-34}\)
2) chronic cartilage overloading due to residual incongruity\(^\text{110-112}\)
3) pathological load patterns due to instability\(^\text{58, 59, 113}\)

1.2.3 Outcomes of PTOA

1.2.3.1 Outcomes of PTOA in tibial plateau fractures.

Long-term follow-up studies help to give an idea of the prevalence and significance of PTOA. It is important to look at the management of the fractures in these studies as operative methods have changed over time,
meaning extrapolation of results is not always possible. In two of the largest
studies in the literature, Hohl and Luck in 1956(26) and Rasmussen in 1973(60)
menisectomies were performed routinely when treating tibial plateau
fractures, and patients were immobilised for three months. Allen et al. (114)
publishing results from 210 patients at 10-22 years post menisectomy
showed 18% radiographic degenerative deterioration and 7% symptomatic
patients, with worse results when the lateral meniscus was removed(114).
Jorgensen et al. also published a longitudinal study of 147 athletes 14.5
years post menisectomy showing 49% radiographic deterioration again with
lateral meniscectomy being more significant than medial(115). Jensen et al.
showed radiological results were poor in patients managed operatively due to
PTOA, especially in those who underwent meniscectomy(116). Evidence of
PTOA was seen in 74% of cases that underwent menisectomies in the study
by Honkonen et al.(28). Apley showed 80% satisfactory results when treated
with traction and mobilisation compared to 50% satisfactory results when
treated immobilised in plaster(23) and Roberts showed, in undisplaced
fractures, 94% acceptable results when treated with traction and mobilisation
compared to 72% when treated in plaster immobilisation(117). Both of these
studies together with studies by Palmer, Weissman and Herold, Leadbetter
and Hand, and Marwah et al.(118-121) provided evidence for early mobilisation
of patients after tibial plateau fracture and led to more modern treatment
standards that would recommend early mobilisation and retention of the
menisci to improve outcomes when treating intra-articular fractures of the
knee.

The time it takes PTOA to develop after injury is contentious. In
severe intra-articular fractures PTOA may develop early, with Slee
suggesting development 18 months to 3 years after fracture(22). Honkonen
and Volpin et al. however proposed a longer duration at 6 to 8 years post
injury(26, 122). The satisfaction rates after tibial plateau fracture have been
shown to decrease at the 6-10 year follow-up compared to the 3-6 years
follow-up(42) which maybe due to PTOA, signifying a longer duration of
progression.
The assessment of prevalence of PTOA is influenced by how it is diagnosed. Honkonen(28), described radiological PTOA in 44% of his 131 cases followed up for 7.6 years. Primary osteoarthritis was diagnosed from the initial radiographs at time of injury, which were non-weight-bearing and therefore underdiagnosed OA. This means PTOA was overestimated, mistaking some of the undiagnosed OA for PTOA. The development of the arthritis was however seen in the same compartment affected by the fracture(28). In the Netherlands, Houben et al.(42) looked at 46 patients followed up for on average five years (61 months). Arthritic changes were seen from five years post fracture but did not correspond with functional deficit. Weigel and Marsh in 2002 looked at functional results and development of arthritis after 24 high energy bicondylar tibial plateau fractures at greater than five years post injury and showed 18% showed one grade of progression of arthritis(44). This series included high energy severe fractures and therefore overestimates the development of PTOA if extrapolated to all tibial plateau fractures. Rademakers et al. in 2007 published a large series of 202 patients, 109 were followed up for 14 years on average. PTOA was seen in 31% but well tolerated in 64% of these(15), suggesting a rate of approximately 11% symptomatic PTOA. These studies recognise the difference between radiographic and symptomatic arthritic changes but report a wide variety of rates of PTOA (18-44%) with radiological PTOA seen far more often than symptomatic PTOA after intra-articular fractures.

A summary of the long-term outcomes is very difficult and part of the reason for the controversy in management. The variety of outcome measures, classification systems, lengths of follow-up and management options means the studies are not comparable. These factors combined with the difficulty in measuring fracture severity and displacement, and the lack of understanding of the aetiology of post-traumatic osteoarthritis leave the management of tibial plateau fractures largely unsolved. The agreements in the literature include delayed weight-bearing, early mobilisation and the generally poor prognosis. No satisfactory method of treatment for all cases
Management options vary from non-operative e.g. traction, cast bracing and closed reduction techniques to operative e.g. ORIF with a variety of plate configurations, incisions and techniques, minimally invasive, percutaneous and arthroscopic fixation with or without grafts, external fixators in various configurations and for different durations of treatment often combined with other fixation devices, and also arthroplasty techniques.

Despite the growing technology and improved management options available, poor outcomes and PTOA continued to be widely reported. More recently attention turned to the management of PTOA. In 2012, Mehin et al. conducted an 11 year follow-up study of patients requiring reconstructive surgery post-injury identified from trauma database and cross referenced with a health database. It was a retrospective cohort in a level 1 trauma centre and therefore had an increased incidence of complex fractures. They identified 311 patients, 77% of the initial fractures were treated operatively and the patients had a mean age of 46. Road traffic accidents (RTA) were the cause of 52% of the fractures and 15% were open injuries again suggesting a higher incidence of complex fractures. Despite the complex group of fractures only 4.5% required reconstructive procedures for endstage osteoarthritis, at a mean of 4.6 years post injury, and only 2% of these were total knee replacement (TKR). This study only looked at operatively-managed tibial plateau fractures caused by high energy mechanisms making the results difficult to extrapolate to the range of tibial plateau fractures. Although the low number of reconstructive procedures despite the complexity of the fractures is encouraging, these fractures were all treated by surgeons treating high volumes in a level 1 trauma centre and therefore reduces generalisability.
1.2.3.2 Outcomes of PTOA in patellar fractures.

The long-term outcomes in patellar fractures are less well documented, with the majority of the literature concentrating on fixation techniques in small studies. As with tibial plateau studies, the satisfactory outcomes range from 45% - 90% and depend on age, fracture management, outcome measure and length of follow-up. The range of fixation techniques is less than in tibial plateau fractures but on review of the literature there has also been less research performed. Again, as with tibial plateaus, rates of PTOA vary when the diagnosis is made clinically or radiologically.

Haut, 1989(154) measured the impact loading pressure on patellofemoral articular cartilage in humans in biomechanical studies. Patellofemoral joint pressure exceeding 25MPa were required to fracture the bone in 60% of cases(154). Thompson et al.(34) reported that impact injury led to PTOA in canine patellofemoral joint. The joints were subjected to a standardized transarticular load of 2170 N and six months after injury osteoarthritic changes were seen. Edwards et al. used reduced patellofemoral joint space on radiographs as a measure of osteoarthritis. They showed reduced joint space in patients with >1mm incongruency compared to the contralateral knee and compared to patients with <1mm displacement. They also showed osteophytosis in 27 patients compared to nine in the contralateral patella(155). This study did not look at patient symptoms. Nummi et al. found 76% of 155 patients with operatively-managed patellar fractures had arthritic changes on radiographs at follow-up however only 30% were symptomatic. The treatment methods in Nummi’s study included patellectomy, in 112 cases, differing from the more modern operative techniques of tension band wiring and making extrapolation to current populations difficult(30). Sorensen looked at 64 patients, 18.7 years after fracture and showed similar results with 19 (30%) cases of symptomatic arthritis and radiological changes were seen in 45 (70%) of the patellofemoral joints(156). The results of these studies suggest radiographic arthritic changes alone are not a useful measure for the burden of PTOA.
Sorensen et al. also noted nine patients with symptomatic arthritis in the contralateral knee and 20 with radiological changes on the contralateral side(156) showing with the passage of time patients can develop primary osteoarthritis and that PTOA may be over-diagnosed if this is not taken into account.

Debate remains concerning how much recovery is limited by PTOA. Shabat et al.'s study in 2003 suggested 82% of patients achieved the same mobility as pre-injury(157) and Sorensen showed 64% of patients symptom free at follow-up almost 20 years later(156) compared to LeBrun et al. suggesting significant symptomatic complaints on patient reported outcome measures (PROMs) and functional extension deficits of 26% persisted on Biodex testing at 6.5 years(158). LeBrun’s paper had a very high non-responder rate with only 36% patients followed up, possibly creating a bias towards those experiencing problems and requiring follow-up and a high open fracture rate at 28%, 7% post operative infection and 52% removal of metalwork (ROMW), which could all contribute to the poor outcomes reported(158).

1.2.3.3 Patient Reported Outcome Measures

Patient reported outcome measures (PROM) are a way of assessing the impact of injury/disease on a patient. Their use marks a move away from clinician driven outcomes, allowing the efficacy of an intervention to be measured from the patients’ perspective, giving health care providers a better understanding of the effect of disease and treatment on patients lives. There are two main types, site-specific and generic health related questionnaires. These are often combined in outcome studies to allow comparison with the general population.

EQ5D- 3L is a standardised generic instrument for describing and assessing health-related quality of life (QOL). It uses five domains, mobility, self-care, usual activities, pain and anxiety/depression and offers three levels of severity for each. An update to this has five levels of severity for each domain and is called EQ5D-5L but is not yet widely used so not comparable
between groups. A perfect score is 1.0 and anything lower than zero is described as a state worse than death.

A systematic review in Journal of Knee Surgery in 2010 of PROM in knees recommended the use of the Oxford Knee Score (OKS) and the Knee injury and Osteoarthritis Outcome Score (KOOS) for OA/TKR\(^{159}\).

The OKS was designed to look at patients following total knee replacement. It involves 12 questions and is used widely due to its brevity and site-specific nature. Its use has increased to include assessment of other management options for OA. Due to its wide use it can allow comparisons between treatment methods and patient groups. A ceiling effect can be seen with a PROM like OKS where approximately 15% of the individuals in the population achieve the highest score possible\(^{160}\). This prevents discrimination at the top end of the scale. Therefore the KOOS was used in conjunction to help reduce the ceiling effect.

The KOOS is a patient-reported outcome measure to assess the patient’s views about their knee problem. It involves 42 questions in five separately scored subscales: pain, symptoms, activities of daily living (ADL), sport/recreation and QOL. It was developed to be used in patients from 13-79 years old with a knee injury that can result in PTOA\(^{161}\).

1.3. Cartilage Injury

1.3.1 Surgical Injury

Articular cartilage in human joints can withstand normal mechanical loads that cause peak contact stresses as high as 15-20MPa \textit{in vivo} without injury\(^{162}\). However non-physiological loads are associated with chondrocyte death and cartilage degeneration. Buckwalter et al.\(^{159}\) suggested that the rate of loading affects the amount of articular damage. When loading occurs more quickly than fluid can move through the matrix, the macromolecular framework sustains a greater impact and chondrocytes are exposed to higher levels of mechanical stress. If the force exceeds the ability of the
cartilage to distribute the load, the matrix may rupture and the chondrocytes
die\textsuperscript{(163)}. Experimental injury to cartilage is associated with a zone of
chondrocyte death and extracellular matrix degradation at the wounded
site\textsuperscript{(71, 72, 75)}. Chondrocyte viability is poor at the injured interface and lateral
integration often occurs by fibrocartilage formation\textsuperscript{(46, 74- 76, 82)}. A major
limitation to successful articular reconstruction is the paradoxical mechanical
injury to healthy cartilage from instruments and implants during the surgical
procedure, unintentional iatrogenic injury\textsuperscript{(75, 78, 164)}.\textsuperscript{1}

Sharp iatrogenic injury\textsuperscript{2} to cartilage by trephine, scalpel, osteotome
and suturing has been studied in a number of situations\textsuperscript{(67, 71- 73, 75)}. Hunziker
et al.\textsuperscript{(73)} showed localised cell death from suturing cartilage in goats that
progressed with a similar appearance to early osteoarthritis three weeks
later. Tew et al.\textsuperscript{(71)}, Houston et al.\textsuperscript{(46)} and Amin et al.\textsuperscript{(67)} all used bovine
cartilage to show chondrocyte death after sharp injury of trephine, screws
and scalpel respectively. Huntley et al.\textsuperscript{(75)} showed similar cartilage injury with
chondrocyte death in human cartilage \textit{ex vivo} when performing mosaicplasty
for cartilage defects with a circular osteotome.

Thermal injury by drilling\textsuperscript{(46, 165)} and chemical injury with local
anaesthetic\textsuperscript{(89, 166-173)} have been shown to decrease chondrocyte viability \textit{in vitro} and \textit{in vivo}. Nole et al.\textsuperscript{(172)} were the first to show bupivacaine (a local
anaesthetic drug) chondrotoxicity in the pig and dog model in 1985. They
reported inhibition of cartilage synthesis with increasing concentrations of
bupivacaine. Dogan et al.\textsuperscript{(174)} showed significant histopathology changes in
the rabbit knee joints injected with bupivacaine with neostigmine. Chu et
al.\textsuperscript{(170)} measured chondrocyte viability with confocal laser scanning
microscopy (CLSM), showing 99% cell death with bupivacaine versus 20% in
controls. Gomoll et al.\textsuperscript{(173)} used rabbit shoulders with the addition of
bupivacaine with epinephrine. Piper et al.\textsuperscript{(166)} showed in bovine cartilage,
bupivacaine produced greater chondrocyte death if combined with thermal

\textsuperscript{1}Iatrogenic injury is defined as caused by medical or surgical treatment.

\textsuperscript{2}Sharp injury is defined as caused by an object that has a thin edge or point that
is able to cut or pierce something. Blunt injury is defined as caused by a
mechanical force that does not penetrate the object.
stress for example in knee arthroscopy. Later Piper et al.\textsuperscript{(167)} showed that 30-minute exposure to 0.5% bupivacaine significantly reduced chondrocyte viability in human articular chondrocytes retrieved after hip and knee arthroplasty\textsuperscript{(167)}.

Blunt trauma e.g. impact loading, may cause chondrocyte death directly with no sharp injury\textsuperscript{(83, 99, 100, 104)}. Based on \textit{in vitro} and \textit{in vivo} experimental studies of the effects of impact loading of articular surfaces, it is reasonable to assume that more intense acute impact loading of articular surfaces causes more extensive chondrocyte death and matrix damage at the time of injury\textsuperscript{(100, 175)}. This study aimed to investigate the two ends of the spectrum, of clinically relevant trauma, the arthroscopic probe and intra-articular fracture (Figure 1.1).

![Image of various tools and surgical procedures]

\textbf{Figure 1.1:} Spectrum of clinically relevant trauma to articular cartilage. A graded approach to the trauma experienced by cartilage in a clinical setting, showing increasing cell death with increasing intensity of trauma.
1.3.2 Evaluating Cartilage Injury

Accurate evaluation of cell death in chondrocytes is essential to studying cartilage injury. Several methods are used in studies including TUNEL, identifying cell death through DNA fragmentation, DNA denaturation analysis using antibody specific for single stranded DNA, immunohistochemistry using caspases, critical enzymatic mediators of programmed cell death and oligonucleotide ligation detecting DNA fragmentation. The results however can lack consistency due to the lack of classic apoptotic features in chondrocytes\(^{178}\). An method for evaluating chondrocyte death in situ (chondrocytes embedded in their native extracellular matrix) has been employed using a two-fluorophore viability assay with CLSM\(^{67, 75, 80, 179}\). This method does not attempt to identify the mechanism of cell death, just that cell death occurred.

1.3.2.1 Confocal Laser Scanning Microscopy

CLSM allows quick, direct and non-invasive imaging of intact, thick living biological specimens with minimal sample preparation and eliminating artefacts that occur during physical sectioning\(^{180, 181}\). This technique was used to allow the chondrocytes to be imaged in situ, embedded within their native extracellular matrix.

CLSM is a technique for obtaining high-resolution optical images from selected depths in a process called optical sectioning. Confocal microscopy was patented in 1957 by Martin Minsky and progressed with the development of lasers and 3D detection of biological objects labelled with fluorescent markers at the end of the 1980s in Amsterdam. The principle involves:

1) a laser/point light source
2) a deflection system for scanning
3) a lens system consisting of
   1. objective lens
   2. object stage
   3. spatial filter (pinhole or slit)
   4. detector
4) electronic control and image processing system

The laser beam is focussed within the specimen by the deflection system and the scattered, reflected and fluorescent light is recollected by the objective lens. A beam splitter can be used to separate selective wavelengths of light into detection apparatus, blocking the original excitation wavelength.

The light travels through the spatial filter, rejecting any out of focus light, to sharpen the image. This is in contrast to the technique of epifluorescence microscopy where the out of focus light from elsewhere in the specimen provides poorer quality, more time consuming imaging of specimens. The scanning portion comes from oscillating dichromatic mirrors that allow the beam to move across the sample in a horizontal plane. Assembling a stack of these 2-D images from successive focal planes can generate a 3-D picture.

The disadvantages of confocal microscopes are few but include the high cost of purchasing and operating the systems and the potentially harmful nature of the high intensity laser irradiation to the tissue\(^{(181)}\).

1.3.3 Modelling cartilage injury

1.3.3.1 Experimental models

Various models have been used to study cartilage injury as there is a rarity of appropriate human tissue\(^{(166)}\), the opportunity to inspect a joint after injury in
vivo does not occur often\(^{37}\) and it is difficult to assess chondrocyte viability \textit{in situ} in patients following articular fractures\(^{106}\).

Experimental models such as Meachim’s\(^{182}\) where surface injury is produced by direct scalpel laceration are used to look at the response of the cartilage. Caution must be used when extrapolating from \textit{in vitro} results to the \textit{in vivo} situation. \textit{In vitro} the bony and soft tissue stabilisers of the cartilage are removed and may lead to higher stresses and gradients of load in the vicinity of the injured area. \textit{In vivo}, where subchondral bone is attached to the cartilage, the load required to cause injury is greater than \textit{in vitro}\(^{183}, 184\). Progression of chondrocyte death after injury appears also to be affected by attachment to subchondral bone\(^{12}, 80, 99, 102, 185, 186\), with subchondral bone exerting a protective effect on the chondrocytes\(^{187}\). This may be due to reduced disruption or radial confinement of the ECM\(^{188}, 189\), the loss of matrix stability\(^{184}\) and, or, the swelling of the cartilage when detached from the subchondral bone\(^{100}\). Even the majority of current \textit{in vivo} models require opening the joint capsule to apply an injury directly to the cartilage. The physical disruption of the joint capsule is a potential confounding factor, inducing an inflammatory response that may initiate degradation processes\(^{104}, 109\). Caution must also be used when extrapolating from various animal models to human cartilage as the thickness and architecture of the joints vary greatly altering the impact tolerance\(^{76}\).

1.3.3.2 Animal models

A number of animal species have been used to model cartilage injury with the earlier models in dogs and horses. DePalma et al. showed cartilage healing in immature canine articular cartilage and the differences between partial and full thickness cartilage defects reparative potential in mature femoral condyles\(^{79}\). Convery et al. used defects in the large femoral condyles of horses to show variable degeneration in the opposing tibial condyles\(^{191}\). Canine humeral explants were also used by Chen et al. to
show the percentage cell death increased with duration of loading in vitro with no subchondral bone attached\(^{(183)}\).

Rabbit models have been used to look at injury to cartilage in vivo, for example, the early work of Radin et al.\(^{(12, 13)}\), in the 1970s found that impact trauma alone to the patellofemoral joint led to osteoarthritis in rabbit models. These focused on the relationship between fractures at the bone-cartilage interface and subsequent endochondral bone thickening and cartilage degradation. Leftkoe et al.\(^{(112)}\) showed no cartilage repair in step-off deformities in rabbits, with decreased proteoglycan content similar to early osteoarthritis. Newberry et al.\(^{(33)}\), showed cartilage matrix degradation occurred 3-12 months after a load was dropped on the knee of a mature rabbit. Lovasz et al.\(^{(113)}\) also used rabbit models to show instability had more effect than incongruity on development of PTOA. Costouros et al.\(^{(165)}\) compared chondrocyte death in vivo and in vitro following drilling of femoral condyles in rabbits. They showed chondrocyte death in both groups but statistically worse in vivo, attributing this to the pro apoptotic conditions of haemarthrosis, reactive oxygen species and inflammatory cells. The rabbit models provide a readily available source of cartilage with the ability to manage their environment post injury and then investigate the subsequent cartilage deterioration. A problem with the rabbit models is that often the cartilage is immature, i.e. there was a growth plate still present, altering the reparative potential.

Bovine cartilage has also been widely used to investigate cartilage injury since the mid 1990s. It is another readily available source of cartilage, producing reproducible responses after surgical wounding, indicative of early trauma in the joint\(^{(164)}\). It provides a model system to study the basic mechanisms behind cartilage repair, but unlike in vivo rabbit models, does not allow follow-up post injury as easily due to the environment needed to keep animals of this size. Jeffrey et al.\(^{(163)}\) observed an increase in chondrocyte death in bovine cartilage after impact loading using a drop tower. They reported the presence of underlying bone reduced cell death after an impact load on the cartilage. This suggests that the bone may
absorb some of the impact in vivo(12). However, the method of assessing cell death may underestimate viability as they isolated chondrocytes by collagenase digestion and some chondrocytes may have remained viable after injury but be too fragile to survive enzymatic digestion(104). Loening et al.(99) also showed injurious compression in bovine tissue, when radially unconfined by subchondral bone in vitro, caused degradation of the collagen fibril network at 7-12MPa. A much lower load of 4.5MPa can cause chondrocyte death and increases in a dose dependent manner with loads above 20MPa causing 50% cell death. The chondrocyte death occurred at lower loads than those that caused matrix degradation but could be driving later degradation, with cell death being one of the earliest responses to tissue injury(99). Torzilli et al.(179) studied the effects of impaction damage to bovine articular cartilage in vivo, showing stresses of 15-20 MPa caused matrix damage with a rupture of the collagen fibril network. By staining the cartilage in situ cell death was found to occur at a threshold around 17.5 MPa, suggesting, that damage to the cartilage occurs when a threshold in peak stress is reached during an injury. Tew et al. D’Lima et al. and Patwari et al. all used bovine models to look at cell death after injury using TUNEL, GAG levels and mRNA expression(71, 102, 104) respectively. Grogan et al. used CLSM, histology and TEM to study the response of bovine cartilage to injury(90). D’Lima et al.(83) later used loading platforms and drill holes to cause injury in bovine cartilage. They showed more cell death with drill holes than sharp injury possibly due to thermal effects. Lewis et al. used mature bovine models to study cell death after impact loading as a function of location and time, finding cell death at the edge of the impactor where the stress gradient was greatest but not at the centre of impact if no crack occurred(185). Bovine models have been used to look at surgical situations. Gilbert et al. used inhibitors of apoptosis and necrosis to try to increase the number of viable cells and integration of wound edges in cartilage repair surgery(184). Houston et al. used an ex vivo bovine model studying chondrocyte death in situ to determine whether metal screws were better than bioabsorbable screws in maintaining cell viability and showing 50% reduction in cell death after drilling
by irrigating with saline, to prevent thermal necrosis\(^{(46)}\).

The appropriate model for a study depends on the specific hypothesis. When trying to quantify the temporal sequence of joint degeneration as in Furman et al.’s study\(^{(109)}\), a readily available and easy to keep animal must be used, to allow injury and then sacrifice of the animals at 2, 4, 8 and 50 weeks post fracture: they chose mice. Their model allowed a closed articular fracture, not disrupting the joint capsule, for a more clinically relevant evaluation and radiographic and histological analysis of the joint. They showed progressive osteoarthritic-like changes as early as 8 weeks post fracture with little or no degeneration in the contralateral joint. A porcine model has also been used to create a closed joint model of impact loading to maintain the physiological environment with a drop tower on the whole intact joint\(^{(192)}\) and in comparing the pattern of cell death after blunt impact with fracture\(^{(189)}\). Stolberg et al.\(^{(189)}\) showed blunt impact resulted in uniform necrosis across the specimen. If however, the specimen fractured, focal necrosis was seen adjacent to the fracture sparing the other chondrocytes. Animal models aim to model the human situation as much as possible, therefore a large animal whole joint model that was easily obtainable, cheap and had viable cartilage was chosen for section 6.

1.3.3.3 Human models

The best tissue to use to investigate PTOA in humans is human cartilage. Sources of non-degenerate human cartilage are rare. The most readily available source is cartilage samples taken from patients undergoing joint replacements, however these samples are likely to have already undergone pathological arthritic changes necessitating the arthroplasty surgery\(^{(75, 193)}\). Small osteochondral fragments may be taken from the zone of injury in patients with intra-articular fractures undergoing surgery if they are not being used for the reconstruction\(^{(100, 105)}\). These fragments are relatively rare as ideally the articular surface is restored anatomically and the cartilage will vary in size and quality for use. Cartilage samples from patients undergoing limb
salvage procedures or amputations\(^{(178)}\) are more rare and may also have undergone pathological processes secondary to reduced weight-bearing or the reason for the operation, e.g. malignant disease. In the author’s opinion the most problematic tissue to source is from cadaveric donors, due to the ethics surrounding donation. If samples are taken from cadaveric donors the cartilage must be taken close to the time of death to prevent changes in the cartilage properties\(^{(61, 83, 85, 102, 106, 194)}\).

The first human cartilage model, that the author is aware of, was reported by Repo et al. in 1977\(^{(85)}\). They studied the response of human articular cartilage from the tibial plateau, less than 12 hours after death in eight renal transplant donors, looking at impact tolerance to blunt trauma from a drop tower. They showed using light and scanning microscopy that human cartilage could withstand impact loads as high as 25 MPa (25 N/mm\(^2\)) without apparent cell damage. Impact loads exceeding this level caused chondrocyte death. D’Lima et al. published three studies of human cartilage in 2001\(^{(83, 102, 194)}\). They used femoral, tibial, patellar and talar dome articular cartilage, harvested within 72 hours of death from fresh donor cadavers without visible evidence of arthritis or degeneration. They looked at temporal death between 48 and 96 hours in a time course study to suggest a potential for therapeutic modulation during this window\(^{(102)}\). They also showed using electron microscopy, TUNEL and GAG, a reduction of cell death in human cartilage like bovine cartilage, using caspase inhibition\(^{(194)}\). McKinley et al.\(^{(61)}\) used cadaveric tissue in a different type of model looking at fresh frozen ankles with normal motion and no radiographic abnormalities. The soft tissue was removed and the joints were potted in cement blocks, attempting to recreate physiological loading with axial and anterior posterior load to study dynamic contact stresses. Kim et al.\(^{(100)}\) and Hembree et al.\(^{(109)}\) used osteochondral fragments from traumatic joint injuries that could not be used for articular reconstruction. Kim et al. took 15 fracture specimens and controls from limb amputation and salvage surgery, to show higher chondrocyte death in intra-articular fractures\(^{(100)}\). Hembree et al. compared the fracture fragments with cadaveric controls showing significantly increased

\(\text{impact tolerance to blunt trauma from a drop tower. They showed using light and scanning microscopy that human cartilage could withstand impact loads as high as 25 MPa (25 N/mm}^2\text{)}\) without apparent cell damage. Impact loads exceeding this level caused chondrocyte death. D’Lima et al. published three studies of human cartilage in 2001\(^{(83, 102, 194)}\). They used femoral, tibial, patellar and talar dome articular cartilage, harvested within 72 hours of death from fresh donor cadavers without visible evidence of arthritis or degeneration. They looked at temporal death between 48 and 96 hours in a time course study to suggest a potential for therapeutic modulation during this window\(^{(102)}\). They also showed using electron microscopy, TUNEL and GAG, a reduction of cell death in human cartilage like bovine cartilage, using caspase inhibition\(^{(194)}\). McKinley et al.\(^{(61)}\) used cadaveric tissue in a different type of model looking at fresh frozen ankles with normal motion and no radiographic abnormalities. The soft tissue was removed and the joints were potted in cement blocks, attempting to recreate physiological loading with axial and anterior posterior load to study dynamic contact stresses. Kim et al.\(^{(100)}\) and Hembree et al.\(^{(109)}\) used osteochondral fragments from traumatic joint injuries that could not be used for articular reconstruction. Kim et al. took 15 fracture specimens and controls from limb amputation and salvage surgery, to show higher chondrocyte death in intra-articular fractures\(^{(100)}\). Hembree et al. compared the fracture fragments with cadaveric controls showing significantly increased
cell death along the edge of the fracture and in the superficial zone of the fragments using TUNEL and CLSM\(^{109}\). They showed a general decrease in chondrocyte viability in the injured cartilage regardless of its spatial location compared to the fracture. They saw no correlation between time of injury and cell viability using confocal techniques but TUNEL data demonstrated a small peak in cell death 24-48 hours after the injury\(^{100}\). Amin et al.\(^{67}\) looked at sharp injury rather than fracture, using human articular cartilage from patients undergoing total knee replacement (TKR) and showed no further increase in cell death 2.5 hours to 7 days after sample taken, extending the group’s findings from animals to human models. The same group in 2011\(^{193}\) using the human cartilage model looked reducing cell death following sharp injury to cartilage with hyperosmolar solution. The only whole organ model that the author is aware of is from Tochigi et al.\(^{106}\) who used seven human ankles harvested less than four hours after amputation secondary to malignant tumours near the knee. The ankle was subjected to compressive impaction and osteoarticular fragments were sampled with subchondral bone. Percentage chondrocyte death was assessed using CLSM at various time points and from samples taken near and away from the fracture edges. This whole organ model with intact joint capsule was used to closely replicate the physiological conditions of in vivo human intra-articular fracture. Using post amputation tissue means the ankle joints could have been non weight-bearing prior to surgery and the patients may have undergone neoadjuvant chemotherapy potentially altering the biomechanical properties of the cartilage and therefore making the results less clinically relevant\(^{106}\).

The human model used in this study (Section 7) was a cadaveric donor whole joint, to try to replicate the in vivo situation as much as possible.

### 1.3.4 Management of PTOA

Outcomes of PTOA vary in different joints, however current intra-articular fracture fixation techniques have not been able to reduce PTOA completely. Cartilage injury appears to be the next important process on which to focus
our research, hoping to target treatments to prevent the development of PTOA. Cartilage damage in intra-articular fractures appears to be closely associated with chondrocyte death as seen in blunt impact studies[32, 71, 72]. Chondrocyte death has been shown in a bovine model to occur in two phases[80]. Bush et al. showed initial focal cell death due to mechanical stresses from the fracture, occurred in the first two and a half minutes causing approximately 20% cell death. In the second phase occurring between two and a half minutes and 20 minutes, chondrocyte death propagated in time and space, causing approximately 25% more cell death possibly due to delayed cell death[80]. Whilst clinically preventing the first phase would be difficult other than avoiding the injury altogether, there may be a window of time during which the secondary phase could be prevented. A biological treatment to inhibit or reduce cell death, chondroprotection could be utilised during this window. Furman et al.[194] inhibited the proinflammatory cytokine interleukin-1 locally with an intra-articular injection in mice, immediately after tibial plateau fracture and saw a reduction in cartilage damage with no adverse affects on bone healing or bone morphology. Combining timely, accurate reduction and fixation of the intra-articular fractures with preservation of the chondrocytes may decrease the risk of PTOA after injury[46, 106, 109].

1.3.5 Chondroprotection

Chondroprotection is a term used to describe protection of chondrocytes against injury. Clinically chondroprotection has been used to describe substances including pharmaceutical agents e.g. Tumour Necrosis Factor alpha blocking agents[106] and additives e.g. glucosamine sulphate (GS) and chondroitin sulphate (CS) that may protect the chondrocytes during the course of osteoarthritis. The combination of GS and CS been studied extensively but the evidence is still inconclusive. Two recent large level one evidence trials have produced opposing conclusions as to the efficacy of combination therapy in knee osteoarthritis[197, 198]. Surgical techniques that
attempt to create cartilage healing or prevent further damage are also termed chondroprotective, e.g. microfracture(78).

In basic science and cell biology studies the term chondroprotection is used to describe an intervention that protects chondrocytes against an insult. The literature relating to this type of chondroprotection is sparse with only a few methods of reducing chondrocyte death after injury described. These include reducing exposure of the cartilage to extracellular calcium in a sharp injury bovine model was shown to reduce cell death compared to a high calcium environment in the acute phase (within hours)(199). Keeping cartilage hydrated has been shown to reduce chondrocyte death by a study showing that the drying effects of laminar airflow cause extensive cell death in an in vivo rat model(200). The use of caspase inhibitors has become more popular to try to prevent chondrocyte death. Caspases are a family of enzymes critical to pathways leading to cell death(87, 201, 202). Selective inhibitors have been used to reduce human chondrocyte death in vitro maintaining viable cells(201) and to reduce cartilage degeneration in a rabbit model of osteoarthritis(202). Another method in the literature is increasing osmotic pressure to reduce chondrocyte death after sharp trauma in bovine and human cartilage models e.g. hyperosmolar irrigation fluid(189, 203, 204).

The chondroprotection investigated in this study relates to osmolarity of irrigation fluid and will be discussed further in Section 6. If a higher osmotic pressure can protect chondrocytes from blunt injury as well as sharp injury then changing the irrigation fluid for arthroscopic procedures could be a simple, cheap and applicable method of chondroprotection.
Aims, research questions and hypotheses:

Six studies were performed to address the epidemiology and clinical outcomes of tibial plateau and patellar fractures and the nature of chondrocyte death after blunt trauma in a bovine model and a human model.

Tibial Plateau Fracture Epidemiology. (Section 2)

Aim: To define the number of tibial plateau fractures with corresponding patient factors, mechanisms and management in a large well defined population over 25 years.

Research Questions:
- a) What is the incidence of tibial plateau fractures in the general population?
- b) Who gets tibial plateau fractures and how?

Outcomes of tibial plateau fractures. (Section 3)

Aim: To investigate the patient reported outcomes from tibial plateau fractures.

Research Questions:
- a) What factors predispose these patients to complications, specifically post-traumatic osteoarthritis?
- b) How many patients require late salvage arthroplasty?
- c) How are patients with tibial plateau fractures affected in the long-term?
Epidemiology of patellar fractures. (Section 4)

Aim: To define the numbers of operatively-managed patellar fractures with corresponding patient factors, mechanisms and management in a large well-defined population over 15 years.

Research Questions:

a) What is the incidence of patellar fractures requiring operative management in the general population?

b) How do these fractures occur and to whom?

Outcomes of operatively-managed patellar fractures. (Section 5)

Aim: To investigate the complications, surgical interventions and patient reported outcomes following patellar fractures.

Research Questions:

a) What factors predispose patients to complications and post-traumatic osteoarthritis?

b) How many patients require late salvage arthroplasty surgery?

c) How does having an operatively-managed patellar fracture affect patients in the long-term?

Chondrocyte death following blunt trauma, a bovine model. (Section 6)

Aim: To study the response of chondrocytes to blunt trauma in the form of iatrogenic arthroscopic probe pressure and high energy impact and to investigate the influence of the irrigation fluid on cell death.
Research Questions:

a) What is the affect of blunt trauma on cartilage?
b) Is raising the osmolarity of the irrigation fluid prior to impact chondroprotective?

Hypothesis:
Increasing the osmolarity of the irrigation fluid is chondroprotective.

Transferability of the bovine model to human tissue. (Section 7)

Aim: To study the response of chondrocytes from human fresh cadaveric knee joints to blunt trauma and compare this to the bovine model.

Research Questions:

a) Is human tissue affected by blunt trauma in the same manner as bovine cartilage?
b) Is raising the osmolarity of the irrigation fluid prior to impact chondroprotective in human tissue?

Hypothesis:
Human cartilage behaves in a similar manner to bovine cartilage after blunt trauma and chondroprotection occurs with hyperosmolar irrigation solution.

Thesis Hypothesis

Cartilage injury due to intra-articular trauma to the knee is important in the development of post-traumatic osteoarthritis and this therefore affects the long-term outcomes of tibial plateau and patellar fractures.
General Statistical Overview

Parametric and non-parametric statistical methods were used as required, with the assistance of GraphPad Prism Version 7 and SPSS software package version 21. A difference was taken as significant when the $p$ value reached 0.05 or less. The specific tests employed for each analysis are detailed in each chapter.
Section 2 - Tibial Plateau Fracture

Epidemiology

Aim: To define the number of tibial plateau fractures with corresponding patient factors, mechanisms and management in a large well defined population over 25 years.

Research Questions:

a) What is the incidence of tibial plateau fractures in the general population?

b) Who gets tibial plateau fractures and how?

2.1 Introduction

Tibial plateau fractures are common intra-articular fractures, estimated at 13.3/100,000 in the adult UK population\(^1\). This estimate was taken from a paper looking at all fractures in a fixed population over one year only and included all proximal tibial fractures not just intra-articular tibial plateau fractures. The management of these fractures is controversial and prognosis is generally considered poor\(^{205, 206, 207}\). The largest series in the literature was from the 1970s with fewer than 300 patients until 2015 when a paper with 355 patients was published\(^{208}\). The numbers reported were small and in the majority used historic management protocols (Appendix 1\(^3\)). The present study aimed to up date the literature using modern management techniques

\(^3\)Appendix 1 – Tibial Plateau Epidemiology and Outcome Literature. Blank cells represent when data could not be extracted from the corresponding study.
of these complex fractures in the largest non-registry series to date. The study looks at the changing epidemiology over 25 years, the effects of social deprivation, the mechanism and patterns of injury and the management of these fractures, to allow a greater understanding of these fractures and to improve clinical management.

2.2 Methods

A large prospective database was compiled of all patients who sustained tibial plateau fractures over a 25-year period (January 1988-January 2013). This database was compiled from six prospectively recorded databases (Table 2.1) from our institution, for any acute presentations of tibial plateau fractures and the data were retrospectively reviewed. The databases overlapped and all duplicated records were removed. The databases included all tibial plateau fractures managed in inpatient and outpatient departments. All available notes and radiographs were reviewed to confirm a tibial plateau fracture. Soft tissue injuries and other diagnoses were excluded. Demographic details, occupation, medical history and injury details including, side, mechanism, whether the fracture was open, fracture classification, associated injuries and management were collected. The fracture pattern was classified using the Schatzker classification\(^{(209)}\), a widely used classification for tibial plateau fractures (Figure 2.1). The patient’s address at time of injury was used to calculate the Scottish Index of Multiple Deprivation economic quintile, using 2011 data\(^{(210)}\). The first quintile represents the most deprived and the fifth the least deprived on a national level.

<table>
<thead>
<tr>
<th>Year</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1995</td>
<td>336</td>
</tr>
<tr>
<td>1988-2004</td>
<td>1338</td>
</tr>
<tr>
<td>1995-2011</td>
<td>1264</td>
</tr>
<tr>
<td>1996-2002</td>
<td>64</td>
</tr>
<tr>
<td>2000</td>
<td>72</td>
</tr>
<tr>
<td>2010-2011</td>
<td>61</td>
</tr>
</tbody>
</table>

Table 2.1: Prospective tibial plateau databases from our institution.
Figure 2.1: Schatzker classification of tibial plateau fractures. Image modified from Schatzker et al. 1979(209).

All inpatients and outpatients from City of Edinburgh, Mid or East Lothian were included, as the population in these regions is clearly defined. All adults were treated at The Royal Infirmary of Edinburgh as it is the only orthopaedic trauma service for this defined population. Children, under the age of 12 years, who were treated at the local paediatric hospital, were excluded from analysis. The local adult population based on a national census(3) during the study period was 517,555 (Census 2001). This study was classed as an audit by local guidelines and therefore did not require formal ethical approval.

Statistical analysis was performed using SPSS Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.1.0. Continuous data were presented as mean and standard deviation (St Dev). Categorical data were presented as frequencies and percentages. Incidence was presented as fractures/100,000/year. The Spearman’s correlation coefficient was used to assess correlation between non-parametric ranked
data, fracture incidence each year over the time period, age-adjusted incidence and age groups, operative management each year over the study period and age and mechanism of injury (MOI). Fisher’s exact test was used for comparing management in the two time periods and open injuries with fracture classification. An independent t test for unpaired data was performed to compare age at time of fracture in males and females. The categorical nominal outcome variable of mechanism of injury was compared for two time periods, gender, open or closed injury, age groups and transverse or comminuted fractures (categorical predictor variables) using Pearson’s chi-square test. This was also used to compare fracture classification with gender, management and MOI. Multinomial logistic regression was used to compare the associations between age, gender and mechanism of injury to find the stronger predictor for injury mechanism. The Pearson’s chi square test was also used to compare the observed and expected frequencies of tibial plateau fracture in the deprivation quintiles. A p value of <0.05 was considered to be statistically significant.

2.3 Results

There were 1423 patients in the study cohort with a mean age at injury of 55.94 years (range, 13-99 years) and 57% were female. Falls caused over half the fractures (740, 52%) and RTAs accounted for a further 26% (370). Open injuries were seen in 6 cases (0.4%). Approximately half the fractures (726, 51%) were left sided and 58% (825) were managed operatively using a variety of techniques.

2.3.1 Annual Incidence

The overall incidence of tibial plateau fractures was 11 per 100,000 population, 57 fractures a year seen in the study population. This showed a statistically significant increase over time from 6.69/100,000/year (1988-2002) to 12.71/100,000/year (2008-2012) (Spearman’s correlation coefficient
0.564  p=0.0034) (Figure 2.2), with the incidence appearing to plateau after 2003. A higher proportion of tibial plateau fractures were treated operatively by the end of the study period 42 to 63% (Figure 2.3). Comparing the operative percentage each year also revealed a statistically significant rise from 1988 to 2013 (Spearman’s Correlation Coefficient = 0.5720  p=0.0028).

Figure 2.2: Changing incidence of tibial plateau fractures, showing the yearly incidence during the study period between 1988 and 2013.

Figure 2.3: The proportion of tibial plateau fractures managed operatively over the study period.
2.3.2 Age – Adjusted Incidence

Age was normally distributed when tested for skewness and kurtosis using SPSS. The age-adjusted incidence increased with increasing age and was statistically significant (Spearman’s Correlation Coefficient = 0.9833 p<0.0001) (Figure 2.4). The average age of plateau fractures decreased over the twenty-five years from 59 to 54 years old (Spearman’s Correlation Coefficient = -0.4938 p=0.0121) (Figure 2.5).

![Age-Adjusted Incidence of Tibial Plateau Fractures](image1)

Figure 2.4: Age-adjusted incidence of tibial plateau fractures

![Mean Age at Time of Injury Over Time](image2)

Figure 2.5: Mean age at injury over the study period.
2.3.3 Mechanism of Injury

In the first five years of the study, RTA accounted for 43% of tibial plateau fractures, with sports causing only 1%. Twenty years later RTA accounted for only 17% and sports 16%. Falls accounted for 52% of all tibial plateau fractures; 45% in the first five years increasing to 60% twenty years later. The rate of fall from standing height (FFS) stayed at about 30% with the rise due to falls from height (FFH) increasing from 10% to 30% (Figure 2.6). The mechanism of injury (MOI) has changed significantly over time ($p<0.0001$). RTA was classified further by type of RTA, the patient being injured as the pedestrian (62%), on a motorbike (17%), as the driver of a motor vehicle (8%), whilst cycling (4%), as the passenger on a motor vehicle (4%) and in an unknown RTA (5%).

**Changing Mechanism of Injury over Time**

![Figure 2.6: Changing mechanism over study period. Mechanisms classified as road traffic accident (RTA), sport, fall from standing (FFS), fall from height (FFH) and other.](image)

The mechanism of injury, using Pearson’s chi square test, also changed with age ($p<0.0001$). FFS increase as age increased, FFH remain around 20% with no significant difference over time. The percentage of tibial plateau fractures...
fractures caused by RTA decreased with age but did not reach statistical significance. Sports significantly decreased with age (Table 2.2).

<table>
<thead>
<tr>
<th>Age</th>
<th>Total Fractures over 25 years</th>
<th>RTA (%)</th>
<th>Sport (%)</th>
<th>FFS (%)</th>
<th>FFH (%)</th>
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</tr>
<tr>
<td>90-99</td>
<td>38</td>
<td>13</td>
<td>0</td>
<td>63</td>
<td>8</td>
</tr>
</tbody>
</table>

Table 2.2: Mechanism of injury varies with age at time of injury. Mechanisms include road traffic accident (RTA), sport, fall from standing (FFS) and fall from height (FFH).

2.3.4 Gender

Tibial plateau fractures are more common in young men. Under 50 years old the ratio male to female was 7:3 changing to a ratio of 2:8 male to female over 50 years old. Affected women were statistically older than affected men (p<0.001). Approximately half (53%) of the female patients (average age 64) were treated operatively compared to 64% of the male patients (average age 45). The average age of patients treated operatively was 10 years younger than those treated non-operatively (52 and 62 years respectively). There are statistically significant differences between the mechanisms suffered by men and women (p=0.0004) Women and men suffer tibial plateau fractures from FFH at similar frequencies (20%) but men sustain tibial plateau fractures after sport (18%) and RTAs (34%) more commonly than women (7% and 21% respectively). FFS are the cause of 43% tibial plateau fractures in women compared to only 18% in men. Due to the association between gender and age, multinomial logistic regression was performed showing that age is the main predictor of mechanism of injury rather than gender. (Age chi square 486.996 p<0.0001 compared to gender chi square 34.005 p<0.0001).
2.3.5 Fracture Classification

The fracture pattern classification was unknown in 10% and those under 15 years old were discounted from this classification, as they had skeletally immature patterns (Salter Harris Classification). A quarter of the fractures were Schatzker II (split depression) and Schatzker V and VI made up 7% and 8% respectively (Figure 2.7). There was no significant difference in Schatzker classification in males and females using Pearson’s chi square test ($p=0.757$) (Figure 2.8).

![Fracture Pattern by Schatzker Classification](image)

**Figure 2.7:** Fracture classification using the Schatzker classification (100).

![Tibial Plateau Fracture Classification by Gender from 1988-2013](image)

**Figure 2.8:** Fracture classification and gender.

The fracture classification corresponded to management with 83% Schatzker II, V and VI managed operatively and only 43% of Schatzker I, III and IV
(p<0.0001) (Figure 2.9). Fracture classification was also associated with MOI (p=0.0007). Schatzker I and II fractures were seen following sporting injuries, III and IV after FFS and V and VI fractures after high energy mechanisms like FFH and RTA (Figure 2.10).

The percentage of fractures each year, classified into the Schatzker groups I-VI varied, with I, II, V and VI staying constant, III decreasing and IV...
increasing (Figure 2.11). Medial plateau fractures showed a trend to increase whereas, when, Schatzker I, II and III were combined to lateral plateau fractures and V and VI combined as complex bicondylar fractures the trends remained level (Figure 2.12). There was no statistical association between Schatzker score and year of injury ($p=0.537$).

**Schatzker Classification of Tibial Plateau Fractures between 1988 and 2012**

![Graph showing the distribution of Schatzker classifications from 1988 to 2012](image)

*Figure 2.11: Tibial plateau fracture Schatzker classification over the study period.*

**Fracture Pattern between 1988 and 2012**

![Graph showing the distribution of fracture patterns from 1988 to 2012](image)

*Figure 2.12: Tibial plateau fracture patterns over study period*
2.3.6 Open Injuries

Open injuries were seen in six (0.4%) of tibial plateau fractures. The mechanism of injury was associated with open fracture ($p<0.0001$) with 50% (3) of the open injuries seen in RTA, 33% (2) in sports and 17% (1) in FFH. The average age was significantly lower ($p=0.0071$) at 32.5 years old compared to the total study group. Two thirds were male and 83% were operatively-managed.

2.3.7 Deprivation Index

The Scottish Index of Multiple Deprivation (SIMD) suggests tibial plateau fractures occur more in the most deprived and the fourth quintile. Figure 2.13 shows the proportion of the Edinburgh population in each quintile. When the observed data were compared with the expected number of tibial plateau fractures in each group using the chi square test there was a statistically significant difference ($p<0.0001$) with the least deprived least likely to sustain tibial plateau fractures (Table 2.3).

Figure 2.13: Population of hospital catchment area by deprivation quintile according to the Scottish Index of Multiple Deprivation (SIMD). Reproduced from Duckworth et al. (621)
<table>
<thead>
<tr>
<th>SIMD</th>
<th>Edinburgh Population</th>
<th>Expected Number of Fractures</th>
<th>Observed Number of Fractures</th>
<th>Tibial Plateau Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (most deprived)</td>
<td>11%</td>
<td>156</td>
<td>397</td>
<td>28%</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
<td>227</td>
<td>195</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>17%</td>
<td>241</td>
<td>299</td>
<td>21%</td>
</tr>
<tr>
<td>4</td>
<td>19%</td>
<td>269</td>
<td>396</td>
<td>26%</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>37%</td>
<td>525</td>
<td>161</td>
<td>11%</td>
</tr>
</tbody>
</table>

2.3: Tibial plateau fractures in each deprivation quintile.

2.3.8 Summary of Significant Findings

Tibial plateau fractures were seen in 1423 patients over twenty-five years (11/100,000/year incidence). The mean age was 55.94 years old (range 13-99) and 57% were female. Over half (58%) the fractures were managed operatively and only 0.4% were open injuries. Falls accounted for half the fractures (52%) and RTA for a further 26%.

The annual incidence increased over the 25-year study period, with increased age-adjusted incidence seen in the elderly. The mean age of tibial plateau fractures decreased over the study period and proportionally more were operatively-managed by 2013. Tibial plateau fractures secondary to sports and FFH increased whilst those secondary to RTA decreased. FFS were more likely if older, occurring in women. Tibial plateau fractures occurred a higher incidence in younger men until 50 years of age then older women peaking at 38.5/100,000/year when women reached their eighties (Figure 2.14).
Gender and Age-Adjusted Incidence of Tibial Plateau Fractures

![Graph showing gender and age-adjusted incidence of tibial plateau fractures]

Figure 2.14: Gender and age-adjusted incidence of tibial plateau fractures.

2.4 Discussion

To the author’s knowledge this is the largest cohort of tibial plateau fractures in the English language literature. It updates the literature for modern management of these complex fractures and forms the basis for the work on long-term outcomes (Section 3). The quoted incidence of 13.3/100,000\(^{(1)}\) in the adult population refers to all proximal tibial fractures including extraarticular ones; the current study investigated only intra-articular fractures and might explain the slightly lower incidence seen (Figure 2.2). Elsoe et al. (2015)\(^{(208)}\) also looked at population data for tibial plateau fractures with a six-year follow-up. They looked at a quarter of the number of patients, 355, with a slightly younger mean age of 52.6 years (current study 55.94). Similar gender distribution with 53% female compared to 57% in this study. The incidence was almost identical to our findings, 10.3/100,000/year compared to 11/100,000/year. Elsoe et al. (2015) used CT and the AO classification to classify the fracture patterns differing to the current study\(^{(208)}\). Elsoe et al. (2015) showed 35% were split depression fractures equivalent to Schatzker II where the current study only showed 25%. The mechanisms of
injury were not discussed in Elsoe’s paper; along with the differences in classification system and use of CT make comparisons difficult.

CT was only used in our institution for preoperative preparation and not routine for classification. The Schatzker classification was used in the current study rather than AO/OTA classification, as this has been the classification used by the institution for the prospective databases and could be confirmed by medical and operative notes. The AO/OTA classification has similarities to the Schatzker classification with AO B type fractures including Schatzker I, II, III and IV and C type fractures including V and VI. The reliability of classification systems has been questioned even when using CT. Classification systems are most useful if they determine management of the fractures. The Schatzker classification is easy to remember and widely used so can be useful for communicating fracture pattern with others. The AO/OTA classification is more complicated with additional subgroups and is useful for research purposes but does not guide treatment. From the data shown in this study the author does not feel that fracture pattern would provide a useful treatment algorithm and the treatment depends more on displacement and stability.

Over the 25-year study period the incidence of tibial plateau fractures increased and more of the fractures were operatively-managed (Figure 2.3). The increased incidence may be partly due to improved imaging resolution to identify more fractures. Increased fractures undergoing operative management is likely to be secondary to improved implant and techniques available and the awareness of poor outcomes affecting QOL in an aging population.

Over half of the fractures caused by RTA were in pedestrians, agreeing with early descriptions of tibial plateau fractures as fender or bumper fractures to pedestrians whose knee were at the correct height to be hit by a car bumper. RTAs may have reduced as a cause of tibial plateau fractures between 1988 and 2013 due to improved road safety and improved car manufacturing, however sports and falls from height appear to be increasing over this time (Figure 2.6). The reasons for this were less
clear and may be explained by the increased activity levels of an aging population. FFS affecting predominantly elderly women and sports causing tibial plateau fractures in young men was similar to the cause of other injuries\(^{215, 216, 217}\).

Split depression fracture patterns (Schatzker II) made up a quarter of the fractures in this population, and together with the higher energy, complex fractures (Schatzker V and VI) made up the majority of the operatively-managed patients. These fractures were less amenable to conservative management due to displacement and loss of coronal-plane stability. Segel et al. (1993) however, showed the outcomes of Schatzker type III were significantly better if treated operatively\(^{218}\) but in the current study only half (52\%) were treated operatively compared to over three quarters of type II (84\%), V (78\%) and VI (88\%). The age of the patients treated surgically was ten years younger than conservatively managed cases and this was likely to be due to a number of reasons including medical comorbidities and functional level of the older patients. The number of similar but fundamentally different classifications and nomenclature used in the published literature could lead to confusion and difficulty comparing studies. Mikkelsen et al. (1933)\(^{219}\) described 18 types of fracture involving the proximal articular surface of the tibia, Barr et al. (1940)\(^{41}\) used the amount of displacement and then the 3 main types of fracture described in multiple studies\(^{20, 26, 38, 123, 220, 221}\). The problems with classifications for tibial plateau fractures are shown in table 2.4 where the fracture classification patterns were different in three large studies of operatively managed fractures, including the current study. The current study’s institution operated on more pure depression and medial fractures.
Table 2.4: Percentage of operatively managed tibial plateau fractures in each Schatzker classification (206).

<table>
<thead>
<tr>
<th>Schatzker</th>
<th>Current Study (%)</th>
<th>Van Dreumel (%)</th>
<th>Timmers (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>11</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>II</td>
<td>37</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>III</td>
<td>13</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>IV</td>
<td>16</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>V</td>
<td>10</td>
<td>18</td>
<td>23</td>
</tr>
<tr>
<td>VI</td>
<td>13</td>
<td>24</td>
<td>10</td>
</tr>
</tbody>
</table>

Open injuries were seen in higher energy injuries sustained by RTA and FFH in younger men, which combined the findings seen in the study. Interestingly the deprivation results suggested being in the least deprived quintile was associated with the least risk of tibial plateau fractures. The reason for this maybe the education, improved safety aspects of the cars, sporting equipment and activities that money can buy.

The current study presented the largest prospectively collected cohort of tibial plateau fractures in the English language literature, showing an intra-articular tibial plateau fracture incidence of 11/100,000/year. The study showed not only the demographic data of the patients but the deprivation index, MOI, fracture classification and management of these fractures over a 25-year period.

2.4.1 Limitations

The main limitations of the study were the retrospective review of the prospectively collected data. To improve an epidemiological study the data would need to be prospectively reviewed over the same length of time that would be clinically difficult due to the changing personnel and the time commitment of staff. The missing data points were a limitation of the retrospective review particularly regarding 10% of the fracture pattern classifications, again secondary to the retrospective nature of the review. The use of the Schatzker classification rather than AO-OTA was to reduce...
missing data points but restricted analysis and comparison with other published work. For further work on this a prospectively collected and reviewed database has been set up to look at the next 25 years of tibial plateau fractures using the AO/OTA classification.

2.4.2 Conclusions

The incidence of tibial plateau fractures was 11/100,000/year and occurred in elderly women secondary to falls from standing and in young men due to road traffic accidents and falls from height. Higher energy injuries leading to complex fractures (Schatzker V and VI) were more likely to be managed operatively and both the incidence and the proportion treated operatively increased over time.
Section 3  - Outcomes of Tibial Plateau Fractures

Aim: To investigate the patient reported outcomes from tibial plateau fractures.

Research Questions:

a) What factors predispose these patients to complications, specifically post-traumatic osteoarthritis?

b) How many patients require late salvage knee arthroplasty?

c) How are patients with tibial plateau fractures affected in the long-term?

3.1 Introduction

Tibial plateau are intra-articular fractures of the knee and are therefore at risk of PTOA\(^{10-13}\). The published rates of PTOA vary depending on the method of diagnosis, whether clinical versus radiological. One particular difficulty in assessing outcomes is that radiological results and clinical results are not always comparable with radiographic criteria leading to higher levels of PTOA being reported\(^{10}\). A surprisingly wide range of estimates, of between 13-83% PTOA, have been proposed\(^{15,16,18,59,60,153,222,223,224,225,226,227}\) using either radiological or clinical criteria or both, confirming the difficulty in considering PTOA to be a dichotomous variable.

Fracture reduction has been shown to correlate with functional outcome\(^228,229,230\) but it was difficult to analyse the impact of injury severity and articular surface reduction separately\(^128,226\). Previous literature had used 2-10mm depression\(^25,28,40,135,138,209,226,231,232,233,234\) and less than 5 degrees angulation\(^28,209,231,235,236\) to be the important determinants of outcome, however good results have been shown after nonanatomical...
reduction\textsuperscript{69, 123} and several studies have shown arthritic changes do not necessarily correspond with functional deficit and therefore outcomes\textsuperscript{42, 237, 238, 239}.

The majority of studies published on functional outcomes have small patient numbers, less than 200, and showed acceptable results in the majority of patients\textsuperscript{228, 229, 230, 238, 240, 241, 242, 243}. Worsening results were seen with more severe fracture patterns\textsuperscript{229, 236, 242}. Functional outcomes also decreased with age\textsuperscript{9, 229} and so pre-injury function may be predictive of clinical outcome in the elderly\textsuperscript{230}. Operative management for the elderly was controversial with some studies showing benefit for the elderly (>65 years old)\textsuperscript{238, 241, 244} and others showing improved function in non-operative management due to the deleterious effects of complications seen in operative group\textsuperscript{229, 238, 240, 245}.

The first study reporting outcomes of TKR following intra-articular fractures of the knee was published in 1990\textsuperscript{246}. In that study, Roffi et al. investigated 13 patients, followed up for 27 months having undergone a TKR after developing PTOA due to fractures around the knee. However, only 7 of their cases were a consequence of tibial plateau fractures. The average time from injury to TKR in their series was 9 years\textsuperscript{246}. In 1999, Lonner et al.\textsuperscript{247} published the results from 31 patients who underwent TKR for PTOA, followed up for 46 months. In their series there was an average of 13 years between fracture and arthroplasty. Of that series, 18 (58\%) of their cases were performed due to fractures of the tibial plateau and were again salvage procedures for late osteoarthritis\textsuperscript{247}. Saleh et al.\textsuperscript{248} published a series of 15 patients that underwent TKR after operative management of tibial plateau fracture. Arthroplasty was performed at 38.6 months after fracture on average and fractures were followed up for approximately 6 years. The average age was 56 years old and 73\% were female. Saleh et al.\textsuperscript{248} discussed the technically demanding nature of a TKR after fracture and the high failure rate, which was 33\% in this series. However, in all of these studies the emphasis was on the outcome of knee arthroplasty performed for PTOA rather than the incidence of TKR in the tibial plateau fracture.
population. The incidence of symptomatic PTOA requiring TKR after tibial plateau fractures has been reported previously at 5.7%\(^{(208)}\) and 7.5%\(^{(249)}\) in two large studies but with methodological limitations.

This study investigated the post-operative complications, surgical interventions and PROMs and the incidence of PTOA requiring TKR in patients who had a tibial plateau fracture in a well-defined patient population.

### 3.2 Methods

The 1423 fractures identified in the 25-year trauma database, included in the epidemiological study (Section 2), were analysed for post-operative complications and the need for further surgery. Symptomatic PTOA was recorded, radiographic OA was not analysed specifically. All patients that remained within the catchment population would have been treated at the institution. All available NHS Lothian notes and radiographs throughout Scotland were reviewed for these patients at a mean of 14.2 years after the injury (range 3-28 years).

Patients with tibial plateau fractures were cross-referenced with a prospective arthroplasty database at the institution. The relationship between demographic features and the requirement for later TKR was assessed.

#### 3.2.1 Management Protocol

Management of all tibial plateau fractures was overseen by trauma consultants, operative intervention was performed by consultants, registrars and fellows. The standard method of non-operative treatment was immobilisation in plaster cast or functional bracing. The majority of displaced fractures were treated by open reduction and internal fixation with plating, supplemented with bone grafting or calcium phosphate cement if considered necessary by the treating surgeon. The operating surgeon determined the postoperative rehabilitation and weight-bearing status with referral to the physiotherapy service.
3.2.2 Follow-Up in Patients over 60 years old.

The mean duration of PROM follow-up was 10.5 years (range 3-26 years). Patients over 60 years old who were alive at the time of follow-up (April 2015) were reviewed by telephone assessment with two validated and reliable outcome instruments (PROMs): EQ-5D and OKS (Figure 3.1).

![Flow Diagram](image)

Figure 3.1: Flow Diagram to show patient reported outcome follow-up for tibial plateau fractures in the elderly.

3.2.3 Statistical Analysis

Statistical analysis was performed using SPSS Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.1.0. Continuous data were presented as mean and St Dev. Categorical data were presented as frequencies and percentages. Incidence was presented as fractures/100,000/year. Age was normally distributed for tibial plateau fractures (skewness and kurtosis) therefore an independent t test for unpaired data was performed to compare age at time of fracture in the total population compared to those who developed PTOA and OKS.
Categorical nominal outcome variables with greater than 2 groups (MOI, Fracture Classification) were analysed using Pearson’s chi square test and variables with 2 groups (Gender, Open/Closed Injuries, Management). Fisher’s exact test was used. Independent t test for unpaired data was used to analyse continuous outcome variables (OKS, age). The Spearman’s correlation coefficient was used to assess correlation between non-parametric ranked data, OKS and age. A \( p \) value of <0.05 was considered to be statistically significant.

3.3 Results

3.3.1 Complications

Post-operative complications were seen in a third of cases. (Table 3.1). Post-operative pain was the predominant symptom with 16% of patients reporting pain during their clinical follow-up. Stiffness was seen in 9% of the patients. Three quarters of the patients that reported pain and stiffness had operative management. There were metalwork complications including prominence\(^4\) and pain in 5%. Infection complicated 7% of cases, and was a deep infection in 3%. The fixation failed in 6% of operative cases and loss of position occurred in 3% of non-operative cases. Compartment syndrome was seen in 1% of cases and medical complications in 2%. Although a third of patients had complications after tibial plateau fractures, operative management led to significantly more complications than conservative management (\( p < 0.0001 \)).

\(^4\)Prominence was described as where there was superficial irritation of the skin and soft tissues by the metalwork as the swelling subsided.
There was no association between age and complication rate ($p=0.2053$) or between post-operative complications and gender ($p=0.1245$) or open injuries ($p=1.00$). There was a significant association between complications and fracture classification ($p<0.0001$) and MOI ($p=0.0027$).

Over half the patients with complex bicondylar fractures (Schatzker V and VI) suffered complications (54%) (Table 3.2). Only a quarter of the patients who sustained a tibial plateau fracture from FFS sustained complications, which was less than the following higher-energy mechanisms, FFH, RTA and sport (37, 37 and 35% respectively). There was also an association between age and fixation failure/loss of position with the mean age of patients 61.64 years being significantly higher than the study population (55.94 years) ($p=0.0328$).

Complications were seen at higher rates after bicondylar fractures and secondary to high-energy mechanisms like FFH and RTA.
### Table 3.2: Bicondylar tibial plateau complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Bicondylar Fractures (n=212)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>31 (15%)</td>
</tr>
<tr>
<td>Deep Infection</td>
<td>21 (10%)</td>
</tr>
<tr>
<td>Metalwork</td>
<td>25 (12%)</td>
</tr>
<tr>
<td>Stiffness</td>
<td>26 (12%)</td>
</tr>
<tr>
<td>Failure Fixation/Loss Position</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>Pain</td>
<td>43 (20%)</td>
</tr>
<tr>
<td>PTOA</td>
<td>11 (5%)</td>
</tr>
<tr>
<td>TKR</td>
<td>7 (3%)</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Compartment Syndrome</td>
<td>12 (6%)</td>
</tr>
<tr>
<td>Nerve Injury</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Instability</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Non Union</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>Total patients with complications</td>
<td>114 (54%)</td>
</tr>
</tbody>
</table>

#### 3.3.2 Further surgery

Further surgery was required in 216 fractures (15%) for stiffness, pain, infection and failed fixation. ROMW was performed after 160 fractures (11%). The other further surgery included 25 arthroscopies, 30 wound procedures, 19 fasciotomies, 15 revisions, eight manipulations under anaesthetic (MUA), seven split skin grafts, seven amputations, four ligamentous procedures, three osteotomies and one fusion.

The age at injury was statistically significantly lower in those that underwent further surgery than the tibial plateau fracture population (Table 3.3). Schatzker V and VI fractures required further surgery in 26% and 29% of cases. Further surgery was required ten times more often after operative intervention (20%) compared to non-operative (2%). Fractures sustained following FFS required only 7% further surgery compared to FFH, RTA and sport (17, 16 and 16%).
Further Surgery | No Further Surgery | *p* value
--- | --- | ---
**Age** (mean (years)) | 48.5 | 57.3 | <0.0001
**Gender**
Female | 115 (12%) | 812 |
Male | 101 (14%) | 611 | 0.303
**Schatzker Classification**
I | 17 (6%) | 257 |
II | 61 (15%) | 338 |
III | 12 (6%) | 195 |
IV | 29 (10%) | 271 |
V | 33 (26%) | 96 |
VI | 46 (29%) | 115 | <0.0001
Unknown | 18 (11%) | 150 |
**Open Injury**
Open Injury | 2 (25%) | 6 |
Closed Injury | 214 (13%) | 1417 | 0.285
**Management**
Operative | 202 (20%) | 813 |
Non-Operative | 14 (2%) | 601 | <0.0001
**Mechanism of Injury**
Fall from standing | 34 (7%) | 458 |
Fall from height | 59 (17%) | 281 |
Road traffic accident | 71 (16%) | 377 |
Sport | 31 (16%) | 163 |
Other | 31 (13%) | 144 | <0.0001

Table 3.3: Further surgery required after tibial plateau fractures.

### 3.3.3 Patient reported outcomes in the over 60 year olds

There were 168 patients in the study cohort with a mean age at injury of 70.3 years (60-92 years old) and 131 (78%) were female. FFS caused 43% (73) FFH 29% (49) and RTA 17% (28). There were no open injuries and 41% were treated operatively.

There were 10 cases of post-operative infection (6%), seven of these required removal of metalwork (70%) and one required revision (10%). Metalwork removal was performed in 18 other patients (11%) for discomfort and symptomatic PTOA was seen in 18 patients (11%).

Figure 3.1 showed the breakdown of follow-up. At the time of follow-up 417 (62%) patients had died, 72 were loss to follow-up and 13 unwilling to participate in the study. Functional follow-up was therefore available for 168
patients (66% of the alive population). There were no significant differences between responders and non-responders in terms of gender ($p=0.2804$), fracture classification ($p=0.2437$) and fracture management ($p=0.2258$). There was no significant difference between responders and non-responders in the number of complications ($p=0.08$) however when looking at individual complications a significant difference was seen, an increased proportion of responder had failure of fixation ($p=0.01$), pain ($p=0.02$), PTOA ($p=0.003$) and TKR ($p=0.001$).

The mean OKS was 32.46 and the average EQ5D 3L score was 0.59. There was no significant difference in EQ5D with gender ($p=0.0855$), the average male EQ5D was 0.668 and female EQ5D 0.565 however the OKS was associated with gender ($p=0.013$), with women scoring lower 31.3 than men 36.4. There was no association between OKS and the likelihood of complications ($p=0.8958$), further surgery ($p=0.7676$) symptomatic PTOA ($p=0.4036$) or fracture management ($p=0.1420$). The general health questionnaire results were lower than the general population with no gender difference but the site-specific health questionnaire showed worse results in female than male patients with both having mild to moderate knee problems ten years post injury.

3.3.4 Post-traumatic osteoarthritis

Symptomatic PTOA was seen after 70 of the 1423 fractures (5%). There was no statistical difference between the age of patients developing symptomatic PTOA (56.8 years) and all tibial plateau fracture patients (55.9 years) ($p=0.7294$). There was a trend of more women (6%) than men (4%) developing PTOA but no statistical difference was seen ($p=0.0842$), there was no statistically significant difference comparing PTOA and fracture classification ($p=0.0717$) but a trend to more PTOA after Schatzker II (7%) and bicondylar fractures (6%) compared to 3% after Schatzker I. There was no association between PTOA and mechanism of injury ($p=0.8925$) or open/closed injury ($p=1.000$). There was a statistically highly significant
difference between operative (7%) and conservative (2%) management and risk of PTOA ($p=0.0001$) and the association between post-operative infection and later development of PTOA just reached statistical significance($p=0.0458$). Increased risk of PTOA after tibial plateau fracture was statistically associated with operative management and post-operative infection.

### 3.3.5 Total knee replacement for post-traumatic osteoarthritis

Arthroplasty surgery was performed in 42 of the 1423 patients (3%). In three of these cases TKR was performed immediately for fracture management rather than for PTOA. TKR for PTOA was performed at an average of 38 months (range 1 month - 23 years). The average age of patients requiring arthroplasty surgery was 64.3 years at the time of injury, statistically significantly older than the general population sustaining tibial plateau fractures (aged 55.9) ($p=0.0143$). More women underwent arthroplasty surgery than men ($p=0.0135$). Fracture classification was statistically significantly associated with need for arthroplasty with Schatzker II (5%) and V (5%) requiring TKR more often ($p=0.0331$) and 4% of operatively managed fractures progressed to TKR (33/846) compared to 1% of conservatively managed fractures (6/607) ($p=0.0005$). Post-operative infection was seen in six cases that went on to require TKR which was just statistically significantly more than the total population ($p=0.0446$). Deprivation score (SIMD ($p=0.6137$)) and mechanism of original injury ($p=0.1137$) had no association with need for TKR. Following on from PTOA, the requirement for a TKR was seen in an older female population following operatively-managed Schatzker II and V injuries and particularly if post-operative infection had complicated the original fracture.
3.4 Discussion

Patient reported outcomes after tibial plateau fractures were investigated for patients over 60 years of age and the whole database was studied for complications, PTOA and arthroplasty surgery. Clear predisposing factors to PTOA and TKR were identified as was the incidence of TKR in the tibial plateau population. Further evaluation would be required to include PROMs for patients under 60 years of age.

3.4.1 Complications and Further Surgery

In this study, all documented complications were studied including subjective stiffness and pain, and a third of the cases had complications documented. Some of the complications described may be inevitable consequences of the injury rather than specific complications from the management of the injuries, as problems experienced after tibial plateau fractures were included to avoid bias. Nearly half of operatively managed cases had complications compared to a fifth of conservatively managed cases. This result was predictable as operative management carries additional specific complications not seen in conservative management, including failure of fixation and metalwork complications, and is used for worse fractures. Compartment syndrome was only seen in operative cases, probably secondary to high-energy injuries requiring operative management. Infection was seen in ten times more operative cases (20%) than conservative cases (2%) proportionally, with a 3% deep infection rate overall. The same rate of deep infection (3%) was seen in Schwartzman’s series of 40 patients. Barei et al. found a slightly lower infection rates at 2% but a higher rate of metalwork removal at 24% compared to 9% in our operative patients. They reported on operatively-managed patients who had sustained intra-articular bicondylar fractures that were likely to have been higher-energy injuries and were shown in the current study to have higher complication rates. They also found a ten times higher DVT rate (20%) but
included asymptomatic DVTs detected on Doppler ultrasound screening. A similar deep infection rate (3%) was seen in Schwartzman's series of 40 patients. The paper by Van Dreumel et al. showed similar complications to the current study with 1% revision (1%), 1% non-union (<1%), 2% compartment syndrome (1%) but only 2% infection compared to the 7% total infection rate seen in the current study. The infection was notably lower as they included superficial wound infection and may be due to the small sample number of 96 and the level 2 nature of the institution meaning more severe injuries went to a different centre or the rates are clinically significantly better and lessons could be learnt from their practice. The removal of metalwork rate at 42% was far higher and may be accounted for by a different implant use that is bulkier, different fixation technique or patient expectations for metalwork removal. This difference is clinically and economically important as the patients are being subjected to further surgery and anaesthetic agents as well as the cost to the individual in missed work, transport etc. and the costs versus profit for the institution performing the operation. Roerdink et al. investigated fixation failure after arthroscopic reduction and internal fixation in patients over 55 years old. The study followed up 30 patients over 5 years and showed 30% failure rate (secondary radiographic displacement). The current study showed only 6% and may be due to the symptomatic follow-up performed rather than radiographic follow-up and the population differences, all ages compared to over 55 years. Fixation failure was shown to be 100% in patients with osteoporosis compared with 22% in less osteoporotic bone. The high incidence of loss of fixation in the elderly patient is important agreeing with the current study where increased age was statistically significant for failure of fixation/loss of position.

Further surgery or additional procedures was not investigated or well documented in the literature in the author's opinion. Rates published depend on what is included in further surgery. In the current study all patients that returned to the operating theatre regarding their knee following a tibial plateau fracture were included. Two previous studies documented total
return to theatre for further surgery. One study of 125 tibial plateau fractures concurred with the current study showing 20 fractures requiring further surgery (16%)\(^{(222)}\), however 30% of the patients in Timmers et al.\(^{(207)}\) required further surgery which was higher than the further surgery rate in the operative cases in the current study (20%). Different thresholds for additional procedures could explain the difference seen. Younger patients after higher energy injuries that sustained bicondylar fractures and needed operative intervention were more likely to undergo additional procedures. The current study’s rates of complications and further surgery were clearly documented and generalizable for a whole population over 25 years add to the literature base allowing us to counsel patients who sustain tibial plateau fractures more accurately. When consenting patients for operative management of tibial plateau fractures a rate of 45% should be quoted for adverse or imperfect outcomes and increased for those with bicondylar fractures and after high-energy mechanisms. This data can be used to quote individual complication rates more accurately for the individuals concerned.

3.4.2 Functional Outcomes

Analysing outcomes after tibial plateau fractures is very difficult due to a number of factors\(^{(252)}\). These include the non-homogenous patient populations and variety of surgeons\(^{(60, 117)}\) the collective reporting of operative and non operative results\(^{(25, 45, 60, 117, 138, 209, 263, 254, 255, 256, 257)}\), the variety of fixation methods\(^{(60, 138, 209, 254, 255, 256, 257)}\) and the variety of experience of the operating surgeon\(^{(231)}\) all combine to make the results difficult to interpret and analyse. The assessment criteria in Hohl’s paper\(^{(25)}\) might be considered arbitrary as they were not validated and fewer than half of the outcome points were patient based measures\(^{(5)}\). The level of function required to be an acceptable result also varied with a general description given\(^{(38)}\);
Marked differences using different outcome measures were seen in a series of 131 fractures where 67% of the outcomes were considered acceptable compared to 86% when a different set of criteria was used\(^9\). The functional outcomes used in the current study in elderly patients (>60 years old) were OKS, a joint specific outcome score for assessing arthritis in the knee, and EQ5D a general health questionnaire. Using these avoided setting levels for acceptable or unacceptable movement, strength and pain levels, as in some of the outcome scores used previously and were patient reported rather than radiographic outcomes. Van Dreumel et al.\(^{206}\) used a joint specific outcome score, KOOS to investigate 96 tibial plateau fractures operatively managed in a level 2 trauma centre. They found no significant difference between functional outcome and age, at odds with the current study. KOOS is often used in younger patients and one of the reasons for the difference seen may be that more elderly patients have a lower functional demand so are less restricted when measured with certain PROMs. Timmers et al.\(^{207}\) also used KOOS and a modified EQ5D, EQ6D that included cognition, showing lower KOOS scores by 15% by including young patients and had a higher rate of further surgery (10% more than current study). The minimal clinically significant difference for the OKS has variously been reported as five or eight\(^{258, 259}\) which suggests the statistically significant OKS score difference seen in men and women is also clinically relevant, with women having lower knee specific functional results but no statistical difference in general health scores (EQ5D). This difference in OKS score at long-term follow-up is particularly interesting as previous studies have shown women wait till they have a lower OKS before having TKR\(^{260}\). A cut off of OKS 18 was suggested as a triage for TKR by some commissioning groups in the UK and an average pre operative OKS of 18 for TKR in a reference population\(^{261}\). Our study showed an average OKS of 32.5 indicating mild to moderate problems with their knees\(^{262}\). The general health questionnaire
score of 0.59 indicated a significant reduction of quality of life scores compared to the general UK population over 65 who have a mean score of 0.78. These results suggested that after tibial plateau fractures patients over 60 sustained a decrease in their general quality of life but for most patients the knee specific score was not decreased enough to require arthroplasty surgery.

The complication difference between responders and non-responders to the follow-up was significantly different for failure of fixation/loss of position, pain, PTOA and TKR, with non-responders having a lower rate of these complications. There is a link between pain, symptomatic PTOA and requirement for TKR as TKR was done because of PTOA in all but two cases and symptomatic PTOA was defined as pain or stiffness due to post-traumatic osteoarthritis. The increased level of these complications seen may have affected the outcome scores seen suggesting that the overall functional outcome may be better than seen here.

3.4.3 Post-traumatic osteoarthritis

The time it takes PTOA to develop after injury is contentious. In severe intra-articular fractures PTOA may develop early, with Slee et al. (1955) suggesting development 18 months to 3 years after fracture. Others have proposed a longer duration at 6 to 8 years post injury. The satisfaction rates after tibial plateau fracture have been shown to decrease at the 6-10 year follow-up compared to the 3-6 years follow-up which maybe due to PTOA, signifying a longer duration of progression. The follow-up in the current study was 14.2 years to try to include as many patients that would develop PTOA as possible. The rate of PTOA in the current study was low at 5% symptomatic PTOA reported by patients, however radiographs were not performed. Symptomatic PTOA was chosen for this study for two reasons. Functional outcomes are described as more useful than radiological outcomes and to understand the effect of radiological findings on functional outcome, the findings must be measured in a consistent manner.
Difficulties have been shown in reliably interpreting fracture radiographs in complex injuries. Martin et al. showed articular depression and condylar widening in tibial plateau fractures had the lowest agreement with tolerance levels of 12mm for depression and 9mm for widening. CT scans consistently improved agreement and narrowed the tolerance limits but the improvements were modest and not statistically significant. Holt et al. (1995) showed radiographs often missed the split component of a Schatzker type II fracture misdiagnosing it as Schatzker type III. The difficulty with measuring radiological outcomes agrees with the differing outcome results published. Osteoarthritis has been shown to worsened by one grade on the radiological classification by Resnick and Niwayama (Table 3.4) after tibial plateau fracture and the rates of radiographic PTOA range from approximately 10-60%. Rademakers et al. (2007) reported 11% radiographic PTOA after operatively managed fractures. Volpin et al. (1990) concluded there was no significant difference between operatively and conservatively managed plateau fractures with respect to the 23% radiographic PTOA that was seen after femoral and tibial intra-articular fractures in a small study sample (n=31). A high rate of radiographic PTOA (26%) was seen in a study with follow-up of less than two years and even higher at 58% in bicondylar fractures on radiographs at one year.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>None</td>
</tr>
<tr>
<td>1</td>
<td>Minimal joint space narrowing, mild sclerosis</td>
</tr>
<tr>
<td>2</td>
<td>Moderate narrowing, osteophytes, moderate subchondral sclerosis and bony aberration, intra-articular osseous bodies</td>
</tr>
<tr>
<td>3</td>
<td>Marked joint space narrowing, bony collapse, severe subchondral sclerosis, marked deformity and severe bony aberration</td>
</tr>
</tbody>
</table>

Table 3.4: Resnick and Niwayama Radiological Osteoarthritis Criteria.

Symptomatic PTOA is less well documented than radiographic PTOA in the author’s opinion. In the current study 5% of cases developed symptomatic PTOA, far lower than the radiographic PTOA seen and in contrast to the relatively high rate of symptomatic arthritis, fusion and salvage.
arthroplasty reported for equivalent intra-articular fractures of the lower limb affecting the acetabulum\(^{(266)}\), femoral head\(^{(267)}\), tibial pilon\(^{(268)}\) and subtalar joint\(^{(269)}\). The reasons for this difference may be the method of treating hip PTOA is a successful THR with satisfaction rates of 96% even when including PTOA\(^{(270)}\) and ankle PTOA often ends with fusion with satisfaction rates greater than 93\%\(^{(271)}\) or arthroplasty with improved quality of life in 87\% of patients\(^{(272)}\), whereas TKR for primary osteoarthritis has a satisfaction rate of only 80\%\(^{(273)}\) and this is lower after tibial plateau fracture\(^{(225)}\). The two factors found to be associated with symptomatic PTOA were infection and operative management. The link between post-operative infection and PTOA can be explained by the knowledge septic arthritis leads to osteoarthritis with recent evidence suggesting that alpha toxin from *Staphylococcus aureus* bacteria, a common cause of septic arthritis, caused rapid chondrocyte death and therefore the development of PTOA\(^{(274)}\). Operative management was used in higher energy injuries that may have caused more direct cartilage damage irrespective of the fracture management required leading to PTOA. There was a trend to more PTOA after Schatzker II and bicondylar fractures but this was not statistically significant (section 3.3.4). Koval et al.\(^{(131)}\) also showed unacceptable outcomes were in patients with Schatzker II fractures in 20 displaced tibial plateau fractures treated with percutaneous fixation, these also accounted for 80\% of the non-anatomic reductions recorded. Stokel et al.\(^{(242)}\), Blokker et al.\(^{(253)}\) and Savoie et al.\(^{(275)}\) however found the best results in split depression fractures and the worst in medial plateau fractures. Some of the difference in the literature can be explained by the difficulty classifying tibial plateau fractures as previously discussed.

### 3.4.4 Total Knee Replacement

Several studies with smaller patient cohorts than the present series have reported the incidence of knee arthroplasty. The reported rates of knee arthroplasty have been variable. Weigel and Marsh published a series of high energy fractures treated with external fixation and minimal internal fixation.
with none requiring TKR at a minimum of five years. Weiss et al. reported a larger series of 62 patients undergoing TKR, treated initially for tibial plateau fractures by ORIF in 61% of cases. The series was predominantly female patients (65%) and 61% of the fractures involved the lateral plateau matching this study. The average time between fracture and salvage TKR was 13.6 years but the relationship to exact fracture type was not established. Simpson and Keating published a comparison of buttress plating with minimal internal fixation and injectable calcium phosphate cement finding 15% of the former group required late arthroplasty compared to none of the latter. A further study by Keating et al. (1999) showed despite 68% of his study group showing progressive OA on radiographs, only two of the 151 cases required TKR within 2 years. A similar low percentage was reported by Rademakers et al. (2007) who followed up 119 operatively-managed tibial plateau fractures for an average of 14 years finding only 2% required TKR.

The incidence of TKR secondary to PTOA after tibial plateau fractures varies in the literature. Manidakis et al. (2010) in a study with only 20 months follow-up showed 4% of 125 tibial plateau fractures required TKR. This study was limited by small study sample and short follow-up. In 2012 Mehin et al. published a series of 311 fractures with a minimum of 2 years follow-up, showed 2.7% required TKR. Their findings were from a level 1 trauma centre with 8% open fractures and a 30% incidence of Schatzker VI fractures compared to 5% in our series. Interestingly they found 4.5% of the non operatively managed group required TKR in comparison to 2.3% of the 220 operatively managed patients. These results show a comparable overall rate of TKR as a salvage procedure (3%) but show non-operative management to be a risk factor. This could be explained by the study being conducted at a level 1 trauma centre, where the rate of low energy tibial plateau fractures would typically constitute a smaller proportion of fractures treated and non-operative management may have been used due to patients concurrent injuries or medical condition. A limitation of their study was that the follow-up data were taken from an administrative database.
A 2014 study based on analysis of an administrative health database\(^{(249)}\) looked at the requirement for TKR in patients who had previously had operative management of a tibial plateau fracture. The incidence of TKR in these patients was 5.3 times the rate of the matched general population. At 10 years post-injury 7.3% of patients had undergone TKR compared with 1.8% of the matched population. The mean age for TKR in the uninjured, matched population was 59 years, 10 years older than the mean age of those sustaining a tibial plateau fracture. The substantially higher rate of TKR may be due to the lack of information on laterality of the fracture and the arthroplasty surgery, meaning some of the TKR could have been performed on the contralateral limb leading to an overestimate of the rate of TKR. The study was limited by lack of information relating to fracture type or the influence of fracture management on the requirement for TKR. The risk factors they identified were increasing age and bicondylar fractures and they noted a weak association with women requiring TKR (HR 1.25 \(^{p}=0.029\)) in keeping with our data. The fact that women have a higher rate of TKR after tibial plateau fracture in our study is interesting given that previous epidemiological studies show that men are more likely to receive TKR for end stage osteoarthritis than women\(^{(278)}\). However, our finding is consistent with the gender distribution of patients in series reporting knee arthroplasty after plateau fracture where women usually comprise more than 60% of the cohort\(^{(248, 276)}\). Elsoe et al.\(^{(208)}\) also performed a matched cohort study using country wide registry data. The population had a slightly younger average age 52.6 years with a similar gender split. They reported 5.7% TKR compared to 2% in matched cohort. The study could not report laterality and therefore some contralateral TKR could explain the increased progression to TKR compared to our study (3%). They explained the lower incidence of TKR compared to Wasserstein et al.\(^{(249)}\) as due to the older population studied and the inclusion of non-operative cases. The current study by including all patients that sustained a tibial plateau fracture and recording classification, treatment method and outcomes for over 65 year olds added to
the literature. Interestingly Elsoe et al.\cite{208} showed a hazard ratio of 1.86 at 15-20 years post injury suggesting the risk still increases. In the current study, the follow-up of 14.2 years is slightly less than this but the mean time to TKR (3.2 years) was also less. Some of the increase seen at 15-20 years could be explained by primary OA in the contralateral side rather than PTOA. Van Dreumel et al.\cite{206} also showed a high conversion rate to TKR at 7\% at one year in operatively-managed patients compared to 4\% in this study. This may be due to the high energy nature of the injuries causing more cartilage damage at the time of injury and more PTOA leading to more salvage procedures. The highest rate of TKR published to the author’s knowledge was 22\%\cite{207} in an operative study with high energy injuries requiring further surgery and with a higher proportion of women. They did however see more requirement for TKR after Schatzker II and bicondylar fractures like in the current study.

The lowest incidence of knee arthroplasty in the current study was in those fractures treated non-operatively. This reflects the fact that non-operative management was principally used in low energy injuries with minimal or no articular displacement, or alternatively in displaced fractures in very elderly patients with low functional requirements.

### 3.4.5 Limitations

The study limitations include the lack of preoperative PROMs meaning comparison with the postoperative outcomes is not possible. The limited PROMs data available due to the nature of elderly patients being deceased or uncontactable reduces the generalizability of the data. Due to the retrospective nature of reviewing the prospective database causality could not be established and missing data points may have introduced bias.
3.4.6 Conclusions

Although tibial plateau fractures are commonly associated with degenerative radiographic changes, the incidence of symptomatic PTOA severe enough to warrant TKR is low (3%). Increasing age, female gender, bicondylar fractures and fractures that required operative management had significantly increased risk of TKR.
Section 4 - Epidemiology of Operatively-Managed Patellar Fractures

Aim: To define the numbers of operatively-managed patellar fractures with corresponding patient factors, mechanisms and management in a large well-defined population over 15 years.

Research Questions:

(a) What is the incidence of patellar fractures requiring operative management in the general population?

(b) How do these fractures occur and to whom?

4.1 Introduction

Patellar fractures represent approximately 1% of all skeletal fractures\(^4\). The patella is prone to injury due to its superficial and anterior position in the lower limb with minimal tissue coverage. Transverse patellar fractures are due to forces from the extensor mechanism. Vertical fractures maybe the result of direct impact to a partially flexed knee. Comminuted fractures are usually a result of higher energy direct impact to the patella.

Most papers published are on repair methods rather than classification systems as fracture classification has not been shown to correlate with clinical outcome\(^5\). Management of these fractures is dependent on the fracture pattern, patient factors and functional expectations. The aim of management is to restore joint congruity and the extensor mechanism. The main operative treatments are open reduction and fixation with tension band wiring (TBW), cannulated screw tension band construct or patellectomy; partial or total. Non-operative management is usually reserved for minimally-displaced fractures with an intact extensor mechanism or medical
comorbidities making the patient unsuitable for surgical intervention. Although many fixation techniques have been used, the management most widely used is TBW\(^{(279)}\). The literature has mainly focused on small variations in fixation techniques, with or without cerclage wires\(^5\), screw positions and wire configuration in small numbers of patients with only Nummi et al. researching larger numbers (155 patients)\(^{(30)}\). The most recent epidemiological study the author is aware of including children and adults over a ten year period was of 756 patellar fractures\(^{(280)}\). This study was a retrospective registry data review from Denmark published in 2016\(^{(280)}\). Appendix 2 shows a summary table of the literature. The current study investigated patellar fractures over a 15-year period in adults managed operatively with TBW, the preferred fixation method at our institution.

### 4.2 Methods

A 15-year retrospective review of our prospectively collected trauma database was performed to identify all operatively-managed patellar fractures in skeletally mature patients (≥15 years old) presenting to our unit between May 1995 and May 2010. The time period was chosen for clarity of operative data recorded and to allow a sufficiently large patient group (>250). Patients aged 14 years and younger were excluded from the study. The local adult population based on a national census\(^{(3)}\) during the study period was 517,555 (Census 2001) and our unit provided all elective and orthopaedic trauma services for the defined catchment population. This study was classed as an audit by local guidelines and therefore did not require formal ethical approval. After excluding patellar tendon avulsions or inferior pole fractures that behaved as tendon rupture and were managed with patellar tendon repair, a total of 264 fractures in 262 patients were included, therefore all the operatively-managed patellar fractures were intra-articular fractures. Medical notes and radiographs were reviewed to record patient demographics (age, gender, ...
mechanism of injury, fracture classification (AO-OTA classification – A – extra articular, B – partial articular and C – articular fractures C1 transverse and C2/3 comminuted) and management. The patient’s address at time of injury was used to work out the Scottish Index of Multiple Deprivation economic quintile, using 2011 data. The first quintile represents the most deprived and the fifth the least deprived on a national level.

Statistical analysis was performed using SPSS Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.1.0. Continuous data were presented as mean and St Dev. Categorical data were presented as frequencies and percentages. Incidence was presented as fractures/100,000/year. The Spearman’s correlation coefficient was used to assess correlation between non-parametric ranked data, fracture incidence each year over the time period and age-adjusted incidence and age groups. Age was normally distributed for patellar fractures (skewness and kurtosis) therefore an independent t test for unpaired data was performed to compare age at time of fracture in males and females. The categorical nominal outcome variable of mechanism of injury was compared for males and females, open or closed injury and transverse or comminuted fractures (categorical predictor variables) using Pearson’s chi-square test. To compare means of age (parametric data) for mechanisms of injury an ANOVA was utilised. Multinomial logistic regression was used to compare the associations between age, gender and mechanism of injury to find the stronger predictor for injury mechanism. Fisher’s exact test was used for the 2x2 contingency table of fracture classification and open or closed injury. The Pearson’s chi square test was also used to compare the observed and expected frequencies of patellar fracture in the deprivation quintiles. A p value of <0.05 was considered to be statistically significant.
4.3 Results

There were 264 operatively-managed patellar fractures seen in the 15 year study period, with an average of 18 per year (range 12-28). Approximately half of patellar fractures were right sided (51%) and the average age of the patient sustaining an operatively-managed patellar fracture was 54 years old (range 15-88).

4.3.1 Annual Incidence

The overall incidence of operatively-managed patellar fractures was 3.4 per 100,000 population with no significant change in incidence over this time period (Spearman’s correlation coefficient = 0.09 $p=0.8$) (Table and Figure 4.1).

![Changing Incidence over Time of Operatively Managed Patella Fractures](image-url)
<table>
<thead>
<tr>
<th>Year</th>
<th>Fracture Frequency</th>
<th>Total Incidence</th>
<th>Male</th>
<th>Male Incidence</th>
<th>Female</th>
<th>Female Incidence</th>
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<tr>
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<td>18</td>
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<td>9</td>
<td>1.74</td>
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<td>8</td>
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<td>1997</td>
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<td>9</td>
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</tr>
</tbody>
</table>

Table 4.1: Yearly operatively-managed patellar fracture frequency and incidence according to gender. (Incidence/100,000/year)

4.3.2 Age-Adjusted Incidence

The age-adjusted incidence increases with increasing age but this did not reach statistical significance (Spearman’s Correlation Coefficient = 0.6905, p=0.0694) (Table and Figure 4.2).
<table>
<thead>
<tr>
<th>Age</th>
<th>Population</th>
<th>Fracture Frequency</th>
<th>Age-Adjusted Incidence</th>
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<tr>
<td>15-19</td>
<td>36229</td>
<td>15</td>
<td>2.76</td>
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<tr>
<td>20-29</td>
<td>108687</td>
<td>34</td>
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<td>30-39</td>
<td>98335</td>
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</tr>
<tr>
<td>80-89</td>
<td>25878</td>
<td>32</td>
<td>8.24</td>
</tr>
</tbody>
</table>

Table 4.2: Age-adjusted incidence of operatively-managed patellar fractures.
(Incidence/100,000/year)

Half of the patients were female (129, 49%) with a significant difference between the average age at injury in males (44.43yrs) and females (63.59 yrs) ($p<0.0001$) (Figure 4.3).
4.3.4 Mechanism of Injury

The mechanism of injury was divided into four categories; 190 (72%) were caused by falls, 35 (13%) in RTAs and 16 (6%) whilst playing sports, the remaining 23 (5%) fractures were ‘other’, caused by direct blows, assault, twisting injuries or unknown.

There was a significant difference in mechanisms of injuries due to gender \((p=0.01)\) with more women sustaining patellar fracture in falls and more men sustaining fractures in RTA and sport. The mechanism of injury varied according to age \((p<0.001)\) (Table 4.3). Owing to the association between gender and age multinomial logistic regression was performed showing that age is the main predictor of mechanism of injury rather than gender. (Age chi square 47.036 \(p<0.0001\) compared to gender chi square 1.489 \(p=0.685\)).

<table>
<thead>
<tr>
<th>Mechanism of Injury</th>
<th>Average Age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fall</td>
<td>52.6</td>
</tr>
<tr>
<td>RTA</td>
<td>26.1</td>
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<tr>
<td>Sport</td>
<td>38.7</td>
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<tr>
<td>Other</td>
<td>59</td>
</tr>
</tbody>
</table>

Table 4.3: Average age for each mechanism of injury causing operatively-managed patellar fractures.

4.3.5 Open Fractures

Open injuries were seen in 21 (8%) of patellar fractures. The mechanism of injury was associated with the rate of open fracture \((p<0.0001)\) with 31% occurring after RTA, but only 6% in sports and 4% in falls.
4.3.6 Fracture Classification

The fracture patterns included 144 (55%) transverse fractures (AO/OTA 34 C1), 96 (36%) comminuted fractures (AO/OTA 34 C2 and C3) with 24 (9%) unknown. Open fractures were seen more commonly in association with comminuted fractures at 13% compared to 4% in transverse fractures \((p=0.02)\). Comminuted fractures were also seen at a statistically higher rate after RTAs (77%) compared to falls (35%) and sports (33%) \((p<0.0001)\).

4.3.7 Deprivation Index

The Scottish Index of Multiple Deprivation (SIMD) suggests patellar fractures occur more in the least deprived but once the population in each category is taken into account they occur with equal frequency regardless of deprivation. The local authority of Edinburgh has the second highest proportion of the most deprived quintile in Scotland but it is only approximately 7% compared to approximately 50% in Glasgow according to SIMD data. Figure 2.13 shows the proportion of the Edinburgh population in each quintile. When the data were compared with the expected number of patellar fractures in each group there was no statistical difference \((p=0.398)\) (Table 4.4).

<table>
<thead>
<tr>
<th>SIMD</th>
<th>Edinburgh Population</th>
<th>Expected Number of Fractures</th>
<th>Observed Number of Fractures</th>
<th>Patellar Fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (most deprived)</td>
<td>11%</td>
<td>29</td>
<td>37</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
<td>42</td>
<td>47</td>
<td>18%</td>
</tr>
<tr>
<td>3</td>
<td>17%</td>
<td>45</td>
<td>44</td>
<td>17%</td>
</tr>
<tr>
<td>4</td>
<td>19%</td>
<td>50</td>
<td>43</td>
<td>16%</td>
</tr>
<tr>
<td>5 (least deprived)</td>
<td>37%</td>
<td>98</td>
<td>93</td>
<td>35%</td>
</tr>
</tbody>
</table>

Table 4.4: Operatively-manage patellar fractures in each deprivation quintile.
4.4 Discussion

The classic fracture epidemiology\(^1\) paper by Court-Brown and Caesar documented 49 patellar fractures a year in the same Edinburgh population studied here. In the current study only operatively-managed patellar fractures were included explaining the lower incidence seen of 18 a year. Operatively-managed patellar fractures were chosen to avoid non articular patella fractures and soft tissue injuries often grouped together under patellar fractures when non-operative management is considered. The differences in the study population also explain the lower average age of 54 compared to 65 years old and when combined with the knowledge that more of the older patients were female may explain the 10% difference in gender distribution. Open fractures occurred in 6% of the total number of patellar fractures\(^1\) compared to 8% in the current study again explained by the difference in population reported.

The epidemiological paper by Larsen’s group in Denmark also showed a significantly higher incidence as it included all patellar fractures including children without reference to management\(^2\). The mechanisms of injury seen in the Denmark study were directly comparable with the data presented in the current study with falls causing 73%, RTA 14% and sport 7% despite including all non operative cases. Their population was 579,119 (including children) again not dissimilar to Edinburgh. The fracture classification differed with 25% reported at C3 and only 23% C1 compared to 60% of the current study C1 and 40% C2 and C3. The percentages of C1 and C2/C3 compared to Larsen et al.\(^2\) can be explained by TBW being more suitable for transverse fractures. The average age was 54 but was hard to compare with the current study as children were included. An earlier paper by Sorensen from 1964 showed younger males sustaining patellar fractures than females but the average ages were significantly lower with males at 31 and females at 42 years of age\(^3\). This maybe explained by changing life expectancies and activity levels.
The paper by LeBrun et al. also reported operatively-managed patellar fractures only but not as an epidemiological study, focussing on outcomes\textsuperscript{(158)}. The patient cohort had an average age of 46 years old and a far higher open fracture rate at 28\% suggesting higher energy injuries. The open injury rate seen in the current study agrees with previous studies including the Edinburgh paper mentioned\textsuperscript{(1)} reporting 7\% open fractures\textsuperscript{(4, 281)}. Torchia's paper\textsuperscript{(281)} on open fractures of the patella reported >90\% caused by RTA, this study was from 1976-1989 and road traffic laws have changed considerably in this time and may explain the variation to the current study. Catalano et al. (1995)\textsuperscript{(282)} published a similar paper on open patellar fractures again with 90\% secondary to RTA again from a similar time period and from a level one trauma centre so biasing the data to high energy injuries rather than a full population study\textsuperscript{(282)}.

The general findings strengthen the literature base supporting the incidence of operatively-managed patellar fractures, mechanisms of injury and open fracture rates. The differences with the recent epidemiological papers are explained by the population studied. The findings were not novel but update the literature for modern operative techniques in a large well-defined population. Future work could update the literature further from 2010 to present date.

4.4.1 Conclusions

In the population investigated the incidence of operatively-managed patellar fractures was 3.4/100,000/year. They were seen in older females and young males with age being the main predictor of mechanism of injury. Elderly patients were likely to have sustained the patellar fracture secondary to falls and younger patients secondary to RTA or sport. RTAs were more often associated with comminuted and open fractures.
Section 5 - Outcomes of Operatively-Managed Patellar Fractures

Aim: To investigate the complications, surgical interventions and patient reported outcomes following patellar fractures.

Research Questions:

a. What factors predispose patients to complications and post-traumatic osteoarthritis?

b. How many patients require late salvage arthroplasty surgery?

c. How does having an operatively-managed patellar fracture affect patients in the long-term?

5.1 Introduction

Intra-articular injury is known to increase the risk for subsequent development of PTOA\(^ {16-19}\). All patellar fractures included in the current study are intra-articular fractures (AO/OTA C1, C2, C3). The rates of PTOA after patellar fracture are not well documented and vary dependent on how this diagnosis is made: using clinical or radiological factors, or both. Nummi et al. \(^ {30}\) found 76\% operatively-managed patellar fractures had radiological OA changes at follow-up however only 30\% were symptomatic. This was echoed by Sorensen et al.\(^ {156}\) reporting 70\% radiological changes with only 30\% of patients experiencing symptoms. These two studies used historic surgical methods e.g. patellectomy, and the results are not necessarily relevant with modern techniques e.g. Tension Band Wiring (TBW). LeBrun et al. using modern fixation methods suggested significant symptomatic complaints and functional deficits at 6.5 years\(^ {158}\).
Patient outcomes have been reported comparing operative techniques including percutaneous versus open and screws versus TBW. Percutaneous techniques were shown to have superior outcomes compared to open techniques if the fractures were amenable to percutaneous fixation\(^{(283)}\). Those amenable were less comminuted and may be expected to have better outcomes in any case. Comparing screw fixation and TBW some papers suggest superior results with screw fixation\(^{(284)}\). There was a lower incidence of removal of metalwork after screw fixation but this appeared to be at the expense of a higher rate of fixation failure\(^{(285)}\). Both techniques provided >90% good or excellent PROMs over a year after injury\(^{(286)}\). Longer term PROMs suggested that although recovery from patellar fractures is limited by PTOA and discomfort from implanted metalwork 91% achieved pre-operative mobility\(^{(157)}\) and 64% were symptom free\(^{(156)}\).

The incidence of symptomatic PTOA requiring TKR is not well documented in the published literature. Larsen et al. (2018)\(^{(287)}\) stated consequences of patellar fractures may be more severe than previously considered, with a slightly elevated lifelong increased risk of TKR. They reported 3.3% of patients with patellar fractures required TKR compared to 2% of the matched population giving a hazard ratio for patellar fractures of 1.83, worse in the first five years. Houdek et al. (2015)\(^{(288)}\) studied all TKR patients between 1990 and 2012 and found 0.5% of patients had had a previous patellar fracture, only 36% of these had been treated with ORIF and 37% of these needed ROMW.

This study investigated the post-operative complications, surgical interventions and PROMs and the incidence of PTOA requiring TKR in patients who had previously undergone surgery for a fracture of the patellar in a well-defined patient population.

5.2 Methods

The 264 fractures identified in the 15-year trauma database, included in the epidemiological study (Section 4), were analysed for post-operative...
complications and the need for further surgery. Symptomatic PTOA was
recorded, radiographic OA was not analysed specifically. All patients that
remained within the catchment population were treated at our institution. All
notes and radiographs available for these patients were reviewed. Patients
with patellar fractures were cross-referenced with a prospective arthroplasty
database at the institution and 51% patients alive at time of follow-up were
able to be contacted by phone to confirm their post-operative course. The
relationship between demographic features and the requirement for later
TKR was assessed.

5.2.1 Management Protocol

Management of all patellar fractures was TBW with supplementary bone
graft, cerclage wiring, partial patellectomy, cannulated screws and tendon
repair at the surgeon’s discretion. The definitive treatment was overseen by
trauma consultants, performed by consultants, registrars and fellows. The
post operative rehabilitation was determined by the operating surgeon and
varied between cylinder casting and hinged knee braces for 6 weeks on
average, with postoperative physiotherapy. The most common regimen was
fully weight-bearing with a hinged knee brace 0-30 for 2 weeks, 0-60 for 2
weeks, 0-90 for 2 weeks and then unrestricted for 4 weeks, discontinuing
brace at 10 weeks.

5.2.2 Follow-Up

The mean duration of follow-up was 12.5 years (range 5-20 years). Patients
were divided into over and under 60 years old for PROMs follow-up. Patients
over 60 years old were reviewed by phone assessment at a minimum of five
years and a mean of thirteen years after injury. Patients under 60 years old
were reviewed at a minimum of five years and a mean of 11 years after injury
(Figure 5.1). The ease of follow-up in the two groups differed markedly due to
the mobility of a younger population including adolescents and students. The
PROMs used comprised three validated and reliable outcome instruments: EQ-5D, OKS and KOOS in under 60 year olds. Those that could not be contacted by phone were contacted by post as well.

Figure 5.1: Flow Diagram to show patient reported outcome follow-up for patellar fractures divided by age at time of injury.

5.2.3 Statistical Analysis

Statistical analysis was performed using SPSS Statistical Package for Social Sciences version 21.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism version 8.1.0. Continuous data were presented as mean and St Dev. Categorical data were presented as frequencies and percentages. Incidence was presented as fractures/100,000/year. Age was normally distributed for patellar fractures (skewness and kurtosis) therefore an independent t test for unpaired data was performed to compare age at time of fracture in the total population compared to those who developed PTOA and OKS. The categorical nominal outcome variables of complications, further surgery and development of PTOA and the categorical predictor variables of gender, fracture classification mechanism of injury and open injury, were compared using the Pearson’s chi-square test. Pearson’s chi square test was also used to compare responders and non-responders for PROMs with the categorical predictor variables. To assess any association between age and PROMs response and between OKS, complications, ROMW and PTOA the independent t test for unpaired data was used. The independent t test was
also used to compare the KOOS domains between populations. The Spearman's correlation coefficient was used to assess correlation between non-parametric ranked data, OKS and age. A \( p \) value of <0.05 was considered to be statistically significant.

5.3 Results

5.3.1 Early complications

Post-operative complications were seen in 62% of cases (163 fractures). There were metalwork complications including prominence and pain in 123 patients (47%). Infection complicated 24 cases (9%), two thirds of these required ROMW to clear the infection, two underwent debridement and the remainder were treated with antibiotics only. The fixation failed in seven cases (3%) and two patients sustained a further fracture. Non-union occurred in one case, patella instability was reported after one fracture and one patient suffered a neurapraxia post-operatively. Medical complications included one pulmonary embolism, one deep vein thrombosis.

Younger patients were statistically more likely to have complications \( (p=0.0142) \). The average age of patients with complications after operatively-managed patellar fractures was 48.7 years old compared to 53.9 years old for all operatively-managed patellar fractures. There was no association between post-operative complications and gender \( (p=0.3200) \), fracture classification \( (p=0.5928) \), MOI \( (p=0.4318) \) and open injuries \( (p=1.00) \).

Complications affected over 60% of patients treated operatively for patellar fractures and were more likely to occur in the younger age groups.

5.3.2 Further surgery

Further surgery was required in 135 fractures (52%) for stiffness, pain, infection and failed fixation. One case required manipulation under anaesthetic for stiffness and 14 cases were revised (5%). Almost half the
patients (128 cases, 48%) required removal of metalwork (ROMW) for pain or prominence (108), infection (15), failure of fixation (3) or refracture (2). Patellectomy was required in three cases, the same number required debridement. The age at injury was statistically significantly lower at 46 years compared to 54 years ($p=0.0005$) in the patients that underwent further surgery. Gender ($p=0.2038$) fracture classification ($p=0.3042$) and open injury ($p=0.7031$) showed no association with need for further surgery. Mechanism of injury and need for further surgery did not reach statistical significance at ($p=0.0895$) but suggested RTA and sporting injuries led to further surgery compared to falls. Half of all operatively treated patients required removal of TBW for pain or prominence and young patients required further surgery more often.

5.3.3 Post-traumatic osteoarthritis

Symptomatic PTOA defined as pain or stiffness attributable to PTOA was seen after 24 of the 264 fractures (9%). There was no statistical difference between the age of patients developing symptomatic PTOA (49.7 years) and all operatively-managed patellar fracture patients (53.6 years) ($p=0.362$). No baseline characteristics were predictive for symptomatic PTOA; gender ($p=0.8326$), fracture classification ($p=0.6624$) mechanism of injury ($p=0.7325$) or open/closed injury ($p=0.2345$). There was no statistical significance between patients that suffered postoperative infection and later development of PTOA ($p=1.000$) but patients requiring further surgery were more likely to develop PTOA than those who did not ($p=0.0097$).

Patellectomy was performed in one case for chronic knee pain. Three patients required arthroplasty surgery (1.1%). TKR was performed in two cases, at 22 months and 121 months, with a further case listed for theatre 54 months post fracture but developed a life-threatening condition preventing surgical intervention. The ages of patients that required arthroplasty surgery were 58, 66 and 71 years at the time of injury. All three fractures were
caused by simple falls, one male right sided and the other two female, one left and one right sided. Due to the small numbers that required conversion to arthroplasty statistical tests were inappropriate.

5.3.4 Patient reported outcomes in the over 60 year olds

There were 127 patients in the study cohort with a mean age at injury of 73 years (60-88 years old) and 72% were female. Falls from standing were the cause of 84% of the patellar fractures in the elderly and only 4% were open injuries. Three quarters (76%) of patients had significant comorbidities. The complications included 11 cases of post-operative infection (9%), seven of whom required removal of metalwork. Metalwork removal for discomfort was performed in 33 other patients (26%) and symptomatic PTOA was seen in nine patients (7%).

Figure 5.1 shows the breakdown of follow-up. 54 (43%) patients had died at time of follow-up, 6 were uncontactable and 4 unwilling to participate in the study. Functional follow-up was therefore available for 63 patients (86% of the alive population). There were no significant differences between responders and non-responders in relation to gender ($p=0.6891$), fracture classification ($p=0.2243$) and open injuries ($p=1.00$).

Only 13% of the cohort were still working at the time of injury and 50% of these were able to return to work. Almost half (49%) of the patients were regularly playing sport at the time of injury and 52% continued. The mean OKS was 39 indicating mild problems and the average EQ-5D 3L score was 0.79, similar to the UK mean for over 65 years of age, 0.78$^{(263)}$. There was no significant difference in OKS with gender ($p=0.65$). Complications ($p=0.4658$), removal of metalwork ($p=0.631$) and PTOA ($p=0.1503$) did not statistically alter the long-term outcome measured with OKS.
5.3.5 Patient reported outcomes in the under 60 year olds

There were 137 patients in the study cohort with a mean age at injury of 36 years (15-59 years old) and 28% were female. 31% were caused by a fall from standing. 13% were open injuries.

There were 13 cases of post-operative infection (9%), seven of these required removal of metalwork (54%), 80 other patients (58%) underwent metalwork removal for discomfort. Symptomatic PTOA was seen in 15 patients (11%).

Figure 5.1 showed the breakdown of follow-up. 14 (10%) patients had died at time of follow-up and 87 were uncontactable. The high proportion of patients that were uncontactable is common for this age group who are geographically mobile, particularly students, but does reduce the strength of the data. Functional follow-up was therefore available for 36 patients (29% of the alive population). There were no significant differences between responders and non-responders in terms of gender ($p=0.1249$), fracture classification ($p=0.6767$) and open injuries ($p=0.195$). Responders were significantly older at 37 years old compared to 30 years old in non-responders ($p=0.003$). There was, however, no association between age and OKS ($p=0.355$). The mean OKS was 38.4 indicating mild problems$^{262}$ and the average EQ-5D 3L score was 0.84, similar to the UK mean, 0.86.$^{263}$

There was no significant difference in OKS with gender ($p=0.07$). Complications ($p=0.4294$), removal of metalwork ($p=0.4294$) and PTOA ($p=0.09$) did not statistically alter the long-term outcome (measured by OKS). The KOOS scores for under 60 year olds were compared to population data for 18-55 year olds$^{289}$ and showed significant differences after operatively-managed patellar fractures in symptoms ($p=0.0041$), activities of daily living ($p=0.0416$), however neither were clinically significant as the difference was less than the quoted minimal detectable clinical difference (MDCD) (Table 5.1). There was a statistically and clinically significant difference seen in the sports and recreation ($p=0.0025$) and quality of life ($p=0.0037$) domains. No significant difference was seen in pain scores ($p=0.12$).
Table 5.1: Knee Injury and Osteoarthritis Outcome Score after operatively-managed patellar fractures in the current study compared to population data\(^{289}\). Differences less than the minimal detectable clinical difference are shown in red and in green.

The majority of the follow-up cohort were able to return to work after injury, 86% (25 patients), although 20% of these had to change occupation (5 patients). Most (69%) of the patients were able to return to playing sport after the injury but the mean time it took to return to sport was 18 months (range 6-72 months). A comparison of patients over and under 60 years of age is shown in Table 5.2.

Table 5.2: Comparison between patient reported outcome data for operatively-managed patellar fracture patients over and under 60 years of age
5.4 Discussion

Patellar fractures were associated with a high rate of complications and further surgery. Young patients were more likely to suffer complications post-operatively and require further surgery. Fewer than 10% of patients developed symptomatic PTOA and only 1% required arthroplasty surgery secondary to this. The patient-reported outcomes showed despite the high rate of complications, patients only had mild knee problems and a general health score similar to the UK population.

5.4.1 Complications

Almost two thirds of patients who underwent TBW for patellar fracture in this series had post-operative complications. Almost half of the patients required removal of metalwork. The numbers are higher than often quoted to patients in the author’s institution and maybe due to the length of follow-up including late complications. Removal of metalwork has been quoted as 37% in a study that used modern techniques but the follow-up was limited to one year\(^{290}\) and 52% ROMW at 6.5 years\(^{158}\). Our infection rate (9%) is similar to the range in the literature of 3-10%\(^{4, 158, 291, 292}\). Only one case of non-union was seen which is lower than previous studies\(^{281, 293, 294}\). The only statistically significant association identified was younger patients with complications where there was a five-year difference between patients that suffered from complications and the overall population. This difference maybe due to the higher demand placed on the knee in a younger population and therefore metalwork problems.

The need for further surgery, unsurprisingly echoed the complication data with 52% of patients requiring further surgery, 48% for removal of metalwork. The association seen with younger patients was repeated and there was a suggestion of a link with higher energy injuries (RTA) but this did not reach statistical significance (section 5.3.2).
The study does not suggest any factors that predispose to complications and further surgery other than the younger age group and therefore suggests that younger patients should be counseled regarding the high risks of complications and further surgery.

### 5.4.2 Post-traumatic Osteoarthritis and Total Knee Replacement

Symptomatic PTOA was seen in 9% of patients after operatively-managed patellar fractures. The literature on PTOA is varied mainly due to the method of diagnosing PTOA. Higher rates of PTOA are seen in papers that look at radiographic findings. Sperner et al. (1990)\(^{(295)}\) showed 78% PTOA 7.5 years after injury in a small patient group and suggested PTOA was inevitable despite appropriate management, disputing the previous work of Sorensen (1964)\(^{(156)}\) and Bostrom (1972)\(^{(4)}\) who suggested a greater than 1mm step in the articular surface would lead to PTOA. A slightly larger patient cohort using CT and XR criteria showed 53.4% PTOA as early as four years post injury\(^{(296)}\). A recent study by Vedel et al. (2018)\(^{(297)}\) showed 43% of patients had no signs of patellofemoral OA on radiographs using the Sperner classification\(^{(295)}\), at the time of injury and only 10% had no signs 8.5 years post injury. However looking at symptomatic OA Mehdi et al. (1991) reported 8.5% in operatively-managed patellar fractures\(^{(298)}\) agreeing with the current study (9%).

The follow-up in our study was on average 12.5 years (range 5 – 20 years), so whilst some of our study population may still develop symptomatic PTOA, the majority of cases have probably been identified. Two recent studies have looked at the rate of arthroplasty for PTOA after patellar fracture\(^{(287,288)}\). The larger study\(^{(287)}\), looked at 6096 patients using registry data followed up for a mean of 14.3 years (0 - 20 years). They found the highest increase in need for arthroplasty surgery was in the first five years, agreeing with the author’s opinion that the current study follow-up time should include the majority of cases. They found a hazard ratio of 1.83 for TKR after patellar fracture. They included all patellar fractures not just
operatively-managed with TBW and as it was using registry data only the side of fracture and arthroplasty could not be known, the numbers could be an overestimate. Arthroplasty carried out in the private sector would not have been included (pre 2003 when it became compulsory to register private operations), although that could be the case in the current study as patients were contacted for PROMs questionnaires the unknown number was minimised. The other advantage the current study has over Larsen et al. (2018) registry data study\textsuperscript{(287)} is the classification, treatment method, surgical indication and outcome data, which was not available to them. The average age of their cohort was slightly younger at 50.6 years and also had 49% females. The total number of TKR for PTOA after patellar fracture was 3.3% compared to 2% of their general population. This was three times the rate amongst the study population in the current study who required TKR (1%). Houdek et al.\textsuperscript{(288)} showed 0.5% of all TKR performed in their population were secondary to patellar fracture and found worse outcomes of arthroplasty but equal survivorship, 86% at 15 years. The worse outcomes were mainly secondary to reduced range of movement. Knee movement after TKR has been reported as correlating with pre operative motion\textsuperscript{(299)} and as decreased range of movement is the most common complication following patellar fracture\textsuperscript{(300)}, it follow that the outcomes are worse than the general population. Interestingly only 36% of these patients underwent operatively-management for the patellar fractures which may explain the higher number of arthroplasty cases seen in the Larsen et al. (2018) study\textsuperscript{(287)}.

The rate of PTOA was low with fewer than 10% of patients reporting symptoms and only 1% requiring arthroplasty surgery. As TKRs have equal survivorship post patellar fracture but worse outcomes there may be a bias by surgeons to avoid performing them therefore the numbers requiring arthroplasty surgery may be slightly higher than those who underwent TKR.
5.4.3 Patient Reported Outcome Measures

Vedel et al. (2018)(296) looked at PROMs 8.5 years after injury from a cross sectional cohort study including all adults with patellar fractures. The average age of patient was equivalent to the current study at 53.9 years and they reported on 49 patients using EQ5D and KOOS. They used the five limb EQ5D (5L) rather than the three limb EQ5D used in the current study and got a lower index value 0.741 over the whole population. The groups are unfortunately not comparable due to the different versions of EQ5D but could be explained by the inclusion of non-operative patients. They also reported statistically decreased KOOS in all five domains. The trends of the scores were similar to those reported in the current study (Table 5.1). Sports and recreation showed the greatest decline with pain, symptoms and activity of daily living suffering the least. No link was shown between radiographic OA and PROMs but they excluded those who went on to have TKR (9.3%) as they could not assess OA, this was a limitation of the outcome study.

Eggink(301) reported EQ5D 3L for 40 operatively-managed patients with five-year follow-up and the score was more comparable with the current study at 0.83.

Le Brun et al. (158) used 36 item Short Form (SF36) questionnaire rather than EQ5D as a general health outcome questionnaire reporting reduced scores compared to the referenced norms in patients after operatively-managed patellar fractures. The study included 241 fractures and followed up 36% at a mean of 6.5 years. The operative management included cannulated screws and partial patellectomy rather than just TBW. They concluded significant symptomatic complaints and functional deficits persist after operatively managed patellar fractures, which is stronger than the mild reduction in OKS seen in the current study. The KOOS from this population was lower in all 5 domains than the scores seen in the current study (KOOS pain 71.7, symptoms 66.3, ADL 75.1, sport/rec 45.2 and QOL 49.6)(158). The poorer outcomes maybe explained by the younger age at injury (46.3 years) and higher proportion of open fractures (28%) seen. The OKS has not been
reported in these studies, it has a ceiling effect, which was why the current study used KOOS in the younger patient group as well as OKS to try to account for it. In the current study 14% of the respondents scored 100% in OKS rising to 19% in the under 60s age group. KOOS is a validated, well-designed questionnaire to look at post-traumatic knee injuries. LeBrun et al.\textsuperscript{(158)} had a higher rate of patients that were uncontactable or refused (63%) compared to the current study (49%) and only 36% participated in PROM follow-up after exclusion criteria, potentially reducing the generalizability of their findings.

Comparison of the over and under 60 year old outcome data (Table 5.2) showed equivalent EQ5D for their age group in the general population and only mild knee problems. The return to work difference of 86% under 60 and 50% over 60 could be explained by the proximity to retirement age influencing the decision to return to work. Return to sport was also lower in the older age group and this maybe due to poorer general muscle health and more rehabilitation requirements to get back to the sport or less enthusiasm to achieve this goal. The rate of infection and PTOA were similar in each group but over double the percentage of younger patients required ROMW compared to the over 60 year olds. This decision may have been influenced by the risk/benefit assessment of a further anaesthetic in the older age group or the lower demand nature of the elderly patients.

Overall PROMs data suggested good outcomes after operatively-managed patellar fractures with general health outcomes no different to the general population and only mild knee specific problems.
5.4.4 Limitations

This was an observational study so no conclusions can be made regarding causality. The large number of uncontactable patients from PROMs data is expected but must be recognized as a potential source of bias. The inclusion criteria of only operatively-managed patellar fractures limits the generalizability but allows the data to be used to consent and counsel patients who need TBW for patellar fracture.

5.4.5 Conclusions

Tension band wiring for patellar fractures in this population produced satisfactory long-term outcomes although half of patients required hardware removal. Half of those over 60 years old who were working or playing sport at the time of injury subsequently stopped but return to work and sport is better in the younger age group at 86% and 69% respectively. This information may allow us to inform patients better of the prognosis following this injury. To the author’s knowledge, this was the largest series of over 60 year olds in the literature with patient reported long-term outcomes of operative management of patellar fractures.
Section 6 - Bovine Joint Model

Aim: To study the response of chondrocytes to blunt trauma in the form of iatrogenic arthroscopic probe pressure and high energy impact and to investigate the influence of the irrigation fluid on cell death.

Research Questions:
   a) What is the effect of blunt trauma on cartilage?
   b) Is raising the osmolarity of the irrigation fluid prior to impact chondroprotective?

Hypothesis:
   Increasing the osmolarity of the irrigation fluid is chondroprotective.

6.1 Introduction

The bovine fetlock joint is an established animal model for cartilage research\(^67, 80, 183, 195, 199, 302\) using the fetlock joint from the forelimbs, the metacarpalpalangeal joint (MCPJ). In this study the fetlock joint from the hindlimbs, the metatarsalpalangeal (MTPJ) was used due to abattoir regulations. Awareness of the minor differences in articular geometry and cartilage thickness is required if comparisons are to be made between studies using the MCPJ and MTPJ. The fetlock joint cartilage is 0.5mm thick with the bovine MCPJ measuring slightly thicker than the MTPJ\(^303\). The MTPJs are a free, unlimited and readily available source of cartilage and are a similar size to a human knee joint. The condyle anatomy of the human knee joint is very different to the bovine MTPJ (Figure 6.1) and this must be recognised when trying to extrapolate any findings.
Blunt trauma in bovine cartilage was studied in two ways. The first, a simple model of blunt trauma using an arthroscopic probe and the second, a more complex model using a high-energy impact ram. Bovine tissue was used to improve understanding of the loading conditions before transferring to the valuable restricted supply of human tissue as discussed in Section 7.

6.1.1 Iatrogenic Arthroscopic Probe Damage

Arthroscopy is a commonly used procedure in orthopaedics(304), with knee arthroscopy used for both diagnostic and therapeutic purposes. It is generally considered a benign procedure with limited complications 1-8%(305). Dick et al.(306) reviewed nearly four thousand knee arthroscopies. They showed a very low complication rate, with no infection, some minor skin allergies to skin preparation and subcutaneous emphysema from gas insufflation (no longer used clinically). They noted cartilage injury caused by arthroscopic instruments was reported in 2% of cases. These ranged from small superficial scallops, to deep spines or channels, but they were only assessing macroscopically visible damage. They acknowledged this complication was more common during the surgeon’s learning curve and felt it was usually avoidable with experience. Klein et al.(304) agreed with Dick et al.(306) that occasionally articular cartilage is damaged during arthroscopy depending on the instruments used, describing track-like fissures, patch-like...
defects and subchondral bone damage. They used animal models (canine) to show a lack of healing at follow-up of six months, and the importance of iatrogenic injury to cartilage\(^{304}\).

The only study the author is aware of that used arthroscopic probes was by Bae et al.\(^{173}\), in a paper that looked at indentation testing. The study investigated probe design and an indentation protocol for assessing cartilage, using the arthroscopic probe to test the cartilage in a non-clinical manner. They used ex vivo osteochondral blocks and repetitive axial pressure with a mechanical tester. They showed the rate of compression during the loading cycles influenced the cell death and as the magnitude of compression increased the cell viability decreased. It did not assess damage to the cartilage by using the probe in a clinical setting in a whole joint but did show chondrocyte death at the tip of the probe after repetitive axial pressure (Figure 6.2).

In the present study, a single pass of an arthroscopic probe across the articular cartilage to replicate the clinical scenario was used to study iatrogenic blunt trauma with a probe. The model was a whole joint from a large animal equivalent in size to the human knee was used rather than osteochondral blocks to improve the clinical relevance.

Figure 6.2: CLSM image adapted from Bae et al.\(^{173}\) showing chondrocyte death (red cells) after repetitive axial arthroscopic probe indentation testing.
6.1.2 Irrigation Fluid Osmolarity

During articular surgery the synovial fluid is drained from the joint and replaced by an irrigation solution such as normal saline. Normal saline is non-physiological and elutes proteoglycans from cartilage. Reagan suggests it also suppresses proteoglycan synthesis. Normal human synovial fluid is approximately 400 mOsm with the osmolarity decreasing in pathologies like osteoarthritis and rheumatoid arthritis to 297 and 280 mOsm respectively. Normal saline has an osmolarity of 285 mOsm, so chondrocytes may experience a marked decrease in extracellular osmolarity during the surgical procedure. The cells are osmotically sensitive and respond with a reciprocal change in cell volume. Some groups have suggested hypo-osmolar solutions are associated with degenerative changes because of the lower synovial fluid osmolarity seen in arthritides. Synovial osmolarity could affect the biomechanical properties of articular cartilage, which could cause or inhibit degenerative effects. Ringer’s solution and normal saline have been shown to affect human articular cartilage including reducing metabolism but the longer term effects of the irrigating solution on human articular cartilage remains to be determined. Other studies have shown changing the osmolarity of the irrigating solution can reduce chondrocyte death at injury and have proposed that arthroscopic irrigating fluid could be used for chondroprotection.

Several groups have investigated hyperosmolar solutions as chondroprotective agents. Bush et al. used a single impact drop tower on bovine articular cartilage and showed hyperosmolarity protected the chondrocytes. Amin et al. used osteochondral explants harvested from bovine MCPJs and exposed the explants to media of various osmolarity.

6Osmolarity is a measure of solution concentration defined as the number of solute particles (osmoles) per litre of solution. Osmolality is also a measure of solution concentration but as osmoles per kilogram. The osmolarity and osmolality measurements are very similar because the solution concentrations are low (<500 mM); the mass of the solute is negligible compared to the mass of the solvent.
before inflicting a full thickness wound to the articular cartilage with a scalpel. All samples were then placed in the same media for 2.5 hours before being transferred to a culture medium for 7 days. They used CLSM to compare the spatial distribution, percentage cell death and marginal cell death at the wounded edge, as a function of osmolarity and time. They also showed increased cell death with lower osmolarity. No significant change in percentage cell death was seen over time, suggesting exposure to a high medium osmolarity does not compromise in situ chondrocytes function over this time period\(^{(199)}\). They concluded a high osmolarity was chondroprotective in bovine tissue\(^{(67)}\). The group extended this work to a human model, using tissue from knee arthroplasty surgery, showing a six-fold decrease in chondrocyte death in the superficial zone when exposed to 0.9% saline 600mOsm compared to 0.9% saline 285mOsm. The increase in osmolarity was achieved by the addition of sucrose\(^{(189)}\).

One explanation given for the decreased chondrocyte damage at a higher osmolarity is the shrinkage of the cells making them less likely to be directly injured by the scalpel blade\(^{(80,189)}\). Another hypothesis is that disruption of the ECM is intricately linked to chondrocyte death following mechanical injury\(^{(302)}\). At low osmolarity wounded cartilage takes in fluid at the damaged surface, reducing extracellular osmolarity and causing unrestricted swelling of the chondrocytes due to the lack of an intact collagen network. This swelling could lead to cell lysis\(^{(67, 80)}\). This hypothesis is supported by the fact cell death is localised around the fracture in articular cartilage but not in impacted areas without cracks\(^{(185)}\).

The unintentional damage caused by relatively benign surgery and surgical instrumentation should be a concern for patients and surgeons. The knowledge that chondroprotection was achieved in bovine tissue with sharp injury\(^{(67)}\) encouraged this research in intraoperative blunt trauma. This study investigated the osmotic protection to chondrocytes in a bovine model after mild and high-energy blunt trauma.
6.1.3 High Energy Transarticular Compression Impact Ram

Various models of blunt impact to cartilage have been developed to try to model blunt injury in humans. These start with small cartilage explants (5-6mm) taken from dogs, pigs, cows and humans\(^\text{316, 317, 318}\) and hydraulic impact systems used. These explants allow very controlled experiments to be performed but lack the clinical relevance of using the tissue as a whole. The next level is the osteochondral specimens taken from horses, pigs, cows and humans\(^\text{85, 99, 185, 319}\). These require different impact systems including spring loaded\(^\text{319}\), compression chambers\(^\text{99}\), drop towers\(^\text{85}\) and load frames\(^\text{185}\). The osteochondral explants allow the model to include the subchondral bone but remove the explants from the rest of the articular cartilage and the joint itself. The next level of models includes the whole joint (rat, mouse, pig and human) and use drop towers\(^\text{106, 109, 188, 320, 321, 322}\). The drop towers mostly had impact interfaces larger than the joint to produce an even impact on the specimen however the mouse model used by Olsen’s group used a wedge shaped indenter\(^\text{109, 321}\). Tochigi et al. used a porcine and then human model with their drop tower, showing it was possible to create articular fractures with an impaction technique in large animals\(^\text{106, 322}\). The present study also aimed to create an intra-articular fracture in a whole joint large animal model, bovine, using an impact ram rather than a drop tower to then investigate irrigation fluid in high energy impact damage.

6.1.4 Why investigate blunt trauma?

Blunt trauma to the knee has been recognised as a possible cause of PTOA in a variety of studies. In a fracture study by Honkonen it was suggested that blunt trauma without cushioning of menisci can lead to degenerative changes\(^\text{28}\). Wilder et al. in a retrospective study found a knee injury increased the risk of developing OA seven fold compared to individuals that had not sustained a knee injury\(^\text{323}\). Gelber et al. conducted a prospective study using medical students followed up for up to 36 years. 141 injuries
were reported and 14% of participants who suffered an injury later developed 
osteoarthritis compared with 6% of those not reporting injury\cite{11}. In the 
present study the two ends of the spectrum of clinically relevant trauma were 
investigated in the large animal model before transferring to the human 
tissue model (Section 7).

### 6.2 Methods and Materials

#### 6.2.1 Biochemicals and solutions

Biochemicals, including fluorescent indicators 5-chloromethylfluorescein-
diacetate (CMFDA) and propidium iodide (PI), were obtained from Invitrogen 
Ltd. (Paisley, UK) unless otherwise stated. Dulbecco’s Modified Eagle’s 
Medium (DMEM) with N-2-hydroxyethylpiperazine-N’-2- ethanesulphonic 
acid at 25mM and pH 7.4 with antibiotics (Penicillin 50 U/mL and 
Streptomycin 50 µg/mL) was used for osteochondral explant culture. Normal 
Saline (0.9% w/v) was obtained from Baxter Healthcare Ltd (Thetford, UK). 
The osmolarity was measured at 285mOsm. Hyperosmolar solution was 
prepared by adding a measured amount of sucrose\cite{189} to increase the 
osmolarity to 600mOsm. Hypoosmolar solution was prepared by adding 
distilled water to normal saline to decrease the osmolarity to 150mOsm. The 
solutions’ osmolarity were measured with a freezing point osmometer 
(Advanced Micro Osmometer, Model 3300; Vitech Scientific Ltd, Horsham, 
UK). Para-formaldehyde (4% v/v in saline; pH 7.3) from Fisher Scientific 
(Loughborough, UK).

#### 6.2.2 Bovine model and osteochondral explants

Metatarsophalangeal joints of 3-year-old cows from a local abattoir were 
washed, skinned and de-hoofed within 24 hours of slaughter (Figure 6.3).
For the arthroscopic probe experiments the joints were carefully dissected to allow access to the articular cartilage, to allow the cartilage to be subjected to the intervention. For the impact ram experiments, the whole joint was left intact and dissected after the intervention. The joints were carefully assessed and if there was any evidence of macroscopic cartilage degeneration they were not studied further.

After the intervention was performed osteochondral strips with full thickness articular cartilage attached to 1-2mm of subchondral bone were harvested from the joint using a scalpel (Figure 6.4). The explants were not handled further. The strips were tipped into DMEM solution (37°C; 5% CO2; pH 7.4) (Figure 6.5).
6.2.3 Study Interventions

The model was developed to be more clinically relevant using a standard surgical arthroscopic probe (Arthrex hook probe 3.4mm tip with 5mm markings (AR-10010)) (Figure 6.6). The probe was pulled across the metatarsal articular cartilage by hand with a single pass at different subjective manual pressures, soft (light touch), moderate (standard pressure for probe use in arthroscopy) and heavy (deliberate downwards pressure).
Figure 6.6: Arthroscopic Probe used for the surgically relevant mild blunt trauma to the articular cartilage. Image from Arthrex.com

Use of the handheld probe was modeled to mimic the clinical situation but a motorised model was then developed to try to standardise the pressure exerted on the cartilage by the probe and create a more reproducible model. The motorised set-up (Figure 6.7) allowed the articular surface to be passed under the probe at a standard moderate pressure. This was compared to the moderate handheld pressure. The probe remained static due to the available motor set-up; this still allowed an anteroposterior cartilage pressure, consistent with the clinically relevant hand-held model.

Figure 6.7: Standardised Probe Pressure Motorised Set-Up. The metatarsal was held in the clamp with articular surface presented to the static arthroscopic probe. The clamp was attached to motor to allow movement of the articular cartilage under the probe at a standardised pressure.

For impact studies a pneumatic actuator (100mm bore ram, PRA/182000, Norgren Pneumatics, Staffordshire, UK) was used with intact joints held fixed and the pneumatic ram set at various pressures (0-10 Bar) (Figure 6.8)
6.2.4 Osmolarity Studies

To study the osmolarity of bovine MTPJ synovial fluid, the joint was aspirated after the limb was prepared (Figure 6.3) with a sterile needle and aseptic technique. The synovial fluid collected was placed in Falcon tubes at room temperature and measured using an osmometer, after the intervention to the cartilage had occurred (approx. 30 minutes).

A comparison was then made between arthroscopic probe damage to cartilage when exposed to normal saline (285mOsm) instead of its own synovial fluid. The metatarsal cartilage was immersed in normal saline for ten minutes at room temperature prior to exerting the moderate hand held probe pressure. Care was taken to avoid any physical contact with the
articulate surface when immersing the joint in the fluid. Chondroprotection by hyperosmolar irrigating solution was investigated for arthroscopic probe damage in the same manner, using hyperosmolar saline (600mOsm) instead of normal saline.

For the high-energy impact experiment, the osmolarity study used hypoosmolar (150mOsm), normal (285mOsm) and hyperosmolar (600mOsm) saline. The synovial fluid from the joints was aspirated as above and the joint injected with normal saline using a 50 ml syringe at room temperature, whilst leaving the joint whole. The solution was left in the joint at room temperature and the joint impacted ten minutes after injection.

6.2.5 Fluorescent labelling of *in situ* chondrocytes, cell viability assay and fixation

CMFDA and PI were used to assess the extent of *in situ* chondrocyte death around the blunt trauma in articular cartilage. CMFDA is membrane-permeable, and once inside intact cells, reacts with intracellular components to produce an intense green fluorescence, indicating a viable living cell. PI is impermeable, only binding to DNA if the plasma membrane is disrupted producing a red fluorescence and indicating dead cells. The use of these fluorescent dyes to label the cells is a well recognised quantifiable method of distinguishing live and dead cells. The method has its limitations as dying cells may retain the membrane integrity for some time after injury meaning PI is not able to bind to the DNA and CMFDA reacting with the intracellular components suggests the cell is still living. This standard method of assessing cell viability may tend to overestimate live cells. The author recognises the limitations but for the purposes of the study CMFDA (green) stained cells will be defined as living and PI (red) stained cells will be defined as dead.

Osteochondral explants were incubated in DMEM containing CMFDA (10µM) and PI (10µM) (60min; 37°C). Osteochondral explants were rinsed in fresh DMEM and immersed in para-formaldehyde (4% v/v; 30min; 21°C) for tissue
fixation. Samples were then rinsed and finally immersed in phosphate buffered saline (PBS), and visualised by CLSM, within 24 hours.

6.2.6 Confocal Laser Scanning Microscopy

An upright Zeiss Axioskop LSM 510 (Carl Zeiss Ltd, Welwyn Garden City, UK) with low power dry x5 and x10 Plan Neofluar objective lens was used to image in situ chondrocytes on cartilage explants. Excitation of CMFDA and PI was achieved utilising Argon (EX\(_\lambda\) = 488 nm) and Helium-Neon (EX\(_\lambda\) = 543nm) lasers respectively. Upon excitation, CMFDA emits light at EM\(_\lambda\) = 520nm (green) and PI emits light at EM\(_\lambda\) = 600nm (red) which were captured using 500-550nm band pass and >560nm long-pass filters respectively\(^{(67)}\). After optimising image quality, sequential axial optical sections were taken starting from the cartilage surface at intervals of 10 µm in the z-axis to typically 50 µm. The images therefore primarily represent chondrocytes within the superficial zone of cartilage.

6.2.7 Quantification of cell death

The consecutive series of optical sections acquired during CLSM were overlaid using imaging software ImageJ\(^{(326)}\) to create reconstructions from the stacks produced by the CLSM that represent the imaged cartilage volume. The percentage of cell death was measured within 3-D regions of interest on axial projections. To allow analysis, a region of interest was placed surrounding the zone of chondrocyte death from the CLSM reconstructions typically measuring 1843µm\(^2\), overlaid away from the live/dead cell cut edge border. The reconstruction was approximately 100µm depth allowing imaging of the superficial zone. ImageJ was used for each CLSM reconstruction. The area of the individual cells (green) and nuclei (red) were each measured twenty times from different explants. A range was then identified and set to exclude background noise from the count. This meant clumps of cells (too big) and artifact specks (too small) were identified. The range for cells was 64-400µm\(^2\) and for nuclei 10-100µm\(^2\). The colour intensity
threshold was set using a histogram of measured values for all cells identified, with minor adjustments to account for variations in dye uptake and background noise between images. Computerised live/dead cell counts were performed (Figure 6.9). This technique was checked against a visual assessment of the images for accuracy. Percentage cell death (number of dead cells/ (number of dead + number of live cells) x 100) was calculated based on a large number of cells (700-3000 chondrocytes) counted from each explant in the region of interest (typically 1843µm²). A second measurement of the width of cell death was collected for the arthroscopic probe pressure interventions, by measuring the greatest width of the band of cell death from each CLSM reconstruction, using a calibration bar available in ImageJ.

Figure 6.9: Screenshot of the Image J process of quantifying cell death from a CLSM reconstruction. The orange arrow shows the reconstruction of the region of interest with the red ‘dead’ cells shown. The red arrow shows the histogram to fine tune the colour intensity threshold to count the cells. The yellow arrow show the cells counted by the software and the results window shows the area of each cell (nucleus) counted. The blue line shows the width of the band of cell death.
6.2.8 Statistical analysis

Data are presented as means and standard deviation (St Dev), with 95% confidence interval (CI) error bars shown in the graphs. ‘n’ is the number of explants and ‘N’ is the number of animals used. Statistical tests were performed using SPSS version 21. Paired, two-tailed, Student’s t-tests were used to compare observations between paired data set and ANOVA for multiple data sets. A significant difference was indicated when $p \leq 0.05$.

6.3 Results

6.3.1 Arthroscopic Probe Pressure

Pilot studies to describe the appropriate level of probe pressure to achieve cell death were performed (Figure 6.10). In each case a clear band of cell death was seen. The width of the bands of cell death was seen to increase as the pressures increased (Figure 6.11).
Figure 6.10: Reconstructed CLSM images of the region of interest showing red ‘dead’ nuclei and green ‘living’ cells after a single pass of the arthroscopic probe in a posterior to anterior direction over the bovine cartilage. A) Mild Pressure, B) Moderate Pressure, C) Severe Pressure.
Figure 6.11: The width of the band of cell death in bovine cartilage with increasing probe pressure, mild (N=3), moderate (N=6), and severe (N=3). The graph shows the 95% CI and the statistical significance using one-way ANOVA of the data.

The percentage cell death also increased with the increasing pressure from the arthroscopic probe (Figure 6.12).

The standardised moderate pressure model was developed to create a more reproducible model. It was compared with the hand held moderate probe pressure model both producing a mean of 23% cell death in the specific ROI and no significant difference was found (Figure 6.12). The moderate hand held pressure was then used for all further experiments to mimic the clinical scenario with the knowledge that it did not differ from the standardised model.
Figure 6.12: Percentage of cell death following different arthroscopic probe pressures on bovine cartilage. (Control N=4, Mild N=3, Moderate N=7, Standardised Moderate N=4, Severe N=3) The graph shows the 95% CI and the statistical significance using one-way ANOVA for all the data. An unpaired t test was used to compare the moderate hand held probe pressure and the standardised moderate probe pressure showing no significant difference.

Figure 6.13: The osmolarity of bovine MTPJ synovial fluid with 95% CI. Twenty synovial fluid samples were aspirated from four bovine MTPJs (A-D N=4, n=5) at room temperature and the osmolarity was measured within 30 minutes using an osmometer. The pooled osmolarity data with a mean of 303.8mOsm, St Dev=9.49 is shown.
6.3.2 Bovine Synovial Fluid Osmolarity

To investigate the effect of changing the osmolarity of the irrigation fluid, on chondrocyte death, the osmolarity of the bovine synovial fluid that bathes the cartilage was measured (Figure 6.13).

6.3.3 Arthroscopic Osmolarity Studies

The percentage of chondrocyte death was measured after immersion of the femoral condyles in the lower osmolarity normal saline solution was compared to the cell death seen when the cartilage remained bathed in its synovial fluid (Figure 6.14). The 20mOsm difference between the joint fluids showed a 5% difference in cell death. This difference was not statistically significant but may suggest a protective trend of synovial fluid.

A comparison was made between exposure of the cartilage to normal saline and hyperosmotic saline (600mOsm) prior to blunt injury with the arthroscopic probe. 5% cell death was seen after exposure to the increase osmolarity solution compared to 16% with normal saline (Figure 6.15). This was a statistically significant finding for chondroprotection with hyperosmolar solution in blunt trauma with an arthroscopic probe.
The Effect of Joint Fluid on Cell Death with Arthroscopic Probe Pressure

\[ n/s \quad p=0.47 \]

Joint Fluid

Figure 6.14: CLSM reconstructions A) Normal Saline (N=3) and B) Synovial Fluid (N=3) and a graph to show the percentage cell death with 95% CI after the bovine articular surface was exposed to normal saline at room temperature for ten minutes compared to in situ synovial fluid under the same conditions, was not statistically significant (unpaired t test). A non significant reduction in cell death was seen suggesting a possible protective nature of synovial fluid.
The Effect of Osmolarity on Cell Death after Arthroscopic Probe Pressure

\[ p = 0.0006 \]

![Graph showing cell death percentage with 95% CI decreased significantly (unpaired t test) after exposure to hyperosmolar saline (600mOsm, N=6) solution for ten minutes at room temperature prior to blunt trauma with an arthroscopic probe at clinically relevant moderate pressure, compared to normal saline (285mOsm). CLSM reconstructions of bovine cartilage exposed to A) Normal Saline and B) Hyperosmolar Saline prior to blunt trauma.]

### 6.3.4 Impact Study

Percentage cell death was measured immediately after trauma from different strength impacts from the high energy transarticular pneumatic actuator; 0, 4, 8 and 10 bar. The cell death ranged from 1% in the control group to 7% with the highest energy impact achieved in this model (10 bar/1MPa) (Figure 6.16). The highest energy impact was used for the osmolarity studies.
6.3.5 Impact Osmolarity Study

To investigate whether the chondroprotection of hyperosmolar saline seen in blunt trauma from the probe was also seen in high energy trauma to the whole joint, the percentage cell death was measured following blunt impact (10 bar) after exposure to different osmolarity solutions for ten minutes at room temperature. The hypoosmolar solution was used as the percentage cell death measured with synovial fluid was less than the arthroscopic probe damage, with the hypothesis that cell death would increase with reduced osmolarity. There was a trend to lower cell death with higher osmolarity and when comparing hypoosmolarity (150mOsm) and hyperosmolarity (600mOsm) there was a statistically significant decrease in cell death (Figure 6.17).
The Effect of Osmolarity on Cell Death after Impact

![Graph showing the effect of osmolarity on cell death](image)

* * 

Figure 6.17: Changing the osmolarity of the solution the cartilage is exposed to prior to blunt high energy impact shows a trend to decreased cell death with increasing osmolarity. (150 mOsm N=3, 285 mOsm N=3, 600 mOsm N=4) The data for normal saline has very wide 95% CI and a one-way ANOVA showed no statistically significant difference between the different solutions. An unpaired t test was used to compare hypoosmolar and hyperosmolar saline showing a statistically significant difference.

6.4 Discussion

The aim was to study the response of chondrocytes to blunt trauma in two forms, arthroscopic probe pressure and high-energy impact and then to test the hypothesis that increasing the osmolarity of the irrigation fluid is chondroprotective.

6.4.1 Discussion of the Methodology

6.4.1.1 Model

Use of the cadaveric bovine joint model, from animals that had died within hours, has been published previously^{67, 80, 183, 195, 199, 302}(Table 6.1). It is a large animal model that is freely available, cheap and a similar size to the
human knee joint. It is a cadaveric model so the tissue must be used as soon as possible, in the hours following death, to reduce any changes to the cartilage properties. There were a few differences in this study compared to others using the cadaveric bovine model. MTPJs were used rather than MCPJs but any differences in the cartilage between these joints did not affect the results presented, as all experiments in the study used the hindlimbs. This difference may be relevant when comparing the percentage of cell death seen between similar models. This study used the whole joint rather than osteochondral explants to try to mimic the clinical situation, keeping the influence of the subchondral bone(183) and the biomechanical properties of the joint influenced by the bony structure and soft tissues.

6.4.1.2 Explants

The explant process was similar to previous studies(67, 80, 183, 195, 199, 302) (Table 6.1) however the osteochondral explants were taken after the intervention had occurred as the whole joint model was used. The advantage of this technique was to allow the whole joint model with the explants taken to include the zone of injury rather than a certain distance from the cut edge(67, 195). The disadvantage to this process was that the explant was not guaranteed to include the blunt trauma. When the arthroscopic probe had been pulled across the cartilage, no visible damage was observed so the explant was taken from visual memory of where the trauma had occurred. To improve this technique for further work, a mark could be made and used as the start of the probe pressure, providing a visual clue for taking the osteochondral explant. The mark itself however, may cause cell death so the region of interest should start a certain distance from this mark. Identifying the region of interest was also difficult within the whole explant but using distance from a mark would allow to define a more reproducible area for the region of interest to be defined.
6.4.1.3 Cell Viability, Imaging and Quantification

The imaging technique using fluorescent labelling dyes and CLSM has also been published\(^{(67, 75, 80, 181, 183, 189, 195, 199, 302)}\) (Table 6.1). The standard way of assessing cell viability with fluorescent dyes may overestimate live cells, as discussed, a way of reducing this limitation would be using a parallel method of assessing cell viability for example MTT reduction assay that uses cell metabolic activity to assess viability. CLSM allows the chondrocytes to be imaged \textit{in situ}. The cell death analysis was concentrated on the superficial zone due to the high density of cells\(^{(173)}\) and the axial views. A clearer idea of the death in the deeper zones would be interesting but was beyond the scope of this study.

The quantification of cell death was different to the CLSM studies discussed\(^{(67, 75, 80, 181, 183, 189, 195, 199, 302)}\) (Table 6.1), as ImageJ was utilised. The software has been described for use in CLSM studies investigating chondrocytes\(^{(106, 326, 331, 332)}\). Bias was removed from the quantification process using the automated cell counting technique on ImageJ.

6.4.1.4 Comparison of study methodology

Several studies discussed in the methodology were similar to the current design. The main differences are outlined in Table 6.1. Both Amin et al.\(^{(67)}\) and Bush et al.\(^{(80)}\) added an antibiotic to the DMEM solution unlike the current study as prolonged incubation was required for part of the investigation. These two studies\(^{(67, 80)}\) also changed the osmotic environment of the cartilage explants using the addition of sodium chloride or distilled water to the DMEM solution. The current study did not include DMEM in the solution, using sodium chloride only to try to replicate the clinical environment where DMEM is not used.
The significant findings from this study were from the novel blunt trauma interventions used. To the knowledge of the author, the single pass of the arthroscopic probe in a whole joint model, as a clinically relevant mild blunt trauma to the articular cartilage, has not been investigated. Redman et al.\(^{(72)}\) described a difference in the matrix disruption between blunt and sharp trauma. The blunt trauma model used was a trephine compared with the sharp trauma produced by a scalpel blade. In the present study a trephine would be classified as a sharp injury as it has a blade to cut a hole during surgery.

The probe pressure used was hand held to attempt to replicate clinical use of the probe. Mild pressure would be equivalent of the probe touching the articular cartilage unintentionally during arthroscopy. Moderate pressure would be the standard pressure to test the articular cartilage integrity and for manipulating tissues in the joint. Severe pressure would be unusual but may occur accidentally during the procedure, especially during the learning curve of arthroscopies.

The standardised motor model developed for moderate pressure (Figure 6.12) showed no significant difference in percentage cell death compared to the handheld arthroscopic moderate pressure model. The disadvantage of the motor model is that the articular cartilage is moved under...
the probe not representing the clinical scenario as accurately, where the probe would be moved over the cartilage. The finding does however mean the handheld arthroscopic probe pressure is a replicable model, allowing progression to investigate chondroprotection and osmolarity.

The impact ram had previously been used to create fractures in limbs of sheep and the set-up was adapted to allow a transarticular impact to be delivered to a whole joint. The set-up did not create a fracture in the bovine joint and the ram did not allow a higher energy impact to be delivered, limiting the value of this model for intra-articular fractures. It did however allow investigation of a more severe form of blunt trauma, an impact and study of chondroprotection by hyperosmolar saline in this blunt trauma.

6.4.1.6 Osmolarity

The osmolarity of the saline was controlled by adding sucrose to normal saline for hyperosmolar saline. The disaccharide, sucrose, is impermeable across animal cell membranes maintaining the extracellular osmotic pressure gradient without changing the chondrocyte metabolism. Another method of increasing the osmolarity of normal saline is with the addition of sodium chloride, this increases the intracellular ion concentration affecting the cell metabolism. To allow the study to investigate the effect of changing osmolarity whilst keeping variables like ion concentration and chondrocyte metabolism constant, addition of sucrose was used. To produce hypoosmolar saline, distilled water was used, unavoidably reducing the sodium ion concentration.

The bovine model was felt by the author to be the best for this study other than human tissue and the methodology used allowed investigation of two blunt trauma interventions and the use of hyperosmolar solution for chondroprotection.
6.4.2 Discussion of the Results

6.4.2.1 Arthroscopic Probe Experiments

The most surprising finding in the bovine model was that mild blunt injury with moderate pressure from an arthroscopic probe causes significant cell death (23%, Figure 6.12), equivalent to the amount of cell death seen by drilling cartilage\(^{(162)}\). The cell death with severe probe pressure (38%) was similar to that seen in intra-articular fractures\(^{(173)}\). Whilst these studies are not directly comparable, due to the different methodologies and ROI, the amount of cell death in the ROI was surprising to the author as clinically the arthroscopic probe is generally felt to be benign and a mild blunt trauma to the cartilage by clinicians.

A clear band of cell death in the superficial zone seen following blunt trauma from the probe (Figure 6.10) is similar to that seen in sharp scalpel injury (Figure 6.18). The scalpel produced 13% cell death compared to 23% with moderate probe pressure, comparison limited by the ROI chosen in the studies. The percentage cell death is difficult to compare as Amin et al.\(^{(67)}\) used osteochondral explants from bovine MCPJs rather than the whole MTPJ and the cartilage was exposed to culture medium with an osmolarity of 340mOsm at 37°C, compared to synovial fluid (305mOsm) at room temperature. The percentage cell death was measured at a single time point which limited comparisons as the time points were not identical. Even with these limitations for comparison, blunt injury causing more acute cell death in a similar model to sharp injury was likely to be a significant finding. One possible explanation for the increased cell death with the probe compared to the scalpel is the wider area of cartilage in contact with the surgical instruments. There has also been a ‘progressive wave of cell death’ described by Bush et al.\(^{(196)}\) this suggests another possible explanation, where the blunt injury caused damage to the cells, which then released factors that damaged/killed neighbouring cells unlike the sharp trauma that caused focal cell death\(^{(196)}\).
The width of the band of cell death was seen to increase by 30% from moderate (468 µm) to severe (610 µm). The probe end is hemispherical and a wider contact area with the cartilage, with more severe pressure may have caused a wider band of cell death. The increase in percentage cell death with higher probe pressures (Figure 6.12) could also be explained by the larger area of cartilage touched by the probe or by the increased force disrupting the cartilage as seen with increasing loads in other blunt trauma models.\textsuperscript{160, 334}

The cell death seen after even mild pressure from an arthroscopic probe in bovine cartilage (Figure 6.12), if replicated in human articular cartilage, is worrying for surgeons. Previously the articular cartilage was thought to be most at risk when putting the obturator, camera sleeves and ports into the joint as these can cause macroscopic damage to the cartilage.\textsuperscript{335, 336, 337, 338, 339, 340} There is very little evidence in the literature regarding the incidence of iatrogenic damage to the articular surface during arthroscopy.\textsuperscript{340} Vega et al. showed iatrogenic cartilage damage in 31% of ankle arthroscopies.\textsuperscript{335} The amount of cell death in this study was seen a short duration after injury and may increase over time as seen with laser induced injury, increasing up to day 6.\textsuperscript{90} The arthroscopic probe is a commonly used surgical instrument and the findings could have widespread surgical implications. Awareness of the potentially substantial cell death caused will allow surgeons to modify their arthroscopic technique and
consider methods of chondroprotection such as changing the irrigation fluid to a formula with increased osmolarity.

Synovial fluid bathes the articular cartilage in the joint. The osmolarity of synovial fluid was measured to allow a comparison of cartilage damage seen with blunt trauma, when changing the irrigation fluids. The osmolarity value measured for the bovine synovial fluid is at a single time point, where the cartilage is not loaded. Synovial fluid is a complex fluid and osmolarity changes may occur in response to the physiological environment\(^{(309)}\). Although not studied extensively, osmolarity has been shown to change with exercise\(^{(309)}\) and pathologically with OA and rheumatoid arthritis (RA)\(^{(314)}\). The measurement in this study was taken from cadaveric tissue and the biological changes after death may also affect the osmolarity\(^{(341)}\).

*In situ* chondrocytes have been shown to be osmotically sensitive, changing cell volume with variations of osmolarity\(^{(302)}\). The water diffusion from cells in hyperosmotic solution reduces cell volume. This reduction in volume was a mechanism described for the chondroprotection seen with sharp trauma by Amin et al.\(^{(67)}\). The present study showed a statistically significant, three-fold reduction in cell death when the joint was exposed to hyperosmolar saline (600mOsm) compared to normal saline (285mOsm) (Figure 6.15). Different medium osmolarities were used in the sharp trauma study\(^{(67)}\) preventing comparison but showed decreasing cell death with increasing osmolarity from 0-480 mOsm, strengthening the evidence for chondroprotection with higher osmolarity fluid. The osmotic protection in bovine cartilage after blunt trauma has also been shown using a drop tower\(^{(195)}\), providing further corroborating evidence.

The mechanism for the chondroprotection provided by the hyperosmolarity may be the same for focal blunt trauma as in sharp injury\(^{(67)}\), with the reduction of cell volume meaning fewer individual chondrocytes are disrupted by the blunt trauma. An alternative explanation for the changes seen with changing osmolarity was suggested by Bush et al.\(^{(302)}\). They proposed that in a lower osmolarity environment cells swell, leaving the chondrocytes more vulnerable to injury\(^{(302)}\). The author’s opinion was that a
combination of these physical changes to the size of the chondrocytes in response to their osmotic environment contributed to the chondroprotection seen.

The arthroscopic probe pressure as a cause of blunt trauma is a replicable method and has clear clinical relevance if seen in human cartilage as well (Section 7), as it is a tool used in the majority of arthroscopic procedures. The experiments show 23% cell death in the specific ROI at a clinically relevant pressure and a three-fold chondroprotection effect with hyperosmolar saline.

6.4.2.2 Impact Ram Experiments

The impact ram model did not produce the energy necessary to cause a fracture but did allow investigation of cell death after impact without fracture. An impact study using bovine patella by Lewis et al.\(^{185}\) stated that cell death was only seen with impact if macroscopic cracks were seen. The study looked at impact with a 6mm impactor. A criticism of this paper may be that a ‘macroscopic’ crack was not clearly defined. The study methodology suggests that the matrix cracks were seen under microscope. The author believes the results do not contradict the ram findings as microscopic cracks may have been present but were not investigated even though no obvious macroscopic damage was seen. The cell death seen was much lower than the author expected given the nature of the high-energy blunt trauma. The impact ram caused 7% cell death in comparison to 1% in the control, where no impact occurred (Figure 6.16). A previous study however, using a porcine model showed minimal cell death following an axial impact with no fracture caused\(^{188}\). This was attributed to high stress threshold with a transarticular, axial, load in an intact joint.

The percentage of cell death was also small in comparison to that seen with the arthroscopic probe. In the focal damage of the arthroscopic probe the area of damage was the only part of the joint included. In the impact studies the whole joint was affected and only the explanted cartilage was analysed. If the whole joint was imaged in both scenarios the
percentage cell death is likely to be higher with the impact ram, where approximately 7% cell death in the specific ROI was seen in all eight explants taken from one joint (Figure 6.4), rather than 23% cell death seen in one focal area with the arthroscopic probe and presumably no damage more distant to the probe. In future work imaging the whole joint may improve the understanding of how impact trauma affects the articular cartilage as a whole. With normal saline wash out of the joint the cell death seen dropped from 7% with synovial fluid for a 10 bar impact to only 2%. Due to the small percentage cell death achieved it was difficult to assess the effect of changing the osmolarity.

When comparing exposure to 150mOsm solution with 600mOsm solution there was a statistically significant reduction in cell death from 3% to 1% (Figure 6.17). The variation of cell death seen for normal saline and the increased mean percentage cell death in Figure 6.17 is difficult to explain, but may be due to the small number of experiments performed. The small amount of cell death seen means significant differences were difficult to detect without a large number of experiments. Increased cell death may have occurred if a higher energy impact was achieved, as seen in other blunt trauma models. With increased baseline cell death, more of an effect with chondroprotection might have been seen allowing firm conclusions to be drawn. To try to account for this the ram set-up was altered in the human model (Section 7).

A limitation of the model was that the impact exerted on the MTPJs was the same and did not account for the changes in size of the joints used. The joints for impact experiment were done on a different day to the impact osmolarity experiments and the joints were collected from the abattoir the morning of the experiments. The difference in cell death seen in Figure 6.16 with 10 bar impact (synovial fluid) and in Figure 6.17 with 10 bar impact (normal saline) may not be due to the difference joint fluid, as previously synovial fluid showed a trend to chondroprotection (Figure 6.14), as much as the joints may have been smaller from a different herd of cattle slaughtered that day. This change in joint size did not affect the arthroscopic probe study
as the blunt trauma was localised. To overcome this, the size of the joints used could be recorded.

The impact ram model needs further development to improve its use but showed cell death from blunt impact where no fracture was seen and a trend towards chondroprotection with hyperosmolar solution.

6.4.3 Clinical Relevance and Limitations

The long-term outcomes of iatrogenic cartilage damage from arthroscopy are unknown\(^{(335, 338)}\), especially the damage secondary to contact by the arthroscopic probe with articular cartilage as shown in this study. The chondrocyte death investigated is significant as chondrocytes are not replaced after death and are required for matrix repair: cell death may ultimately lead to matrix loss\(^{(181)}\), resulting in cartilage defects that progress to more extensive degeneration of the joint (`secondary’ osteoarthritis)\(^{(11, 47, 76, 318)}\). The amount of cell death required to produce clinically relevant changes is also unknown. Cartilage allografts with >20% cell death\(^{(342, 343)}\) can provide clinically successful outcomes\(^{(344)}\) but ‘successful ‘outcomes are difficult to quantify. The outcomes are often compared to the poor functioning joint prior to surgical intervention, are in young patients (~30 year olds) and have short follow-up times in comparison to that expected for the failure criteria of arthroplasty\(^{(345)}\). Chondrocytes are not replaced when they die, it is the authors belief that these cells should be preserved if at all possible and therefore further knowledge of causes of chondrocyte death, e.g. the arthroscopic probe (Figure 6.12), should be recognised and efforts made to limit the damage caused. A change in irrigation solution not only reduces cell death seen after sharp injury\(^{(189)}\) but also after blunt injury (Figure 6.15). Irrigation fluids in arthroscopy can be changed with relative ease and if chondroprotection for this type of common blunt trauma can be achieved in human articular cartilage as with bovine cartilage, it could limit iatrogenic cartilage damage during arthroscopy.
6.4.4 Conclusions

Blunt injury caused by the commonly used arthroscopic probe caused a band of cell death at clinically relevant pressures. A chondroprotective effect was seen by exposing articular cartilage to hyperosmotic saline (600 mOsm) prior to mechanical trauma. Blunt injury caused by an impact ram caused cell death; increasing with increased impact but in small percentages and the chondroprotective effect of hyperosmotic saline was not conclusively replicated.
Section 7- Human Joint Model

Aim: To study the response of chondrocytes from human fresh cadaveric knee joints to blunt trauma and compare this to the bovine model.

Research Questions:
   a) Is human tissue affected by blunt trauma in the same manner as bovine cartilage?
   b) Is raising the osmolarity of the irrigation fluid prior to impact chondroprotective in human tissue?

Hypothesis:
   Human cartilage behaves in a similar manner to bovine cartilage after blunt trauma and chondroprotection occurs with hyperosmolar irrigation solution.

7.1 Introduction

The various human models used were discussed in Section 1. The supply of healthy human cartilage suitable for research is limited and therefore valuable. The model chosen for this study was fresh cadaveric human tissue to provide whole knee joints that were physiologically normal prior to explantation. Cartilage taken from arthroplasty patients or patients undergoing fracture surgery would not have been suitable as would be limited to osteochondral blocks rather than the whole joint. Tissue from patients undergoing amputation would have provided the whole joint but the pathology necessitating the amputation may affect the cartilage physiology, potentially influencing the results and the contralateral joint is not available as a ‘control’. An advantage of the fresh cadaveric model was knowledge of the patient’s age and medical history, to exclude pathological cartilage as
much as possible. Fresh cadaveric human models, using cartilage explants, have been used successfully for articular cartilage research to investigating blunt trauma using a drop tower (85), showing a stress threshold for cell death; to investigate temporal chondrocyte death (102, 190), showing increasing cell death over time in response to blunt trauma, and the effect of capase inhibition on cell death after mechanical injury (83), showing a reduction in chondrocyte death. The fresh cadaveric whole joint was used in the current study to attempt to model the in vivo situation as accurately as possible, to potentially extrapolate the results to clinical practice. The only human whole joint study into blunt trauma to the author’s knowledge was Tochigi et al. (2011) who showed acute chondrocyte death along fracture lines that progressed over 48 hours following injury (106).

The Scottish National Blood Transfusion Service (SNBTS) is based in Edinburgh with the donation team harvesting tissue for the tissue bank locally. This provided an irregular supply of good quality human cartilage. A method of harvesting knee joints was developed to allow the model to include a whole knee joint with an intact capsule whilst preserving the final limb aesthetics for the donor’s family (see methods).

Blunt trauma in the human model was studied with the same two methods as the bovine model. The first, mild blunt trauma caused by an arthroscopic probe and the second, a greater intensity blunt injury caused by a high-energy impact ram. The set-up of the ram was altered as described below to attempt to create a tibial plateau fracture. The effect of altering irrigation fluid on chondrocyte death was then studied for the arthroscopic probe injury.

7.2 Methods and Materials

The study was in collaboration with the SNBTS: Tissues and Cells Directorate and NHS Lothian (Co-sponsor). Ethics approval was sought and granted by the Regional Ethics Committee (REC 12/SS/0179) and NHS Research and Development approval was granted (IRAS project ID 114609).
The methodology was detailed in Section 6.2 Materials and Methods unless specifically documented below.

7.2.1 Fresh Cadaveric Knee Joint Retrieval

The Tissue Donation Team from SNBTS contacted the author when a donor was available. Donors with previous surgery to their knees, or documented history of osteoarthritis were excluded. The donation team requested the consent from the donor’s relatives for the research study. The knee joints were harvested at the same time as the other tissues for the tissue bank. Harvesting took place at the Western General Hospital mortuary within 48 hours of the donor’s death, in line with SNBTS policy. The cadaver was kept at 4°C. Harvesting was done after the tissues for tissue banking were collected and involved excision of the whole knee joint. This was done by a straight midline incision centred on the patella and careful tissue dissection down to the joint capsule in a similar manner to arthroplasty surgery. Tissue was elevated away from the joint capsule to try to preserve as much soft tissue for reconstruction whilst maintaining an intact joint capsule. A saw was then used to cut the tibia and femur, taking care to leave the joint capsule intact. The knee joint was wrapped in sterile plastic bags for transporting to the laboratory. The joints were used within 2 hours. The first hour was reconstruction and transport to the laboratory, at room temperature and the second, preparatory time where the joints were stored at 4°C. The cadaveric limb was reconstructed (Figures 7.1-7.3) to achieve a satisfactory cosmetic appearance after dissection. This method was trialled in fresh frozen cadaveric tissue in collaboration with the anatomy department of the University of Edinburgh. The wooden rod shown in Figure 7.2D was replaced with a metal rod for the donor reconstruction to provide more stability and the suture material was switched from undyed vicryl (Figure 7.3) to twine to comply with SNBTS procedures. The cartilage collected was largely macroscopically normal non degenerative and from donors without a history of arthritis or joint disuse.
Figure 7.1: The surgical set-up for extraction of the cadaveric knee joint and limb reconstruction in the mortuary. Standard surgical instruments were utilised with a disposable power saw for cutting the bones and scalpels for tissue dissection. The cement, mixing station and gun were used for reconstruction of the limb with metal rod (cut to length with the hacksaw) and gauze. Skin closure with twine suture material and handheld needle, inline with closure of the skin by SNBTS.
Figure 7.2: Extraction of the cadaveric knee joint and limb reconstruction in the trial with a fresh frozen cadaveric lower limb. A) shows the midline skin incision and the knee joint after careful tissue dissection with the tibia cut below the level of the joint capsule. B) shows the preparation of the tibial canal with a 10mm drill, the canal was then cemented, using the cement gun (C). This was repeated for the femoral canal, in preparation for insertion of the stabilisation rod (D) to maintain limb length. The cement in combination with the rod held the limb in the correct rotation. The gauze was then inserted around the rod to fill the void created by removal of the joint.
7.2.2 Study Sample of Human Tissue

The study sample comprised of eight patients with a mean age of 64 years old (range 50-68 years old, 7 males).

7.2.3 Osteochondral Explants

The joints were opened with care to preserve the macroscopically normal articular cartilage (Figure 7.5, 7.6). This was defined as no visible changes to the articular surface, e.g. roughening or erosions. Any joints with macroscopically abnormal cartilage were discarded (one, 13%). Typically four osteochondral explants were taken from the human femoral condyles after the interventions using the same method as Section 6.
7.2.4 Study Interventions

A chondrocyte viability study was performed to check chondrocytes were living within 48 hours post donor death. The first donor used for this study had macroscopic damage to the cartilage and could not be used for any of the other intervention studies but due to the paucity of donors, the decision
was made to use the tissue for the viability study, recognising the limitations. This study used the same methods as Section 6.2 with no intervention performed.

Due to the limited joints available only moderate, clinically relevant pressure from the arthroscopic probe and a control were studied in human cartilage. The probe was pulled across the femoral cartilage in an AP direction with moderate pressure using the same handheld method as in bovine tissue (Section 6.2.3).

For the impact studies, the aim was to create a tibial plateau fracture with the pneumatic actuator used in the bovine model. The set-up was altered to allow 70kg axial weight to be placed on the knee joint, to simulate the weight of a human standing on the joint (Figure 7.6). The knee joint was placed in a vertical orientation and the impactor set to hit the lateral side of the knee (Figure 7.7), simulating a side impact, like a dog running into the outside of a patient’s knee or a pedestrian being hit by a car. The mechanism causing tibial plateau fractures was described as, forcible adduction of the leg to ‘smash the external tuberosity against the fulcrum of the outer condyle of the femur’(35). This impact set-up was tested on saw bones prior to the use of human tissue and produced a tibial plateau fracture seen (Figure 7.8).
Figure 7.5: Building the ram. A) the apparatus to load the 70kg weight axially on the joint and the specimen stage that allowed the joint to pivot with the lateral impact. B) the weights added to the apparatus and a safety pin (yellow arrow) to prevent the weights falling when the joint was displaced by the impact. C) the specimen pot pivoted with the joint displaced after impact and the safety shield in front of the testing area.
7.2.5 Osmolarity Studies

The femoral cartilage was immersed in normal saline for ten minutes at room temperature prior to exerting the moderate hand held probe pressure. Care was taken to avoid any physical contact with the articular surface when immersing the joint in the fluid. Chondroprotection by hyperosmolar irrigating solution was investigated for arthroscopic probe damage in the same manner, using hyperosmolar saline (600mOsm) instead of normal saline.
7.2.6 Human Synovial Fluid Osmolarity

Human synovial fluid was aspirated from both knee joints of one donor after the joint was prepared, using a sterile needle and an aseptic technique. The fluid samples were placed in Falcon tubes at room temperature and were measured using an osmometer after the intervention to the cartilage had occurred (approx. 30 minutes).

7.3 Results

7.3.1 Human Fresh Cadaveric Cartilage Viability Study

Osteochondral explants taken from fresh cadaveric femoral condyles 44 hours post donor death were stained and imaged for chondrocyte viability (Figure 7.9). Chondrocytes were shown to be viable within the timeframe set (<48 hours) with a relatively low percentage of dead cells. The chondrocyte distribution was a little patchy within the explants (Figure 7.9) and this may be explained by the degenerate nature of the knee joint.

Figure 7.9: A CLSM reconstruction of femoral condyle articular cartilage harvested 42 hours post donor death and explants taken and stained two hours later, showing viable chondrocytes (green) and no dead cells (red).
7.3.2 Arthroscopic Probe Pressure

The 'benign' arthroscopic probe applied at moderate/surgical pressure caused 28% cell death in the ROI of human cartilage, significantly more than in the control (no pressure)(Figure 7.10). The chondrocyte death seen using the probe at moderate pressure in human cartilage is comparable to bovine tissue at 23% cell death in the ROI (Figure 7.11).

Figure 7.10: Percentage cell death seen in human cartilage after blunt arthroscopic injury. Graph to show the cell death with 95% confidence intervals (Control N=4, Moderate N=4) and ImageJ reconstructions of human cartilage following arthroscopic probe injury. A) Axial view showing the red ‘dead’ cells in a band of cell death (white lines) through the green ‘living’ cells in the ROI. B) Axial control view shows a few red ‘dead’ cells in the green ‘living’ cells in the ROI.
Figure 7.11: A comparison of the effect of moderate arthroscopic probe pressure on cell death in bovine (N=7) and human cartilage (N=4). 95% CI are shown. (Bovine data from Section 6)

7.3.3 Arthroscopic Osmolarity Study

The arthroscopic probe study was repeated in human cartilage with exposure to normal saline and hyperosmolar saline. There was a trend to reduced cell death in the hyperosmolar saline with a 2.4 fold decrease, but it did not reach statistical significance (Figure 7.12).

7.3.3 Human Synovial Fluid Osmolarity

Synovial fluid was aspirated from two joints from the same patient and five samples were tested using an osmometer with a mean value to the nearest multiple of five, 360mOsm (mean=358mOsm, range 353-364mOsm, StDev =4.32) (Figure 7.13).
The Effect of Osmolarity on Cell Death after Arthroscopic Probe Pressure in Human Cartilage

![Graph](image)

Figure 7.12: Changes in chondrocyte death in human cartilage with osmolarity after blunt trauma with an arthroscopic probe at standard operating pressure. (285mOsm N=3, 600mOsm N=3) 95% CI are shown with p value from unpaired t test.

Osmolarity of Human Knee Joint Synovial Fluid

![Graph](image)

Figure 7.13: Osmolarity of Human Synovial Fluid with 95% CI shown. Each point represents a sample from the individual donor (n=5, N=1).

7.3.4 Impact Study

The results analysed investigated high-energy impact in the single donor available during the time period. The 10 bar impact from the altered ram setup did not create a fracture in the fresh cadaveric tissue in contrast to the
sawbones (Figure 7.11). High impact injury caused 26% cell death compared to 8% cell death in the control with the static 70kg load and no impact (Figure 7.14).

**Cell Death seen after Impact with High Energy Ram in Human Cartilage**

![Graph showing cell death percentage](image)

<table>
<thead>
<tr>
<th>Results - Cell Death (%)</th>
<th>Impact</th>
<th>Control (No Impact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>25.72</td>
<td>8.39</td>
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<tr>
<td>StDev</td>
<td>8.61</td>
<td>7.85</td>
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<tr>
<td>n</td>
<td>8</td>
<td>6</td>
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<td>N</td>
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Figure 7.14: Human chondrocyte death after impact injury. Graph to show explants (n) from single donor (N) with 95% CI. CLSM reconstructions of human cartilage after high-energy impact (A) and control (B) and a table to show the percentage cell death mean, standard deviation and number of specimens.
7.4 Discussion

The aim was to study the response of chondrocytes from fresh cadaveric knee joints to the two modes of blunt trauma and compare these with the response of the bovine model.

7.4.1 Human Cadaveric Model

The human fresh cadaveric model was used thanks to an excellent collaboration developed with the SNBTS. The number of donors however was scarce and sporadic. The donors could be available at any time of day or night. A total of eight eligible donors were available in the study period, limiting the experiments that could be performed. This particularly affected the later impact study where only one donor was available before the study time was finished. The study period was limited by ethics approval, agreed time course with SNBTS to minimise disruption to clinical service tissue needs and the author’s return to clinical duties.

The fresh cadaveric model has disadvantages as well other than the complexities in obtaining the tissue. Post mortem there may be changes to the properties of the cartilage\(^\text{346}\) and the synovial fluid, of particular relevance the osmolarity of the synovial fluid\(^\text{341}\) that may reduce the ability to transfer the results to the living joint. The changes seen shortly after death are minimal and the cell viability hours after death are near 100\%\(^\text{106, 173}\). The nutrients and oxygen found in the ECM are abundant and can sustain the survival of chondrocytes for several days after clinical death\(^\text{346}\) with allografts showing 70\% cell viability at one month when stored at optimal tissue banking conditions as in the current study\(^\text{342}\).

The cell viability seen within 48 hours of death in this model is a significant finding for human cartilage injury research. Cell death measured in the control joint in this fresh cadaveric model was seen at 7\% (Figure 7.11), potentially due to transportation to the laboratory or tissue drying during preparation. This is similar to 8.6\% cell death in human cadaveric tissue 48
hours after death, rising from 1.6% at the time of death\textsuperscript{106}. Despite this baseline cell death in the control joints, significant cell death was seen after both the blunt trauma interventions. The whole joint model attempted to mimic the arthroscopic clinical scenario, as arthroscopy is performed on an anaesthetised patient, making the influence of the rest of the limb less relevant and the procedure is on the whole joint. The main aspect that differed was the cadaveric nature of the model and the lack of systemic reaction to the procedure e.g. swelling and bleeding, meaning only the isolated effect of mechanical injury to the articular surface could be studied. The only other whole joint model, that the author is aware of, that has been used to study human cartilage impact injury is the ankle\textsuperscript{106}. The cartilage thickness of the human talus is comparable at 2.2mm\textsuperscript{347} but in the current study the knee joint was utilised as there was considered to be less variability in chondrocyte viability\textsuperscript{348} and harvesting did not affect the tissue required by the local tissue bank (e.g. Achilles tendon).

7.4.2 Comparison of Bovine and Human Models

Human and bovine cartilage differ in a number of ways, including thickness, cell density, collagen organisation and stiffness. The diffusion distance of nutrients and oxygen in the ECM determines the thickness of articular cartilage. Cartilage thickness has been studied in many different species and different joints. The human femoral condyle, used in the present study, has been measured at 2.3-2.4mm\textsuperscript{76, 347}. The bovine MTPJ cartilage has been measured at 0.5mm thickness\textsuperscript{303}. In general the thickness of the cartilage in mammals relates to the body weight in a proportional manner\textsuperscript{347, 349} however whether human cartilage fits this relationship is debated, possibly explained by the bipedal nature of humans compared to quadrupedal animals\textsuperscript{347}. Cell density appears to vary inversely to the body weight and therefore the cartilage thickness, with bovine cell density measuring 20 cells x $10^{-3}$/mm$^3$ compared to 14 cells x $10^{-3}$/mm$^3$ in humans\textsuperscript{347}. The highest density of cells is seen in the superficial zone\textsuperscript{350}. 
where the affect of load is seen in current study. The collagen arrangement in different species has been described in two forms, leaf like (e.g. human) and columnar (e.g. bovine)\(^{(349)}\) (Figure 7.15). Collagen is important for load transmission and this difference may alter the findings from the bovine model in humans. Bovine cartilage has also been shown to be twice as stiff as human cartilage when studying cartilage of similar thickness\(^{(351, 352)}\). These differences need to be considered when using the models and comparing results. The synovial fluid surrounding the articular cartilage also differs between the species. The most significant difference for this study was human synovial fluid has a higher osmolarity (400mOsm)\(^{(309)}\) than bovine synovial fluid.

![Figure 7.65: Electron Microscopy images of the collagen arrangement in human (A) and bovine (B) cartilage. Adapted from Kaab et al. (1998)\(^{(349)}\)](image)

### 7.4.3 Arthroscopic Probe Experiments

The most significant finding was the cell death seen with the arthroscopic probe at surgical pressure (moderate) in an intact joint (Figure 7.10). The arthroscopic probe experiments were performed on the joints when exposed to their native synovial fluid, the difference in measured osmolarity of the synovial fluid (bovine 305mOsm, human 360mOsm) may have had an effect on the cell death seen. The differences between human and bovine cartilage discussed including thickness (2.3mm and 0.5mm respectively) may also...
have caused the chondrocytes to respond differently to blunt injury. The percentage cell death, however, was not significantly different between the bovine and human cartilage after blunt arthroscopic probe pressure (Figure 7.11). The band of cell death was less well-defined in human tissue (Figure 7.10), this may be due to the thickness of the tissue.

7.4.4 Osmolarity Experiments

The osmolarity measured for human synovial fluid was less than previously published (400mOsm)(306) but not as low as in pathological joints (OA 300mOsm, rheumatoid arthritis 280mOsm)(314). The lower value may be due to the samples being post mortem from an unloaded joint rather than in vivo. Whilst the difference in synovial fluid osmolarity may change the actual percentage of cell death seen it would not change the clinical relevance of the findings. During arthroscopic surgery the synovial fluid is washed out and replaced by an irrigation solution, normal saline, chondrocytes are therefore exposed to a striking decrease in osmolarity, from 400mOsm to 285mOsm, during a surgical procedure(189). This study showed that iatrogenic damage from seemingly benign surgical instruments during arthroscopy could be reduced more than two fold by increasing the osmolarity of the irrigation fluid (Figure 7.12), however this was not statistically significant. The systemic effects of hyperosmolar irrigation fluids including on the synovium, menisci and ligaments have not been studied, to the author’s knowledge. Intra-articular contrast media has a higher osmolarity than synovial fluid and is considered safe to use(353, 354) albeit in very different studies and hyperosmolar saline (600mOsm) has shown a trend to reduce fluid extravasation in a canine model of arthroscopy(355).

The higher cell death seen with lower osmolarity solutions may mean people with lower osmolarity synovial fluid, in pathological situations like primary OA or RA, are more susceptible to cell death with blunt trauma. The trend of chondroprotection in blunt trauma by hyperosmolar irrigation fluid builds on previous literature showing chondroprotection in sharp trauma(189).
providing more evidence for a change in clinical practice but a need for further experiments to confirm this.

### 7.4.5 Impact Ram Experiments

Due to the limited human cartilage available only one impact experiment was undertaken and chondroprotection from hyperosmolality was not investigated. Cell death was apparent at high levels (Figure 7.15) after injury caused by the altered set-up of the impact ram. Cell death of 8% was measured in the control joint, which was not exposed to an impact. This could be due to the 70kg static load used to mimic the joint loading conditions when tibial plateau fractures are sustained.

The set-up was altered from the bovine model to try to create a tibial plateau fracture but did not succeed. The fact the knee joint was in full extension rather than slight flexion may explain why the tibial plateau did not fracture. Atkinson and Haut\(^{(31)}\) conducted a study of 18 pairs of human cadaveric knee joints, subjecting them to a blunt impact at flexion angles of 60, 90 and 120 degrees. They found fracture location and character changed with flexion angle but only noted femoral condyle and patellar fractures rather than tibial plateau. Recreating the mechanism of injury for the tibial plateau fractures may also alter at different angles. A previous study found that cell death only occurred with fracture\(^{(188)}\). This study differed from the current one in several ways. The model was porcine rather than human, the physiological differences of the cartilage and anatomical differences of the joints may affect the results seen. The explants were studied coronally, looking at each of the zones rather than axially looking at the superficial zone. The study showed the greatest percentage cell death was seen in the superficial zone regardless of whether a fracture was created. The superficial zone has been shown to have significantly lower compressive modulus\(^{(170,356)}\), which may account for the higher cell death measured. The most significant difference in the author’s opinion between the two studies was the orientation of the impact. Both models used axial preloading of the joint, however the current...
study used a side impact rather than further axial load. This difference could be explained by the ability of the congruent whole joint to withstand an impact injury crossing the joint axially but not when the intact joint suffers a valgus impact, due to the anatomical structure of the femoral condyles, hitting against tibial plateau. The same group, three years later, showed high compressive strains resulted in significantly reduced chondrocyte viability with or without fracture(185). This was investigated in explants rather than whole joints, but was using non-physiological loading of articular cartilage rather than the transarticular load in the previous study. The only other whole human joint model the author was aware of, discussed earlier, also used a transarticular load, this time to mimic a tibial plafond fracture and showed a significant difference in the cell death occurring at the fracture line and distant to the fracture(106). The current study adds to the literature showing high cell death in cartilage without a fracture present if the load is not physiological, not along the mechanical axis of the joint. The high percentage cell death resulting from the ram development will allow future work to look at the chondroprotection and provides further evidence that a fracture does not need to be present for blunt impact to cause cell death in a whole joint.

The clinical relevance of osmotic chondroprotection during arthroscopy is obvious but after an impact blunt trauma it requires a window of time during which the secondary phase of cell death could be prevented. This window would need to be hours for it to be a practical method of management after the injury. A twenty minute window was shown after impact injury in a bovine explant model(80). This was using osteochondral explants rather than a whole joint. Increasing cell death occurred over seven days in a canine knee model where a drop impact on individual condyles was used(357). Trypan blue exclusion was used to assess cell viability and the whole condyle rather than explants improved the accuracy of the model. A human explant model showed an increase of cell death continuing to 96 hours(102, 190). In a porcine whole joint tibial plateau fracture model no significant effect of time was seen following impact(188). This assessed cell viability using histochemical measures (matrix metalloproteinase and aggrecanase activity
and sulphated glycosaminoglycan release). In the human ankle whole joint, increased cell death, after impact causing a tibial plafond fracture, was seen to increase over 48 hours \(^{(106)}\). Although the animal models have varied results, the two human models, explants\(^{(102, 106)}\) and whole joint\(^{(106)}\) suggest a window for the hyperosmotic protection but not if the cell death is due to disruption of the cells at the time of impact. The osmotic protection seen with cartilage exposure to the hyperosmolar solution prior to impact does not necessarily extrapolate to protection after the impact has occurred especially if the mechanism is cell shrinkage.

Future work in both human cadaveric whole joint models and in vivo animal studies of blunt injuries over time would be useful.

**7.4.6 Conclusions**

The arthroscopic probe produced significant cell death at surgically relevant pressure in human cartilage and hyperosmolar saline (600mOsm) reduced the percentage cell death more than two fold but did not reach statistical significance. Despite the difficulties obtaining the human cartilage, the arthroscopic probe as a cause of iatrogenic chondrocyte death and the trend to chondroprotection provided by hyperosmolar irrigation fluid in blunt trauma are novel findings with a clear clinical relevance.
Section 8: General Discussion and Conclusions

8.1 Introduction

Six studies were performed to address the epidemiology and clinical outcomes of tibial plateau and patellar fractures and the nature of chondrocyte death after blunt trauma in a bovine model and a human model. The hypothesis was that cartilage injury due to intra-articular trauma to the knee is important in the development of post-traumatic osteoarthritis and this therefore affects the long-term outcomes of tibial plateau and patellar fractures.

8.2 Discussion

8.2.1 Post-traumatic Osteoarthritis

Tibial plateau fractures are common intra-articular fractures occurring with an incidence of 11/100,000/year. Operatively-managed patellar fractures occur less frequently, with an incidence of 3.4/100,000/year. Both tibial plateau and patellar fractures are seen more frequently in elderly women secondary to falls from standing and young men due to RTAs. Tibial plateau fractures in young men are also commonly caused by FFH with patellar fractures in young men commonly caused by sport. High-energy injuries from RTA and FFH were associated with more complex fractures in both tibial plateau and patellar fractures. The incidence of symptomatic PTOA was 5% after tibial plateau fractures (0.6/100,000/year) and 9% (0.3/100,000/year) after patellar fractures and only severe enough to warrant TKR in 3% and 1% respectively. The incidence of tibial plateau fractures appeared to be increasing over time with a larger proportion being treated operatively over time. The population is
also aging. Operatively-managed fractures and elderly patients are more likely to suffer PTOA, so the burden of PTOA may also increase. The increased rate of PTOA seen in the elderly in our study and others (96, 111, 136) can be understood looking at the changes in articular cartilage with aging. Chondrocytes undergo a marked age-related decline in their function that affects their ability to repair damage or maintain undamaged articular cartilage following a joint injury (175). These changes include becoming less sensitive to growth factors (e.g. Insulin-like Growth Factor-1) (378) and more susceptible to oxidative damage, decreasing their mitotic activity and cell senescence (82, 441, 663). The loss of proteoglycans seen in aging cartilage may be due to increased degradation or decreased synthesis (52) and leads to decreased cartilage stiffness and increased permeability. These changes make the articular cartilage more vulnerable to further damage from blunt trauma. Osteoarthritis is not an inevitable consequence of aging but there is a strong correlation (379). Magnetic Resonance Imaging (MRI) has been used to demonstrate changes in articular cartilage composition and mechanical properties (380-384). In the knee joint incidental MRI findings of focal cartilage defects, like those caused by blunt trauma, have been shown to be predictive of cartilage loss within two years (385) and in the ankle, focal chondral defects following fractures were closely associated with the development of PTOA at approximately 12 years following injury (386). The observation that the risk of PTOA increases with age and the fact that the function of chondrocytes decreases with age supports the hypothesis that chondrocyte death and PTOA are linked.

Aging cartilage is more vulnerable to abnormal loads like blunt trauma but what is the mechanism of chondrocyte death secondary to trauma? Patwari et al. (104) put forward two hypotheses. One, that matrix damage occurs first, subjecting chondrocytes to increased stresses and disrupting normal cell-matrix interactions due to a change in the biomechanical or physiochemical environment (396). Two, that chondrocytes are directly affected by mechanical injury in the absence of matrix damage and respond accordingly leading to subsequent matrix degradation due to up-regulation of
proteinase expression\[^{104}\]. The author believes that the chondrocytes are directly affected by the mechanical compression, which in turn leads to matrix damage. The load on the matrix although non-physiological is likely to be below the threshold for matrix damage and in the author’s opinion the physical injury to the cells in contact with the trauma is the mechanism of cartilage degradation.

### 8.2.2 Chondroprotection

A chondroprotective effect was seen by exposing bovine articular cartilage to hyperosmotic saline (600 mOsm) prior to mechanical trauma from an arthroscopic probe and after impact injury when the osmolarity change was greater from 150mOsm to 600mOsm. In human cartilage, hyperosmolar saline (600mOsm) reduced the percentage cell death more than two fold but did not reach statistical significance. The chondroprotective effect has previously been described in sharp trauma\[^{189}\] and with no obvious deleterious effects on the human body the author would suggest the osmolarity of irrigation fluid for arthroscopy should be increased. Chondroprotection for impact injury was seen to a lesser extent in bovine tissue and not performed in human tissue as the clinical relevance is less apparent. It would not be possible to inject a person’s joint prior to an impact causing fracture to reduce the chondrocyte death caused by the injury. Impact studies over a longer period of time may reveal a 'golden' window after injury that further chondrocyte death could be prevented with chondroprotection like hyperosmolar irrigation but this was not investigated in the current study.

### 8.2.3 Outcomes

Increasing age, female gender, bicondylar fractures and fractures that required operative management had significantly increased risk of TKR in both tibial plateau and patellar fractures.
Operative management of patellar fractures produced satisfactory long-term results despite the number of patients that required removal of metalwork in the short term. This data was supported by previous studies by Shabat et al. (157) and Sorensen et al. (156). The reverse was true after tibial plateau with worse long-term outcomes than patellar fractures (Table 8.1). The patella differs from the tibial plateau in a number of ways including loading pattern with movement and the thickness of the articular cartilage. Tibial plateau cartilage in humans has been measured as 3.6mm (350) compared to up to 10mm for the patella (5). The bovine cartilage used in Section 6 had a thickness of 0.5mm (303) and the human femoral condyle thickness in Section 7 had a thickness of 2.3-2.4mm (76, 347). When comparing cell death seen after mild trauma (with an arthroscopic probe) between bovine and human cartilage there was no significant difference (Figure 7.11) despite the difference in thickness of the cartilage, however the area of cell death was less well defined (Figure 7.10) in the thicker human cartilage. The difference in thickness between the patella and tibia may be a reason for the differences seen in PROMs.

The outcome literature for intra-articular fractures of the knee concentrates on operative techniques as discussed in Section 1. Studies of operative technique can link to non-physiological loads going through the cartilage as discussed in "step-off" studies. Brown et al. (387) examined, with use of pressure-sensitive film, the effects of experimentally created step-offs

<table>
<thead>
<tr>
<th>Over 60 years old</th>
<th>Tibial Plateau Fracture</th>
<th>Patellar Fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>168</td>
<td>127</td>
</tr>
<tr>
<td>Age</td>
<td>70.3</td>
<td>73</td>
</tr>
<tr>
<td>Responders</td>
<td>66%</td>
<td>86%</td>
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<tr>
<td>Infection</td>
<td>6%</td>
<td>9%</td>
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<tr>
<td>ROMW</td>
<td>15%</td>
<td>31%</td>
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<td>PTOA</td>
<td>11%</td>
<td>9%</td>
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<tr>
<td>OKS</td>
<td>32.46</td>
<td>39</td>
</tr>
<tr>
<td>EQ5D</td>
<td>0.59</td>
<td>0.79</td>
</tr>
</tbody>
</table>

Table 8.1: Comparison of outcomes for intra-articular fractures of the knee.
of human tibial articular surfaces on peak pressure. Local peak pressure near the ledge on the high side of the step-off generally increased with increased step-off but did not occur until the step-off exceeded 1.5 mm. Even 3-mm step-offs only led to local peak pressure that was 75% greater than normal. Brown et al.\(^{(387)}\) also showed that specimens from the tibial articular surface varied considerably in their sensitivity to step-offs. This could explain the confusion in the published literature of how much fracture displacement is relevant and why outcomes were thought to be associated with operative technique rather than initial injury. Brown et al.\(^{(387)}\) also found that the sensitivity to step-offs was inversely correlated with cartilage thickness \((r = -0.58)\). The thickness of the patella could therefore be protective from blunt trauma, like fractures and a small residual displacement in the articular surface compared to the tibial plateau. The thickness of native articular cartilage can not be modified but understanding of how the joints are affected by blunt trauma and the long-term outcomes allows us to inform our patients better.

8.3 Further work

1) A prospectively collected and reviewed database to look at the next 25 years of tibial plateau fractures using the AO/OTA classification has been set up to extend the epidemiology work and to look at DVT rate and delay to surgery.

2) PROMs could be collected, including KOOS, for patients under 60 year olds who sustained tibial plateau fractures to expand the outcome data available and further counsel patients.

3) The human cadaveric fracture model could be developed further using the actuator ram, increasing the force that could be applied to the joint. This would allow the pattern of cell death after fracture to be studied and whether secondary cell death occurs over time to investigate a ‘golden’ window for chondroprotective intervention.
4) Use of hyperosmolar irrigation fluid in arthroscopy patients in clinical practice. This is currently limited by manufacturing companies' reluctance to develop sterile hyperosmolar solution for irrigation due to a perceived lack of financial reward.

8.4 Conclusions

Intra-articular injuries including fractures cause chondrocyte death which can lead to post-traumatic osteoarthritis. The factors influencing the amount of cell death and the progression to arthritis are numerous and some can be modified after injury. The cause of injury, pattern of injury and who it occurs to cannot be modified after the event but prevention of infection, the operative technique and chondroprotection could all be used to reduce the burden of intra-articular injuries leading to post-traumatic osteoarthritis.
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196


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Appendices

Appendix 1 – Tibial Plateau Epidemiology and Outcome Literature Review Table
Appendix 2 – Patella Literature Review Table
<table>
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<th>First Author</th>
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<th>Average Age</th>
<th>Type</th>
<th>Pre-Op</th>
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**Appendix 1:** Epidemiology and outcome studies for tibial plateau fractures. Blank cells represent where data is not available from the published paper.
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<th>Results</th>
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<td>6 years</td>
<td>TBW/Cerclage</td>
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</tr>
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<td>Epidemiological</td>
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<td>radiographic questionnaire</td>
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<td>48</td>
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<td>radiographic questionnaire</td>
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Appendix 2: Patellar fracture outcome studies from literature review. Blank cells represent where data is not available from the published paper.