DEVELOPMENT OF PROTOCOLS FOR MEASURING KNEE KINEMATICS AND CARTILAGE HEALTH IN HIGH TIBIAL OSTEOTOMY

by

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Abstract

Osteoarthritis (OA) is a prevalent and debilitating disease which is characterized by loss of articular cartilage, osteophyte (bony inclusions into cartilage) formation, pain, stiffness, and swelling.

The exact cause of OA is unknown. Many mechanical risk factors are associated with OA, but it is not clear which specific mechanical factors influence its initiation and progression. One such risk factor is varus knee alignment where the medial side of the knee appears to transmit a greater fraction of the joint load than it would normally, causing medial tibiofemoral (TF) OA.

High tibial osteotomy (HTO), which realigns the leg, is one treatment for medial TF OA. Although the clinical results of HTO are mixed, many researchers have reported repair cartilage growth following HTO. This dramatic finding suggests that certain mechanical environments may prevent, delay, or reverse cartilage degeneration. Many authors suggest a range of varus/valgus angular correction, however achieving this correction does not guarantee good results. One explanation for this is that simple alignment may not describe the mechanics of the joint sufficiently well, and that a three-dimensional method may be required.

With the aim of examining the changes caused by HTO, we developed a method for measuring three-dimensional knee kinematics with loading using MR at 3T. We determined that our method successfully measures knee kinematics in subjects with and without hardware, despite the larger metal artifact expected at a field strength of 3T compared to 1.5T.

We also developed a method for measuring cartilage health using MR at 3T, based on the dGEMRIC protocol and determined that our dGEMRIC sequence yields valid results in the presence of titanium surgical hardware. This important development will allow us to evaluate the effect of surgical kinematic changes on cartilage health, specifically in the case of the high tibial osteotomy procedure.

These protocols were tested on three subjects scheduled for high tibial osteotomy. Both kinematic and cartilage GAG concentration results were consistent with values from literature.

These newly developed protocols will allow us to study relationships between knee kinematics and cartilage GAG concentration changes as a result of high tibial osteotomy and other surgical procedures.
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$B_0$ – static magnetic field in MR scanner (T)
$T1$ – spin-lattice relaxation time (ms)
$TI$ – inversion time (ms)
$TR$ – repetition time (ms)
$TE$ – echo time (ms)
$S(TI)$ – signal intensity as a function of $TI$
$S(TR)$ – signal intensity as a function of $TR$
$S_0$ – signal intensity as $TI$ or $TR$ goes to infinity
$f$ – fit factor for adiabatic pulse sequence
$M_z$ – magnetization in the direction of the $B_0$ field at any point in time
$M_0$ – magnetization in the direction of the $B_0$ field as time goes to infinity
List of Abbreviations

OA – osteoarthritis: a disease of articular cartilage
PF – patellofemoral: describing the joint between the patella and femur
TF – tibiofemoral: describing the joint between the tibia and femur
HTO – high tibial osteotomy: a surgical treatment for medial TF OA
PG – proteoglycan: large protein found in cartilage
GAG – glycosaminoglycans: large protein found in cartilage; side chain of PG
MR – magnetic resonance: a medical imaging modality using high magnetic fields
dGEMRIC – delayed gadolinium-enhanced MRI of cartilage
ACL – anterior cruciate ligament
PCL – posterior cruciate ligament
MCL – medial collateral ligament
LCL – lateral collateral ligament
ECM – extra cellular matrix: the solid, non-cellular components of cartilage
FCD – fixed charge density: the negative charges which are immobile in the cartilage
BMI – body mass index: a calculated index which indicates obesity
OW – opening-wedge: one form of the HTO operation
CW – closing-wedge: one form of the HTO operation
HSS – Hospital for Special Surgery score: a quality of life index
TKA – total knee arthroplasty: knee joint replacement
VAS – visual analog scale: a method of answering survey questions
JSN – joint space narrowing: reduction of space between bones in radiograph
qMRI – quantitative MRI: a method for measuring morphologic parameters in cartilage
NMR – nuclear magnetic resonance: a method for spectroscopy
CT – computed tomography: a medical imaging modality
RSA – Roentgen stereophotogrammetric analysis: a method for 3D motion tracking using x-ray
FOV – field of view (mm)
TSE – turbo spin echo: a MR imaging method (also known as “fast spin echo”)
ICP – iterative closest points: an algorithm for registration
SR – saturation recovery: a type of MR scan series for measuring T1
IR – inversion recovery: a type of MR scan series for measuring T1
PACS – picture archiving and communication system
DICOM – digital imaging and communication in medicine: a medical image file format
ROI – region of interest
SNR – signal to noise ratio

xv
WOMAC – Western Ontario and McMaster Universities Osteoarthritis Index
SENSE – Philips name for parallel imaging
GRE – gradient echo: a type of MR scan
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1 Introduction

Osteoarthritis (OA) is a prevalent and debilitating disease which affects one in ten Canadians (140). Direct costs of arthritis (of which osteoarthritis is the most common) were estimated to be $910 million Canadian in 1998, and indirect costs due to arthritis-related disability were estimated to be $3.5 billion. People with arthritis also report more sleeplessness, stress, depression, pain medication use, and physical inactivity than healthy people or people with other chronic conditions (69).

OA is characterized by loss of articular cartilage, osteophyte (bony inclusions into cartilage) formation, pain, stiffness, and swelling (23,129).

The exact cause of OA is unknown. Many mechanical risk factors are associated with OA including abnormal anatomy, obesity, and injury, all of which imply altered loading of the joint (128). However, it is not clear which specific mechanical factors influence the initiation and progression of OA.

Treatments for OA are limited. There are no disease-modifying drugs, and surgery usually involves removing joint surfaces and replacing them with synthetic components which will often require replacement after 10-15 years.

One particular risk factor for OA which appears to have a clear mechanical cause is varus knee alignment (bow-legs). In people with varus malalignment, the inner (medial) side of the knee appears to transmit a greater fraction of the load through the joint than it would normally. The link between increased load and OA is supported by a higher incidence of medial tibiofemoral (TF) OA in persons with this anatomical abnormality (130).

A potential treatment for medial TF OA is to realign the leg and return the loading on the medial compartment to "normal". This is the objective of the high tibial osteotomy (HTO) surgical procedure. HTO involves making a cut in the proximal tibia and either opening or closing the cut to change the alignment of the leg (Figures 1.1 and 1.2).
HTO is often considered a “stop-gap” treatment for patients who are too young to have total knee replacements. The advantage of this treatment is that it preserves bone stock and cartilage surfaces, in contrast with knee replacement surgery.

The clinical results of HTO are mixed. From 50-80% of patients experience an improvement following HTO, which has been reported to be maintained at follow-up of up to 22 years. Many researchers have reported repair cartilage growth in the medial compartment following HTO.
This is a dramatic finding because cartilage is generally thought to have no or very poor capacity to regenerate after it is lost in the OA disease process. This finding suggests that, if a certain mechanical environment can promote cartilage growth, a similar environment may also prevent or delay cartilage degeneration. Identifying such mechanical environments may yield important objectives for surgeons seeking to delay or prevent OA onset.

Exact mechanical parameters for successful HTO have not been published. Many authors suggest a range of varus/valgus angular correction (either relative or absolute). These ranges of angular correction have been correlated with clinical outcome, but since each author suggests a different range, it is difficult to determine an ideal correction. Even with an “ideal” correction, the numbers of patients with good clinical results (e.g. up to 82% at ten years (135)) do not come close to those for total knee replacement (e.g. 95% good or excellent ratings at ten years (121)). Thus achieving a specific target correction in the coronal plane does not ensure a good outcome. One explanation for the limited correlation between alignment and cartilage regeneration is that alignment may not describe the mechanics of the joint sufficiently well.

In addition, HTO provides an opportunity to study the connection between a distinct mechanical change and cartilage degeneration (or regeneration).

To study the links between mechanical change and cartilage degeneration, several important criteria for measurement techniques must be fulfilled. First, the measurements must be made in living humans, because non-living cartilage will not degrade in the same way as vital cartilage. Second, since degeneration is a process that occurs over time, the measurements must be made at several time points. Osteoarthritis follows a disease course that may span decades, which makes pinpointing the triggering event or environment difficult if not impossible in many cases (128). This precludes very invasive techniques for mechanics (such as bone pins) or cartilage health measurements (such as biopsy).

Third, a three-dimensional method for measuring mechanics must be used. As noted above, two dimensional assessments of alignment have not been adequate. Load in joints cannot currently be measured in vivo, but techniques are emerging for assessing three-dimensional kinematics in vivo in living humans. Measurements of kinematics provide insight into load transmission because kinematics describe the relative positions of joint surfaces and the lines of action of structures that transmit joint loads.
Advanced techniques for assessing joint kinematics and cartilage degeneration have not been used in combination, nor has their feasibility been assessed in subjects after HTO surgery. A particular limitation to the application of these techniques is the effect of surgical hardware on many imaging modalities.

The scope of this thesis is the work done to develop and test a protocol for assessing both cartilage degeneration and kinematics in subjects undergoing HTO. This thesis also includes work done to determine the feasibility of conducting a longitudinal study using these techniques.
2 Background

2.1 Anatomy of the knee

The knee is the largest joint in the human body. See Figures 2.1 and 2.2.

2.1.1 Bones

Three bones, the tibia, the femur, and the patella, meet at the knee. The knee is composed of two separate joints: the tibiofemoral (TF) joint and the patellofemoral (PF) joint. The tibiofemoral joint is divided into medial and lateral compartments, which are separated by the tibial spines and trochlear notch on the tibia and femur respectively. The TF and PF joints are both diarthrodial, or synovial, joints – they are freely moveable, restricted only by capsular and ligamentous structures (38).

2.1.2 Muscles

The TF joint is crossed by the gastrocnemius, the hamstrings, and the quadriceps muscle groups. The quadriceps are knee extensors, and act through the patella. The hamstrings and gastrocnemius are knee flexors.

2.1.3 Ligaments

The TF joint is also crossed by four major ligaments, the anterior cruciate ligament (ACL), the posterior cruciate ligament (PCL), the medial collateral ligament (MCL), and the lateral collateral ligament (LCL).

The ACL primarily resists anterior motion of the tibia with respect to the femur. The PCL primarily resists posterior motion of the tibia with respect to the femur. The MCL primarily resists valgus motion of the knee. The LCL primarily resists varus motion of the knee.

The PF joint is the region of contact between the patella and the trochlea of the femur. The patella is the largest sesamoid (meaning, within a tendon) bone in the body. The quadriceps tendon inserts into the tibia through the patella.
Figure 2.1: Anatomy of the knee. Anterior view – left, posterior view – right. Note, the tibial collateral ligament is the MCL, and the fibular collateral ligament is the LCL. Semi-membranous is one of the hamstrings (posterior view) (62).
2.1.4 Cartilage

The joint surfaces in a healthy knee are covered with articular cartilage. This is a viscoelastic tissue that allows low friction ($\mu = 0.002$ to $0.01$ compared to $0.05$ to $0.11$ for an artificial joint) (38) movement between the bones and transmits compressive loads. It is avascular (has no blood supply), and is nourished by the synovial fluid in the joint capsule (38).

Articular, or hyaline, cartilage is composed of extracellular matrix (ECM) and chondrocytes (cartilage cells) which maintain the ECM. The primary component of the ECM is water. Most of this water is bound to ECM proteins called proteoglycans (PG). The rest of the ECM consists of type II collagen fibres and proteoglycans, which together "provide stiffness and resist deformation of the articular surface" (38).
The collagen is the major determinant of tensile and shear strength in the cartilage (63). Collagen fibres are long and thin, and the orientation of the fibres varies with depth. Several zones of differing composition and orientation of fibers are present in cartilage. The superficial zone has the most collagen and the lowest concentration of PGs. Collagen fibres in this zone are oriented tangentially to the surface. The second zone, known as the transitional zone, has large collagen fibers oriented obliquely to the joint and small fibres more randomly distributed. The deep zone contains collagen fibres oriented radially, or approximately normal to the joint surface (38).

![Diagram of collagen fiber direction in cartilage zones](from Burstein et al. (25)).

Proteoglycans are molecules which allow the cartilage to "resist compression and distribute load" (38). They are proteins with glycosaminoglycan (GAG) side chains. Large PGs, called aggrecans, combine in the cartilage into even larger aggregates which effectively immobilizes them within the cartilage. Therefore cartilage has a fixed charge density (FCD) due to the negatively charged GAG molecules. The FCD causes the matrix to be hydrophilic, and the incompressible fluid which is attracted to the matrix gives cartilage its ability to withstand large compressive loads. The repulsion of like negative charges within the cartilage provides compressive stiffness to the tissue (63). Evidence suggests that decreasing FCD is associated with a decrease in compressive modulus (91).
PG concentration is inversely proportional to collagen concentration in any given region of cartilage (38). PGs bind to collagen by their protein core. Their side chains (GAGs) are free to interact with other collagen fibres or their own (117). When in the extracellular matrix, these interactions bind the PGs together in large aggregates, effectively immobilizing them (38).

2.1.5 Motion

The motion of both the TF and PF joints is grossly two-dimensional. They flex and extend in the sagittal plane. However, linked movements in other planes are part of the normal function of the knee as well. For example, there is a noticeable external rotation of the tibia with respect to the femur which occurs from about 20 degrees to full extension. This is known as "screw-home" and is a result of the normal bony and ligamentous structure of the knee (45). Since the knee is not a two-dimensional structure, and does not have purely two-dimensional movement, three-dimensional measurements of kinematics are required to describe joint movement completely.

2.1.6 Mechanics

Joint loads experienced by the TF joint have been determined to range between one and three times body weight for normal walking (100). The PF joint transmits loads ranging from one half times body weight in walking to 3.3 times body weight in stair climbing (112).
2.2 Osteoarthritis

Arthritis is a debilitating condition that affects one in six Canadians (69). The most common form of arthritis is osteoarthritis (OA) (54).

2.2.1 Clinical presentation

Symptoms of OA include pain, stiffness, swelling, crepitus (audible crackling sound from joint), and limited range of motion. OA is characterized by softening, fibrillation and loss of articular cartilage, and osteophyte (bony inclusions into cartilage) formation (23,129).

2.2.2 Damage and diagnosis

Osteoarthritis is not usually diagnosed until there has been significant cartilage loss. Clinical diagnosis is based on pain, stiffness, and functional difficulties. It is often confirmed radiographically.

For the knee, the presence of osteophytes is the accepted definition for a diagnosis of OA. For PF OA, joint space narrowing may also be a required part of the definition. Radiography is recommended by the World Health Organization as the primary outcome for assessing progression of OA (128).

The severity of radiographic OA is often assessed using a grading scale. A common system is the Kellgren-Lawrence grading system, where one of five grades (zero for normal to five for severely affected) are assigned based on specific radiographic features (such as osteophytes and joint space narrowing) and using an atlas (128).

While radiographic OA and clinical OA (where the symptoms appear) are correlated, the correlation is not as strong as one might expect (128). “A substantial portion of patients with radiographic disease are without significant symptoms.” (128)

Cartilage loss “does not appear until cartilage has lost considerable stiffness” (54). This loss of stiffness is due to loss of fixed charge density (FCD), which is a result of loss of proteoglycans (PG) and glycosaminoglycans (GAG). Thus, the loss of GAG precedes radiologically detectable features of the disease.
Cartilage loss may be more rapid in the early stages of the disease (152).

2.2.3 Risk factors

The exact cause of OA is not well understood. Sharma states that “OA development is often attributed to a joint-specific mechanical environment within a systemic milieu, leading to categorization of risk factors as either systemic or mechanical.” (128)

OA is traditionally divided into primary (idiopathic) and secondary types (128). Primary OA develops with no identifiable cause, while secondary OA proceeds from some other condition, usually mechanical in origin. However, some researchers claim these labels are misleading, and that often examples of “primary” OA can be shown to be a result of mechanical problems in the joint (29).

A risk factor is a condition or event which is associated with OA. A risk factor cannot be considered a cause. However, the number of mechanically related risk factors for OA indicates that the cause is likely also mechanical in nature.

Risk factors for the disease can be divided into systemic and biomechanical factors. Systemic factors include age, sex, bone density, estrogen replacement therapy (in post-menopausal women), nutritional factors, ethnic characteristics, and genetics. Biomechanical risk factors include obesity, joint injury, joint deformity, sports participation, occupational factors, and muscle weakness (54). Increased and decreased physical activity are also both risk factors (128). In some cases, specific risk factors correlate with specific OA sites, such as varus alignment increasing the risk of progression of medial TF OA, and valgus alignment increasing the risk of progression of lateral TF OA (130). These alignments tend to influence progression in the medial and lateral compartments, respectively, of the PF joint as well (27).

The long held idea that OA results from normal “wear and tear” on a joint and is a natural process which accompanies aging is disputed by Buckwalter et al. “Moderately intense lifelong joint use” has not been linked to OA (23). Cartilage changes in older individuals have been shown to be different from the cartilage changes caused by osteoarthritis. In early OA, cells proliferate and secretion of matrix components (both collagen and proteins) increases. Collagen fibres are interrupted, which leads to swelling of the cartilage and consequent loss of its ability to redistribute loads. As OA progresses,
chondrocyte activity declines sharply and may cease altogether. In aging cartilage, chondrocyte activity declines, however damage from minor injuries can be slowly stabilized and does not lead to cartilage erosion. Aging cartilage demonstrates modest changes in mechanical properties, including moduli and hydraulic permeability. In OA, early changes are similar to age-related changes, but as the disease advances the changes, such as decreased tensile modulus, compressive modulus and failure strength, become more pronounced (157). It is clear that OA not part of natural aging.

2.2.4 Drugs

The treatment options for patients suffering from OA are somewhat limited. Currently, there are no disease-modifying drugs available. Pharmacological interventions are limited to pain relievers, such as COX-2 inhibitors, which have no effect on the rate of cartilage degeneration (132) and have been found to have potentially lethal side effects (22,106,134).

2.2.5 Surgery

Several surgical interventions are available to the OA patient.

Arthroplasty, or joint replacement, is the primary surgical treatment (61). The joint surfaces of the femur and tibia are cut out and artificial joint surfaces (usually metallic femoral and plastic tibial surfaces) are implanted. For patients with advanced OA this option provides an improvement in quality of life. The long term results are generally good, but the procedure has some significant drawbacks such as loss of range of motion and the need for revision because the implants are susceptible to wear and loosening.

Arthroscopic debridement is sometimes indicated for early OA sufferers with more than fifty percent of their cartilage surface intact (61). This procedure involves removing loose bodies and smoothing the joint surfaces. This method has recently been shown to be no more effective than placebo, and is falling out of favour (102).

Arthrodesis (joint fusion) is possible but not commonly used in the lower limb (61). Fusing the knee would significantly reduce or eliminate pain, however it would present numerous obstacles to daily living, such as difficulty stair climbing or entering and exiting vehicles, as the leg could no longer be bent.
Osteotomy (which means “bone cut”) is used to change the mechanics of the joint by physically altering the structure (61). Often this is considered a “stop-gap” measure to limit degradation in patients considered too young for arthroplasty due to the limited lifespan of the implants, and the desire to avoid complicated revisions.

2.2.6 Repair

Ideally, physicians would like to promote repair of the cartilage. When defects are left untreated they usually fail to heal, and may progress to symptomatic OA. Restoring the cartilage surface is a much more attractive option than the treatments for advanced OA, including joint replacement. Cartilage capacity for repair is hampered by its lack of blood supply and low level of metabolic activity (23).

It has been shown that mechanical loading and joint motion can influence articular cartilage repair and that decreased cartilage contact stress combined with joint movement “may stimulate restoration of an articular surface” (23). It is still unclear what is the optimum contact stress, how we may attain it through treatment, and how much movement may be needed to repair cartilage.

Surgical tactics used to promote repair include penetration of subchondral bone by drilling (stimulates repair cartilage formation), decreasing or changing joint loading through a variety of methods, and implantations of soft tissue, cells, or artificial matrices (23).

Repair cartilage, a type of fibrocartilage which may grow to fill defects, is “composed predominantly of type I collagen and is biochemically and mechanically inferior to normal hyaline articular cartilage” (31). It has fewer PGs than normal articular cartilage (75). It is less stiff and may deteriorate quickly with normal use (23).

2.2.7 Mechanics and osteoarthritis

Mechanics appear to play a large role in the etiology of OA. Many of the risk factors appear ‘mechanical’ in nature, such as obesity and malalignment of the extensor mechanism. The exact relationship between mechanics and OA has not been well defined. Part of the difficulty is the complexity of the mechanical and biological interactions involved, which seem to cause a self-perpetuating degeneration cycle (31), and some paradoxical results in studies into lifestyle risk factors and medical or surgical
interventions. For example, 26% of ex-elite male soccer players in one study were diagnosed with TF OA (128), yet a group of regular, experienced runners had no more knee OA than controls (122).

Specific examples of associations between mechanics and cartilage change follow.

2.2.7.1 ACL injury

Anterior cruciate ligament (ACL) rupture is a common sports injury which often leads to OA later in life.

When the ACL is torn, there is a measurable change in knee kinematics which has been demonstrated in vivo (92,118,120). An ACL injury is often considered an automatic sentence for developing OA. Several studies have demonstrated that from one third to 70% of ACL deficient knees develop OA (153). Surgical reconstruction of the ACL is usually undertaken to improve clinical stability of the joint but there is little evidence that the reconstruction reproduces the original mechanics or prevents OA. Several studies have reported no significant difference, or even degradation, in the radiographic or clinical outcomes between subjects with surgically-repaired ACL injuries and those who did not have surgery (12,94,147). "There are no published data supporting a preventive effect of reconstructive ACL surgery against osteoarthritis" (147).

Many animal models of OA are based on ACL transsection (67,71,126).

2.2.7.2 Varus/valgus malalignment

Varus/valgus malalignments have been shown to be associated with distinct patterns of OA in the knee joint (27,130). These anatomic abnormalities are thought to cause increased loading on one compartment of the TF joint, the same compartment which tends to become osteoarthritic.

2.2.7.3 Obesity

Knee OA has been closely linked to obesity. Increased weight has been found to be associated with both symptomatic and asymptomatic radiographic changes in cartilage at the knee, and has been more strongly associated with severe changes than moderate changes (53). Body mass index (BMI) is strongly associated with TF OA and
combined OA (PF and TF), and moderately associated with PF OA (95). Weight loss can decrease the risk of developing OA at the knee (55).

2.2.7.4 Elite athletes/runners

There are conflicting data on the effect of exercise, and specifically running, on cartilage health. Animal studies have shown both negative effects (11) and no alterations (104) in cartilage due to regular running.

In a human study comparing cartilage health in sedentary, moderately active and elite athletes, higher exercise levels were associated with better cartilage. This implies that cartilage can adapt to higher loading (143). Another study showed that triathletes and sedentary subjects did not have significant differences in cartilage thickness, but male athletes had larger joint surfaces than the sedentary subjects. This may indicate adaptation (40). It is not clear what level of activity causes this adaptation.

While running is often assumed to be linked to the development of OA, the research does not bear this out. One study determined that runners did not have an increased risk of OA (88). Another group studied a small cohort of marathon runners longitudinally and concluded that long-distance running did not have a negative long-term impact on healthy individuals (85). Unlike some other potential risk factors, running is self-selecting: only those who can run without pain or discomfort continue running. Therefore these studies may have an inherent bias and therefore the results may not apply to the larger, non-running population.

2.2.8 High tibial osteotomy

High tibial osteotomy (HTO) is used to treat medial TF OA. The operation is generally indicated for patients with medial TF OA and varus ('bow-legged') alignment of their lower extremity. The surgery realigns the leg to a neutral or slightly valgus ('knock-kneed') alignment. The objective is to reduce loading through the medial compartment and increase the loading through the supposedly intact lateral compartment.

The operation originally outlined by Coventry (34) has two primary variations. Opening-wedge (OW) osteotomy involves making a cut on the medial side of the tibia, above the tibial tuberosity, opening it, filling it with bone graft, and fixing it in place with surgical hardware. In closing-wedge (CW) osteotomy the lateral tibia has a wedge cut out in the
same proximal location and the edges of the cut are closed together and fixed with surgical hardware (65).

The amount of valgus to be introduced is determined pre-operatively from a standing coronal leg-length radiograph. The most accepted objective is to achieve 10 degrees of overall valgus in the femorotibial angle (39). The femorotibial angle is defined as the angle between the mechanical axis of the femur (from the centre of the femoral head to the midpoint between the femoral condyles) and the mechanical axis of the tibia (from the midpoint of the tibial plateau to the centre of the ankle).

Recently, the surgical community has developed a preference for opening-wedge osteotomy as it does not appear to cause as much anatomic distortion as the closing-wedge version and consequently fewer complications at conversion to joint replacement (125).

2.2.8.1 Short-term clinical results

The results of this surgery have been mixed. One study reports 89% of subjects showed partial or full regenerative changes in the damaged medial compartment cartilage (using arthroscopy) and an improvement of about thirty points on a functional score out of 100 (Japanese Orthopedic Association Osteoarthritic Knees score) at 18 months (pre-operative and post-operative angles at 183 and 167 degrees respectively, CW operation) (77). Another study using biopsy prior to and two years following the CW operation showed microscopic cartilage repair (fibrocartilage) in 9 of 19 patients, however there was no correlation between radiograph findings or post-operative varus-valgus angle and the degree of cartilage repair (18). Yet another study found arthroscopic cartilage improvement on the medial tibial condyle at two years in eight of 14 overcorrected (less than or equal to 178 degrees) knees, however no correlation between clinical result and arthroscopic score was found (CW) (107).

2.2.8.2 Long-term clinical results

Long-term studies show moderate success of HTO. At a follow-up of 10-21 years, clinical results for 60 knees were strongly correlated with length of follow-up. Excellent and good results found using the Hospital for Special Surgery (HSS) score comprised 73.5% of knees at a follow up of up to 14 years, and 46% of knees at a follow-up of 15 or more years. No correlation was found between clinical results and amount of
correction. Radiographic progression of OA occurred in 40 knees, with most (21) having progression in both medial and lateral compartments. 25 of 45 knees demonstrated OA progression in the PF joint. Lateral compartment progression occurred more frequently with overcorrection (15 degrees or more of valgus), but this radiographic progression was not correlated with clinical results. The authors suggest that HTO can have a life-span of 15 years (CW) (114).

When revision was used as an endpoint in a study of 101 knees, the operation had an 81% survival rate at ten years. Clinical results were improved at 10 year follow-up compared to pre-operative scores. Patient satisfaction was 7.8 on a 10 point visual analog scale (VAS). Radiographic classification indicates a degenerative trend. The leg angle at follow-up was measured at 1 degree valgus, on average (CW) (56).

A recent study evaluated survival of 76 CW HTO operations up to twenty-two years. They used three endpoints – conversion to TKA, HSS score of less than 70, and patient dissatisfaction (vs. satisfaction). Valgus alignment at one year was divided into groups of 8 to 16 degrees valgus, and <8 or >16 degrees valgus. The group with a one-year angle of 8 to 16 degrees had much higher survival rates than the other group – 80% or more versus approximately 50% at ten years for all three endpoints. By 22 years, the <8 or >16 degrees group had no survival data (the reason was not clear, but presumably there was zero survival beyond 17 years). The 8 to 16 degree group maintained a survival rate of about 60%, 30%, and 45% for conversion to TKA, HSS score, and dissatisfaction respectively (135).

2.2.8.3 Relationship between mechanics and outcome

It is unclear why this is a lasting treatment in certain patients and significantly less successful in others. The results have often been categorized by degree of valgus alignment post-operatively, which may be a clue that determination of success or failure is based on mechanical factors. However, correlations between clinical results and varus-valgus correction angles are poor. A key limitation is that varus-valgus measurements are made using plain film radiography. There is no known published effort to categorize differences in three-dimensional position or movement and link these parameters to clinical outcome or progression of OA.
Few correlations have been found between the measured values of clinical outcome, radiological OA score, arthroscopic OA score, and amount of correction. However, when we consider the two-dimensional and subjective methods used in these studies, there may be subtle differences between two apparently similar subjects which these methods could not detect.

Some of the differences in outcome may be biological. Wakabayashi et al. conducted a study to compare regeneration of fibrillated cartilage to the repair of eburnated (uncovered and "polished") bone in those having HTO, and found that the subjects with full thickness damage (i.e. down to bone) had more potential for healing (148).

2.2.8.4 Cartilage changes
Fujisawa et al. performed an extensive study on a group of patients arthroscopically before and after CW HTO. Prior to surgery, 120 knees were examined for degree of degeneration of the cartilage surface using a grading system. Fifty-four knees were examined post-operatively (four months to six years and four months). Biopsies were conducted at random to examine cartilage microscopically. The results of the arthroscopic examinations showed that the majority of subjects had improved cartilage scores in the medial TF compartment, even at the highest level of degeneration. In the lateral TF and patellar compartments the majority did not show any change in score. However of those that did change, the change was primarily for the worse. The improvements in score were generally due to a fibrous repair tissue which covered the damaged areas. At histological examination, the biopsy samples showed that the repair tissue consisted of both fibrocartilage and hyaline-like cartilage (57).

2.2.8.5 Endpoint considerations
Another consideration for surgeons is how treatment must proceed following the failure of a HTO. The percentage of good and excellent results of total knee arthroplasty (TKA, joint replacement) are somewhat lower following HTO (39). Long-term success rates are comparable to those of revision TKA (at 80%), compared to primary TKA (90-95%) (125).

One of the advantages of HTO over other procedures, such as TKA, is that a patient keeps his/her joint surfaces, rather than having them replaced by synthetic materials (61). Thus the door remains open to use new treatments for OA.
2.3 Assessment of cartilage degeneration

Cartilage degeneration assessment in vivo has been limited by invasive and localized techniques.

2.3.1 Plain film radiograph and fluoroscopy

The most common technique used to assess cartilage health is the plain film x-ray. It can detect several of the diagnostic criteria for OA, namely joint space narrowing, osteophyte existence and subchondral bone thickening (20). Joint space narrowing (JSN) is a reduction of the shortest distance between the projections of two bones. Grading schemes using these criteria and atlases are commonly used clinically. The Kellgren and Lawrence scheme (80) is a scale from grade 0 (normal) to grade 4 (large osteophytes, marked joint space narrowing, severe sclerosis, and definite bony attrition) frequently used in the literature (128).

This method is inexpensive, easily accessible, and non-invasive, but imparts a radiation dose to subjects, does not image cartilage and therefore cannot differentiate between tibial cartilage loss and femoral cartilage loss (24). Radiography also shows only advanced stage of OA, because morphological changes are preceded by biochemical changes in cartilage (145).

2.3.2 Biopsy and histology

Biopsy (removing a small sample of tissue from a living subject) and histology (microscopic evaluation) have been used in previous work (57). These complementary techniques can evaluate GAG concentration and cartilage thickness accurately. However, biopsy is a very invasive procedure and not amenable to repetition for longitudinal studies. Only local values at the plug harvest site are measurable.

2.3.3 Arthroscopy

Arthroscopy is a surgical procedure which involves inserting a small scope into the joint space through an incision and observing the cartilage surface. This procedure is often done as a part of standard medical care (either exploratory or interventional), and thus has an advantage of access. However, it is invasive and therefore cannot be repeated many times; it can only detect lesions (not GAG loss); the viewing area is limited to the cartilage surface; evaluation of cartilage health is qualitative and/or subjective.
2.3.4 qMRI

Quantitative magnetic resonance imaging (qMRI) yields measures of thickness, volume and surface area of cartilage through processing magnetic resonance (MR) images. Using high resolution cartilage-specific MR images of the joint, cartilage is segmented and the resulting areas are combined using a numerical integration. A 3D Euclidean distance transformation is used to calculate localized thickness, volume, and surface area. qMRI has been validated by comparing the results to water displacement of surgically retrieved cartilage following TKA (24), has been shown to be reproducible in vivo (136), and has been evaluated for longitudinal precision (41). qMRI has been used to study the effect of in situ static loading on PF cartilage (cadavers) (70), the effect of in vivo static and dynamic loading on patellar cartilage deformation (42), the relationship between loading history and cartilage morphology (40), the variability and inter-compartmental correlations in normal knee joints (43), and gender differences in knee cartilage morphology (46).

This method images the whole joint, requires no contrast agent, and is non-invasive. The disadvantages of this approach include long scanner time (over seven minutes (59)), and the time-consuming requirement of precise segmentation by trained operators. Most importantly, by the time cartilage thickness loss can be measured, the disease is actually well advanced, since biochemical changes have been demonstrated to occur before morphological degradation (145).

2.3.5 dGEMRIC

Delayed gadolinium-enhanced magnetic resonance imaging of cartilage (dGEMRIC) is a recent technique for assessing cartilage health in vivo. Using a gadolinium-based contrast agent, glycosaminoglycan (GAG) concentrations through the thickness of the cartilage can be estimated. GAGs are macromolecular branches of proteoglycans (PG) which provide much of the mechanical strength of cartilage, particularly resistance to compressive loads (38).

In order to image GAG using MR, a contrast agent must be administered to the subjects. Gadopentatate dimeglumine, or Gd-DTPA^2^- (brand name Magnevist, Berlex Canada Inc., Quebec) is a contrast agent used in MR imaging. It is an ionic substance based on the rare earth element gadolinium. Gadolinium is a strong paramagnetic substance. Such substances cause T1-shortening (bright signal on T1-weighted images) (66). T1 is
a tissue-specific relaxation time which can be measured using MR. Health Canada approval was obtained to use Gd-DPTA$^{2-}$ for this off-label musculoskeletal application. Gd-DTPA$^{2-}$ is negatively charged, which causes it to disperse inversely to GAG concentration or FCD (GAG being also negatively charged). Because it lowers the T1 of the tissue it permeates, the T1 map of the cartilage can be read directly as a map of GAG distribution. It has been shown that, without contrast, T1 does not change significantly even with complete loss of GAG (15).

![Figure 2.5: Illustration of the biochemical foundation of the dGEMRIC technique. Yellow negative circles represent fixed charges due to GAG. Green positive symbols represent positive ions, such as sodium, dispersing relative to the FCD. Pink negative symbols represent negative ions, such as Gd-DPTA$^{2-}$, also dispersing relative to FCD. Near the top of the figure, where PGs are plentiful, there are few pink ions, while in the bottom half (representing degenerated cartilage) the pink gadolinium ions are more concentrated. (From Burstein et al. (25)).](image)

dGEMRIC has been validated by comparison with sodium nuclear magnetic resonance (NMR) spectroscopy (15), by comparison with histological GAG distribution, and by comparison between in vivo and in vitro measurements (16). The protocol has been well
described by Burstein et al. (26) Tiderius et al. have also shown that dGEMRIC can
detect pre-radiographic changes in cartilage of patients known to have early OA (141).

Advantages include full-thickness evaluation and a non-invasive method without a
radiation dose delivered to the subject.

While dGEMRIC is useful in relative comparisons, direct comparison of GAG
concentration values to those from other methods of measurement is not appropriate.
"Estimates of FCD from Gd-DTPA$^2$ concentration ... were consistently 50% lower than
Na$^+$ based FCD calculations over a broad range of FCD." (15). Therefore, the calculated
T1 gives an estimate of GAG. Another disadvantage is long imaging time (under one
hour to complete series for two slices (26)).

dGEMRIC has been used to study GAG loss in acute ACL injury (142), the relationship
between GAG distribution and mechanical stiffness of cartilage (116), recovery of GAG
(5,149), distribution of GAG in autologous chondrocyte transplants (58), adaptive
capacity of human knee cartilage (143), relationship between local GAG concentration
and local mechanical properties (86), and early OA in hip dysplasia (81).

Due to its non-invasive nature and low-risk imaging modality, dGEMRIC was chosen to
be developed for the application in this study.

2.4 Assessment of joint mechanics

Ideally, researchers would measure forces in the structures of the knee in order to relate
them to cartilage degeneration. In vivo mechanics measurements are extremely invasive,
however. The opportunity to introduce strain gauges or pressure sensitive devices is
generally limited to a surgical situation (7). It is not possible to conduct either a
reasonably sized study or a longitudinal study using these methods.

Although mechanics are difficult to evaluate in vivo, they are important to the etiology of
OA, so reasonable surrogate measurements are made to try and determine their effect.
While direct quantification is not feasible, the mechanics of a joint may be inferred from
measurements of the kinematics of the joint. Kinematics parameters are readily
measurable in vivo with minimal invasiveness. As indicated earlier, although knee motion
is primarily in two dimensions, the movement is more complex than a simple hinge in the sagittal plane. Therefore, a three-dimensional method is required for measuring knee kinematics accurately. Since joints are intended to move, images in only one position - such as standing leg-length radiographs to measure varus/valgus angles - do not provide a complete picture of the mechanical situation of the joint.

Direct links between kinematics and joint forces have been made through ex vivo experimentation, such as the link between patellar spin and elevated lateral patellar force (151).

Kinematics parameters describe bone alignment, which directly affects the lines of action of muscles and ligaments, and the relative positions of contact surfaces. Thus, changes in kinematics reflect changes in contact force distribution in the joint.

Most of the work in the area of knee mechanics has been done with cadaveric specimens or computer models, due to the limitations of in vivo work.

2.4.1 Ex vivo

Cadaveric experimentation allows direct measurement of force, pressure, and contact area parameters (2-4,113,133). Limitations include no active muscle forces, no healing, necessary dissection of specimen to introduce instrumentation, potential for material property changes, and complex test set-up attempting to recreate in vivo motions and loads.

2.4.2 Models

Some groups have used computer models to investigate the motion of the knee joint (33,44,68,155). These models are often based on a limited number of specimens, and rely on assumptions about the placement and action of muscles and material properties.

There are a number of methods that have been used for measuring joint kinematics in vivo.
2.4.3 Skin markers

Skin markers, or grids of skin markers, have been used to study joint motion (8,9,33,115). They are non-invasive and simple to apply and track using motion capture methods. Skin moves with respect to the bones below, so there is substantial inherent error. One study determined the amount of skin marker movement with respect to bone to be from a few millimeters to 40 mm, with the largest displacements in the vicinity of joints (28). It is not feasible to determine patellar motion with this method.

2.4.4 Bone pins

Bone pins have also been used to measure kinematics in vivo. Small incisions are made in the skin above the insertion site, and a hole is drilled into the bone to accommodate a rigid pin. Koh et al. used them in one subject to measure knee kinematics, using a motion capture system (83). Results are very accurate and the motion capture software often provides readily accessible results. However, the method is very invasive, which limits its use. There may also be a limited range of motion due to soft tissue impingement on the pins. Some patients report discomfort as the skin moves and pulls on the pins.

2.4.5 2D Kinematic Imaging

Several groups have published work on two-dimensional or quasi-three-dimensional kinematics in the knee. They have used either one mid-patellar slice (103) or two mid-condylar slices (92,93,118-120) in a tomographic imaging modality (such as CT or MR). They rely heavily on assumptions of the slice position and orientation, which cannot be easily verified. Especially in the patella, the rotation of the bone about an axis which lies in the image plane is difficult to ascertain. These methods may be adequate to evaluate certain signs in a diagnostic situation, but cannot be used to measure three-dimensional joint kinematics.

2.4.6 Radiography and fluoroscopy

The simplest of the medical imaging methods is radiography or fluoroscopy. Radiography is a static "picture" taken at one time point. Occasionally biplane radiography is used. Fluoroscopy combined with video capture provides continual imaging (a "movie") using essentially the same technique. These are fundamentally two-dimensional methods, however they have been used to make three-dimensional results with in situ components of total knee arthroplasty (13,36,78,156) by using bone shape-
matching techniques with a standard 3D model (10) or with a subject-specific model from CT scans (37), or by matching implanted radio-opaque fiducial markers to their known 3D orientations (138). They are relatively inexpensive and easy to access, but the computation is extensive and these methods involve ionizing radiation. If markers are required they must be implanted, which is invasive.

2.4.7 RSA

Roentgen stereophotogrammetric analysis (RSA) uses two x-ray sources and detectors along with small very radio-opaque beads (tantalum) implanted into the tissue to track three-dimensional motion (138,139). This method is considered very accurate (reported error of 0.6 degrees and 0.25 mm (138)), however the bead insertion is invasive and usually permanent. Biplanar radiography using orthopaedic implants or bone models from CT (154) instead of fiducial markers is also possible. These methods do not require bead insertion, but do involve ionizing radiation.

One study has determined that knee kinematics can be measured in MR as accurately as using RSA with CT in vitro (96).

2.4.8 CT

Computed tomography (CT) is a modality which produces axial slices from reconstruction of the attenuation of x-ray beams originating from numerous directions. This three-dimensional method images bone very well, soft tissue moderately to poorly, but delivers a radiation dose to the subject. Several groups have used CT to determine knee joint kinematics (123,124,127,137). The measurements made in these papers are limited to planar motion, however. One paper suggests that MR should be used over CT for kinematic imaging of the PF joint (103).

2.4.9 MR

A number of MR-based methods have been developed to measure kinematics.

2.4.9.1 Majumdar, University of California San Francisco, US

The method used at UCSF is technically sound, but presents some practical difficulties. This method requires images in five positions of flexion. Load-bearing was accomplished through the use of a MR-compatible device that subjects pushed against with their foot. TF flexion was measured directly on sagittal images. Images were segmented and three-dimensional reconstructions were made. The femurs from each
image were registered, and then the patella and tibia in each of the flexed images were aligned with the respective bone in the extended image. The transformation matrix from this registration provides the rotations and translations of the bones with respect to the femur.

Both normal tibiofemoral motion (111) and normal patellofemoral motion and contact area (110) have been studied using this method. In vivo kinematics following total knee arthroplasty have been studied as well, using oxidized zirconium and cobalt-chrome implants and specialized MR pulse sequences (89).

Accuracy of this method has been reported by the authors as within 1.8 mm and 3 degrees (110,111). A key limitation of this method is that subjects must hold the weight long enough to obtain images which are of high enough quality to use for precise kinematic measurements. This was around seven minutes. In the case of the scans involving metal components, this was over ten minutes, which limits the load that may be applied. The risk in such long weight-bearing periods is that the subject may get tired and move, which causes motion artifact in the images and may lead to inaccuracies in the results. Also, the use of a purely sagittal image to measure TF angle may lead to small errors.

2.4.9.2 Graichen, University of Frankfurt, DE

Another recent method uses an open MR system to record joint position at 90 degrees of flexion, which is practically impossible in a traditional closed-bore magnet. Volunteers lie on their side to be imaged at two flexion angles (30 and 90 degrees). A MR-compatible device held their legs in position, and a weight was applied to the lower third of the shank to produce a torque in the knee. Segmentation of the bones was performed. Anatomical coordinate axes were assigned to the bones and the kinematic parameters were determined from them.

This method has been used in normal subjects (146) and in subjects with varus alignment and mild OA (74).

While this measurement has been shown to be reproducible (CV% around 5% for both PF and TF), two flexion angles seem insufficient to characterize this complex motion. The coordinate systems used do not relate directly to the anatomy of the bones they
are applied to (the centroids of various structures used as origins can be in quite
different positions relative to important features). Also, it is unclear whether a purely
torsional load applied to the leg, an unusual loading situation in daily life, has the same
effect as a compressive load at the foot.

2.4.9.3 Sheehan, Stanford University and NIH, USA

The use of cine phase contrast MR in musculoskeletal research is novel. Originally
created to map velocity fields in the beating heart, it was used to track the velocity field
of the bone of the knee as a subject flexes and extends the joint along with a
metronome.

Cine MR is based on cyclic movement, such as heart beats or breathing. It captures
data over a number of cycles and averages them together. Errors are created when
the cycles are slightly different. Phase contrast MR is usually associated with blood
flow. A phase differential is applied to a volume of tissue and an image is taken after a
wait time. Any blood which has moved into the imaged slice during the wait time was
originally in a different location and therefore is out of phase with the rest of the slice.
The phase can be plotted and moving objects or fluids can be identified. When both
methods are applied together, kinematics of a cyclic motion may be measured. The
error was reported as less than 3.5% (0.7 mm). The cycling rate varied at maximum
1.4% for all subjects.

Dynamic loading more closely resembles the joint movement in daily activities.
Several drawbacks to this method exist. Only one slice can be imaged. While velocity
into and out of the slice plane is measured, the errors may be significant when the
movement is on the order of the slice thickness (10 mm). The subject must have
coordination and be able to execute the cyclic movement twenty-four times in series.
Imaging time was 7 min 30s, which is a long time to have patients moving under load.
Finally, the motion of the tibia was not quantified using this method (131).

2.4.9.4 Fellows and Hill, Queen’s University, CA

Using fast, loaded, low-resolution scans along with shape-matching to reduce loading
time, this method has fewer limitations than the similar UCSF method (49-52).
It involves using a MR-compatible loading rig to load the lower limb, and bone shapes are segmented from the resulting images. However, initially a high-resolution scan is taken in a relaxed position. When segmented, this provides detailed and subject-specific bone models. Then a series of short, low-resolution scans are taken at a series of TF angles. When segmented, these low-resolution images are shape-matched with each of the bones from the high-resolution scan. Position and orientation information can then be obtained from anatomical coordinate systems on each of the bone models. Precise TF flexion angles are calculated from the three-dimensional, registered models. Mean error was found to be less than 1.75 degrees for angular measurements and less than 0.88 mm for linear measurements. Intra-subject variability was found to be less than 1.5 degrees for angular measurements and less than 1.0 mm for linear measurements (51).

The advantage of this method is it allows for much shorter loaded scans (about thirty seconds under load), which minimizes subject fatigue and motion artifacts. This method has also been used in the presence of surgical hardware (73), and in subjects with OA (98). Limitations include the long overall scan time and the difficulty of segmenting the lower quality loaded images.

Due to the accuracy, three-dimensional capabilities, the limited risk involved with repeated scanning, and the decision to use a MR-based cartilage method (dGEMRIC), an MR kinematics method was preferred. The MR method of Fellows and Hill was chosen for this study.

2.5 Summary

1. The initiation, progression, and arrest/reversal of osteoarthritis (OA) appear to be linked to abnormal joint mechanics. However, it is not clear which specific mechanical environments are associated with changes in osteoarthritis severity.

2. High tibial osteotomy (HTO) is a procedure which alters the mechanics of the knee. It is a treatment for medial tibiofemoral OA due to varus alignment. HTO has been shown to promote cartilage regeneration in some patients. However, it is not clear what specific mechanical objectives must be attained to provide an optimal environment for cartilage regeneration.
3. The degeneration of cartilage may be measured in a variety of ways in vivo. To date, assessments of cartilage changes following HTO have been made with biopsy or radiographs, which are of limited use due to either the information they produce (single location histology, or two-dimensional joint space measurements) or due to the risks associated with repeated application (invasive tissue collection, or radiation dose). Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) has shown excellent promise for assessing in vivo cartilage degradation. However, it is not clear whether dGEMRIC can be used to assess cartilage health following surgery where metal hardware is implanted because metal distorts MR scans.

4. Recently developed methods can be used to measure joint kinematics rather than joint alignment, the only mechanical assessment typically made in studies of HTO. The method of Fellows and Hill has been chosen as the best method for assessing in vivo kinematics in this study. However, it is not clear whether this method can be performed on UBC’s 3.0T magnet, especially with metal hardware from HTO near the joint.
3 Knee kinematics

A new MR scan protocol was developed and tested to measure kinematic parameters in the knee at 3.0T. The method for determining knee kinematics was based on the approach by Fellows and Hill (52). This method had previously only been used with 1.5T images. We developed appropriate pulse sequences to perform this analysis on the 3.0T Philips scanner at UBC and assessed these sequences in a normal subject and a subject with implanted titanium hardware. It was critical to test this method on a subject with metal hardware to allow post-operative HTO patients to be scanned. This is because metal artifact increases with increasing field strength, so we would expect to have difficulty segmenting images which include metal from a 3T scanner.

3.1 General Protocol

All subjects were screened for potential MR risks, such as metal in the eye or pacemaker, by the technologist. The subject was asked to remove metal jewelry. The subject was given ear protection.

All subjects were scanned using the 3.0 Tesla Philips Intera Gyroscan at the UBC High-Field MRI Centre. The coil used was a Philips body coil.
High-resolution MR imaging:
Relaxed position

Low-resolution MR imaging:
Loaded at six flexion angles

Segment high-resolution images to bone models

Segment low-resolution images to bone contours

Select anatomical landmarks for coordinate systems

Apply coordinate systems to each bone model

Shape-match bone models to bone contours

Calculate kinematic parameters from coordinate system transformation matrices

Figure 3.1: Flow-chart of kinematic measurement process.
3.1.1 High-Resolution Imaging

A high-resolution scan of the knee was obtained from which a very accurate model of the bones of the knee was developed.

The subject was asked to lie supine on the scanner bench in a feet-first orientation with legs relaxed. A soft strap encircled the legs and a blanket between the knees kept them apart to reduce the possibility of phase wrapping (an artifact which appears as a ghost image of the contralateral knee overlaid on the joint of interest). The subject was requested not to move.

The field of view (FOV) was positioned so that the joint was approximately centered in the image.

The images were obtained using a multi-slice fast spin echo sequence. This is the same basic sequence used by Fellows and Hill. Parameters were varied in development to improve visibility of bone and its contours while maintaining reasonable scan times. See Table 3.1 for high-resolution scan parameters.
Table 3.1: High-resolution scan parameters.

An example of a segmented high resolution MR image can be seen in Figure 3.2.
3.1.2 **Low-Resolution Imaging**

Fast, low-resolution images were obtained for a range of loaded positions of knee flexion.

3.1.2.1 **Loading device**

A custom-built MR-compatible rig was designed to load the leg while the subject was supine in the scanner (Figure 3.3). The load applied at the foot was about 80 N (97), using MR-compatible sandbags. This is much lower than the ground reaction force during activities of daily living (usually one body weight or more), but was chosen to reduce patient fatigue and associated motion.
The loading device was modified slightly to be secured on the scanner couch.

![Custom MR-compatible loading rig](image)

**Figure 3.3**: Custom MR-compatible loading rig. The foot is placed on the pedal (left), and weights are placed on the platform (right).

### 3.1.2.2 Subject positioning

The subject was positioned with the foot of the study leg on the pedal of the loading device. The tibiofemoral (TF) joint line was marked on the subjects’ skin and TF flexion angles were estimated using a goniometer. The leg was supported in the correct position with foam wedges, and the subject was moved into the scanner on the couch.

### 3.1.2.3 Scanning

Upon completion of the preparatory scans, the technologist signaled an investigator in the scanner suite to remove a block within the loading device which caused the load to be applied. The subject was asked to maintain his/her position by pressing on the pedal against the weight. A signal was then given to the technologist who ran the scan sequence. During the scanning, the investigator observed coincident markings on the loading device for any movement during the scan. When the scan was complete, the investigator reinserted the block and removed the weight from the subject. The subject was then moved out of the scanner and repositioned for the next flexion angle.

### 3.1.2.4 Pulse Sequence

The sequence was a multi-slice T1-weighted fast spin echo sequence. Each scan lasted 28 seconds. The short scan time was imperative to minimize subject fatigue.
See Table 3.2 for low-resolution scan parameters. Figure 3.4 shows one segmented low-resolution image.

<table>
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<tr>
<td>Matrix size (reconstructed)</td>
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<td>Slice Thickness</td>
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</tr>
<tr>
<td>Number of slices</td>
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</tr>
<tr>
<td>TSE factor</td>
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</tr>
<tr>
<td>TE (echo time)</td>
<td>10 ms</td>
</tr>
<tr>
<td>TR (shot interval)</td>
<td>700 ms</td>
</tr>
<tr>
<td>Scan duration</td>
<td>28 seconds</td>
</tr>
</tbody>
</table>

Table 3.2: Low-resolution scan parameters.
3.1.2.5 Flexion Angle Range

The flexion angle range that could be studied was limited by the size of the scanner bore, and also the "shutter size", or usable imaging area inside the scanner, which was generally smaller than the bore size (Figure 3.5). Thus, the range of flexion angles was variable between individual subjects of different sizes. For example, a short subject could achieve higher flexion angles within the shutter than a tall person could. We attempted to image at every ten degrees from 0 to 60 degrees. However, if the flexion limit was reached before six low-resolution scans were completed, the remaining images were taken at five degree intervals between already acquired images.

Because measuring the knee flexion angle in place in the MR with the goniometer was difficult and inaccurate, the actual flexion angles measured were somewhat different from the evenly spaced angles attempted. Flexion angles used in the analysis were those calculated using the kinematic analysis technique rather than the rough positioning measurements made with the goniometer.
3.2 Analysis

3.2.1 Segmentation of images

To create the three-dimensional high-resolution model point cloud and the low-resolution data contours, all three bones were segmented in each slice of the scans. Segmentation involves defining a region on an image that corresponds to one physical structure (such as a femur). Using medical image processing software (Analyze, Mayo Clinic, USA), a spline was manually created following the edge of the cancellous bone in each image. Cancellous bone was segmented because cortical bone is black on MR images and could not be distinguished from other structures. Adjustments were done by hand, and finally the outline was saved in a data file known as an object map. A semi-
automated segmentation approach, using seed growing with thresholding, was attempted, but the segmentation was not as accurate as when done fully manually, and the shape matching tended to give a poor result in these cases.

For the high-resolution images, 3D surfaces of each of the bones (femur, tibia, patella), created from segmented slices, were saved as separate surface point clouds using Analyze. Low-resolution contours of each bone were saved. Approximately twelve contours were created for the tibia and femur, and about seven for the patella, depending on the size of the joint and the exact position of the slices in relation to it.

### 3.2.2 Coordinate system application

To calculate relative positions and orientations of the three bones of the knee, specific anatomical points were identified and used to systematically create anatomical coordinate systems fixed to each bone model. The specific points chosen are listed in Sections 3.2.2.1 – 3.2.2.3. In order to select the points, the high-resolution images (without segmentation) were re-loaded and interpolated to create cubic voxels and were viewed in orthogonal planes using Analyze, which allowed us to page through slices quickly and easily. Points were then selected with a mouse pointer and the values were recorded. A simple transformation of the Analyze coordinate space to the Matlab (MathWorks, USA) coordinate space was performed. The coordinate axes and origin were defined in a Matlab program.

We used the point selection convention defined by Fellows and Hill (48,72).

#### 3.2.2.1 Femur

**Origin:**
The sagittal plane slice in which the intercondylar notch was most superior was identified. The most distal aspect of the femur (cancellous bone) on this slice was chosen to be the origin of the femoral coordinate system.

**Flexion axis:**
The axial plane slice on which the intercondylar bridge disappeared was identified, and the slice immediately superior to it was selected. On this slice, the most posterior points of the medial and lateral condyles were selected to define the flexion axis of the femur.
Long axis:
From the high resolution scan, the centroid of the most proximal axial slice of points of the point cloud femur model was calculated using a Matlab program. This point and the femoral origin defined the long axis of the femoral coordinate system.

Third axis:
The third axis was defined by taking the cross product of the long and flexion axes.

Figure 3.6: Femur coordinate system. Red is long axis (superior), blue is flexion axis (lateral), and green is third axis (posterior). The yellow outline shows the femur model reconstructed from the high-resolution scan.

3.2.2.2 Tibia
Origin:
The origin was chosen as the highest point on the medial tibial spine (selected from the sagittal plane slices).

Flexion axis:
The most superior point on the fibula was identified on the sagittal plane images. The axial plane slice containing this point was viewed and the most posterior points of the medial and lateral tibial condyles were selected. These points defined the flexion axis of the tibia.

Long axis:
From the high resolution scan, the centroid of the most distal axial slice of points of the tibial point cloud was calculated using a Matlab program. This point and the tibial origin defined the long axis of the femoral coordinate system.

Third axis:
The third axis was defined by taking the cross product of the long and flexion axes.

![Figure 3.7: Tibia coordinate axes. Red is long axis (superior), blue is flexion axis (lateral), and green is third axis (posterior). The yellow outline shows the tibia model reconstructed from the high-resolution scan.](image)

3.2.2.3 Patella

Origin:
The most posterior point on the axial mid-patellar slice was identified as the origin.

Temporary flexion axis:
The axes of the patella were identified by finding the mid-patellar slices in the axial and sagittal planes. In the axial plane, the most lateral and most posterior points of the patellar cancellous bone were identified. These points defined the temporary flexion axis.

Long axis:
In the sagittal plane, the most superior and inferior points were identified. These points defined the long axis of the patella.
Third axis:
The cross-product of the long axis and the temporary flexion axis defined the third axis.

Flexion axis:
The long axis was crossed with the third axis to produce a true flexion axis. This was different from the temporary flexion axis because the long axis and the temporary flexion axis are not orthogonal.

Figure 3.8: Patella coordinate axes. Red is long axis (superior), blue is flexion axis (lateral), and green is third axis (posterior). The yellow outline shows the patella model reconstructed from the high-resolution scan.

3.2.3 Shape-matching
We shape-matched the high-resolution bone models and their associated coordinate systems to each position of loaded flexion defined by the low-resolution scans.

The segmented bone shapes were loaded into custom software written in Matlab. A preliminary match was achieved by eye as a starting position for the algorithm. The investigator input rotations and translations, and checked a plot showing a match of the models (high-resolution) to the data (low-resolution). This was necessary to avoid divergent solutions when the shape-matching algorithm was started.
Occasionally, either the model set or the data set for a particular bone contained more of the tibial or femoral shaft than the corresponding data or model set (due to positioning, flexion angle, etc.). This can reduce the accuracy of the iterative closest points (ICP) algorithm used for the registration (48). The set with more bone was truncated to the length of the shorter bone by manually selecting a truncation point and then visually confirming a good correspondence.

The iterative closest points (ICP) algorithm was employed to match each of the high-resolution bone models to each of the low-resolution segmented images. This method minimizes the sum of the distance between the points of the model cloud and the data contours. Shape-matching errors were calculated as the mean distance between the model and the data, in millimetres.

Figure 3.9: One flexion angle, shape matched (red is femur, blue is patella, green is tibia, yellow lines are low resolution bone contours) - left. All flexion angles for one subject - right.

3.3 Representation of kinematic patterns

Following the shape matching procedure, positions and orientations of associated bone coordinate systems were determined at each position of flexion, then attitude and position were represented with a joint coordinate system (32,64). This results in twelve
parameters (tibial flexion, tibial adduction, tibial internal rotation, tibial proximal translation, tibial lateral translation, tibial anterior translation, patellar flexion, patellar spin, patellar tilt, patellar proximal translation, patellar lateral translation, patellar anterior translation) at each of six flexion angles for each subject, measured with respect to the femur at the anatomic origin of each bone. The parameters were plotted against tibial flexion angle to obtain motion curves for the tibia and patella relative to the femur.

Since it has proven difficult to characterize motion curves for analysis, previous investigators have fit straight lines to data to describe patterns of motion for statistical analysis (97). While detail is reduced when they are linearized, we believe the increased ease of comprehension and statistical analysis outweighs this disadvantage.

Figure 3.10: Patellar kinematic directions used in this study. (1) Patellar flexion, (2) patellar tilt, (3) patellar spin, (4) patellar proximal translation, (5) patellar anterior translation, (6) patellar lateral translation. From Fellows Thesis (48).
3.4 Kinematics with metal

To determine the feasibility of using this protocol at 3T in patients with surgical hardware implanted near the joint, two volunteers were imaged using the protocol as described above. This same kinematics procedure was completed with metal in place at the proximal tibia at 1.5T following HTO by Hill et al. (72,73), but had never been attempted at 3T. Metal artifact generally worsens with increased field strength, so it was not clear if it would be possible to determine bone outlines for segmentation at 3T.

This protocol was reviewed and approved by the UBC Clinical Research Ethics Board. All volunteers gave informed consent. See Appendix B for a copy of the ethics application.

Volunteers with metallic implants were contacted through their surgeons. Each volunteer was sent an information package and consent was asked for on the scan day.

Subjects with metal implants were approved for scanning on a case-by-case basis by the supervising radiologist. Due to the higher field strength, there is a greater potential for heating of an implant, particularly stainless steel, and therefore these scans were performed with caution. Patients were warned of the possibility of heating and were asked to ring the technologist to stop the scanning if they experienced any heating. The scans were closely monitored.

3.4.1 Subjects

The two subjects were patients who had undergone HTO and had metal implants in place. One subject had a stainless steel implant (Synthes small fragment plate, West Chester, PA, USA) and the other subject had a titanium implant (Puddu plate, Arthrex, Naples, FL, USA). They were screened for MR risks by the technologist, and approval to scan was obtained from the radiologist in charge. The subject with titanium plate had previously undergone post-operative assessment of kinematics at 1.5T.

3.4.2 Methods

Each subject underwent the standard kinematics scans described above: one relaxed high-resolution scan and six loaded low-resolution scans at various flexion angles.
3.4.3 Results

High- and low-resolution images from two subjects, one with a titanium implant from HTO and one with a stainless steel implant from HTO, are shown in Figures 3.11 and 3.12. Imaging with stainless steel was not viable. Segmentation of the bones was not possible.

Figure 3.11: Stainless steel images – high-resolution (left) and low resolution.

The images of the patient with titanium were also distorted, but not as much as the images of the patient with stainless steel. Enough of the bone outline was clear to allow segmentation and shape-matching.
Figure 3.12: Titanium high-resolution segmented image. The tibia is shown in green, femur in red, and patella in yellow. Dark oval shapes in the tibia are artifacts caused by the titanium plate.
Kinematic parameters for the TF and PF joint were calculated for the range of loaded flexion from the six segmented low resolution scans.

**Figure 3.13: Tibial flexion v. tibial rotations for the subject with titanium hardware.**

In the subject with titanium hardware, the tibial abducted and rotated externally with flexion (Figure 3.13).
In the subject with titanium hardware, the tibial translated proximally, laterally and posteriorly with increasing tibial flexion (Figure 3.14).
Figure 3.15: Tibial flexion v. patellar rotations for the subject with titanium hardware.

The patella flexed with tibial flexion, where there was almost no change in spin and tilt through the range of flexion (Figure 3.15).
In the subject with titanium hardware, the patella translated distally, laterally, and posteriorly with increasing tibial flexion (Figure 3.16).

### 3.4.4 Discussion

The kinematic procedure at 3T with metal near the joint yielded images that could be successfully segmented and shape-matched. Manual low-resolution image segmentation was challenging: segmentation in this case was performed by relying on the high-resolution image to interpret artifacts and real bone. High-resolution image segmentation was straightforward.

The subject imaged for this test was imaged as part of the study by Hill (72), subject number 080663. This allows us to make direct comparisons to the same procedure at 1.5T, keeping in mind that these measurements were made more than one year apart, and that Hill reports data for only a limited range of flexion (30 to 50 degrees).
Figure 3.17: Tibial rotations for a subject with titanium using the 3T protocol compared to results from the same subject using the 1.5T protocol (72).

3.4.4.1 Tibial rotations

The rate of adduction decrease with flexion and the value of adduction at full extension at 3T are very similar to those reported at 1.5T by Hill (Figure 3.17). Internal rotation was different: Hill reported little change in adduction with flexion, with the value of adduction remaining at around 5 degrees, while this study shows a decreasing adduction with flexion.
3.4.4.2 Tibial translations

The rate of tibial anterior translation with tibial flexion at 3T was very close to those reported by Hill at 1.5 T, with a slightly higher value of anterior translation at full extension (by about 3 mm) (Figure 3.18). Proximal translation and lateral translation at 3T are very close to those reported for 1.5T by Hill.
3.4.4.3  Patellar rotations

Patellar flexion (increasing with tibial flexion) and patellar spin (slightly decreasing with tibial flexion) at 3T are nearly identical to the curves reported at 1.5T by Hill (Figure 3.19). Patellar tilt increased at a similar rate with tibial flexion and the value of tilt at full extension measured at 3T is slightly lower (about 2 mm) than that reported by Hill.
Patellar Translations

Figure 3.20: Patellar translations for a subject with titanium using the 3T protocol compared to results from the same subject using the 1.5T protocol (72).

3.4.4.4 Patellar translations

Anterior translation at 3T was very close to that reported at 1.5T by Hill, with a slightly steeper decrease with tibial flexion in the current study (Figure 3.20). The rate of decrease of proximal translation with tibial flexion is very similar; the value of proximal translation at full extension is higher in Hill’s study (by about 10 mm). Lateral patellar translation has a similar rate of increase with tibial flexion, but again the value at full extension is about 10 mm higher in Hill’s study at 1.5T.
Generally, the data in this study and in Hill's study are very similar. Hill applied slightly different tibial axes to his post-operative patients, to reflect the change in their bone geometry and allow a more relevant comparison with their pre-operative data. This may explain some of the differences between the tibial kinematic results in the two data sets. The differences in patellar kinematics between the two studies are generally limited to intercepts. Since the coordinate systems were assigned by two different observers, there may be small differences in placement and direction of axes. This is one of the most sensitive parts of any kinematic analysis. In repeatability tests between experimenters using the same 1.5T data sets and performing segmentation and axes assignment, the inter-experimenter error has been shown to be 2.14 degrees or less for rotation measurements, and 0.68 mm or less for translation measurements (47). Note that these are not the same data sets, however. These could also be true differences in kinematics which naturally occurred in the time between the two sessions due to healing, morphological changes in bone, changes in muscle balance, or loss of correction.

3.4.5 Conclusions

The kinematic method at 3T in a subject with titanium surgical hardware worked very well. We have demonstrated that the results are very similar in the same subject with a titanium implant imaged at 1.5T and 3T, despite these imaging sessions taking place more than one year apart and the analysis having been done by different experimenters.
4 Protocol development for delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) in the presence of hardware at 3T

I would like to acknowledge the help of Dr. Burkhard Mädler with the software, analysis, and presentation of results in this chapter.

4.1 Introduction

This chapter describes the development of a protocol for assessing cartilage changes non-invasively pre- and post-HTO. Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) is a method used to assess glycosaminoglycan (GAG) content non-invasively in cartilage. GAGs are macromolecules that contribute to the material strength of cartilage and have been shown to be depleted in osteoarthritic cartilage (145).

We developed and assessed pulse sequences and analysis techniques to perform dGEMRIC before and after HTO using UBC's Philips Intera 3T magnet. While details of several dGEMRIC studies have been published (Table 4.1), no study had assessed dGEMRIC in the presence of surgical hardware, only one was at 3T, and no study used a Philips scanner.

<table>
<thead>
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<th>Manufacturer</th>
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<th>Hardware?</th>
<th>Subjects</th>
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<td>Siemens</td>
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<td>3.0T</td>
<td>Yes</td>
<td>Medial TF OA, HTO patients (knee)</td>
</tr>
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</table>

Table 4.1: Summary of published in vivo studies using dGEMRIC.
4.2 Original dGEMRIC protocol

A description of a dGEMRIC protocol for 1.5T was published in 2001 by Burstein et al. (26)

A double dose (0.2mmol/kg or 0.4 mL/kg) of gadopentetate dimeglumine (Gd-DTPA\textsuperscript{2-}, Magnevist, Berlex Laboratories, USA) was administered intravenously to an anticubital vein. Following administration of the contrast agent, the subject was asked to exercise the joint for 10 minutes. This exercise was 5 minutes of active flexion-extension and 5 minutes of walking.

Imaging began two hours following the contrast administration. The imaging window continued until three hours post-injection, when the contrast agent would begin to diffuse out of the cartilage.

The scanner was a Siemens Vision 1.5T and used a small flex coil or a dedicated extremity coil. Scan parameters are shown in Table 4.2. This protocol has been used in several studies (26,141-143).
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<th>Value</th>
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<tr>
<td>Scan durations</td>
<td>Total approx. 12 minutes</td>
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Table 4.2: 1.5T dGEMRIC scan parameters (from Burstein et al. (26)).

4.3 Safety, Ethics, and Health Canada

This protocol was reviewed and approved by the UBC Clinical Research Ethics Board. All subjects and volunteers gave informed consent. See Appendix B for a copy of the ethics application.

Subjects were recruited through their orthopaedic surgeon. The surgeon asked for permission to give the investigators the patients' contact information. I mailed each subject a letter and information package with a copy of the consent form. I then contacted the subject by telephone. If he or she was interested, I did a pre-screening for the MR to determine whether any special approval was required to scan. A scan time was booked, and consent was asked for on the scan day.

Volunteers were recruited through various channels. Volunteers with metallic implants were contacted through their surgeons, in a similar way to subject recruitment. Normal
volunteers were recruited from personal contacts. Each volunteer was sent an information package and consent was asked for on the scan day.

Approval was obtained from Health Canada to use the contrast agent, Magnevist, for an off-label use in the musculoskeletal system (dGEMRIC). Protocol, consent forms, and product monograph were submitted. A qualified study physician was identified. Important considerations were an accurate, up to date explanation of potential adverse reactions in the consent form (see Appendix D for Health Canada application).

Magnevist is often used off-label in the clinical setting for musculoskeletal contrast enhancement; however there is a higher standard when it comes to research and procedures that are not medically necessary. Approved indications for Magnevist include contrast enhancement for cranial and spinal lesions, and lesions of abnormal vascularity in the head and neck (19).

There are no contraindications for the contrast agent, however several precautions were observed, and the contrast agent was not administered to those with a history of seizure, those with kidney or liver dysfunction, those who were pregnant or breast-feeding, or anyone with severe asthma or allergies (19).

All subjects and normal volunteers were screened using a standard MR screening form by the technologist. If there was a suspicion of metal in the subject’s eye, or if the subject had been a metal worker or machinist, an orbital x-ray was performed. Normal volunteers were not x-rayed or scanned if there was a possibility of metal in the eye. Subjects with metal implants were approved for scanning on a case-by-case basis by the supervising radiologist. Due to the higher field strength, there is a greater potential for heating of an implant, particularly stainless steel, and therefore these scans were performed with caution. Patients were warned of the possibility of heating and were asked to ring the technologist to stop the scanning if they experienced any heating. The scans were closely monitored.

4.4 dGEMRIC on the Philips Intera 3.0 T magnet

Our objective was to develop a T1 measurement protocol suitable for dGEMRIC after surgery on UBC’s Philips Intera scanner. Although we had protocols suitable for other
scanners (most at 1.5T), we could not apply these directly because of differences in field strength, coils, and scanner programming, the effect of which is that a sequence optimized for one set of equipment may be sub-optimal on another. Each manufacturer programs their equipment slightly differently – limitations on scan parameters can be different and the exact pulse sequences can be different. Gadolinium-doped phantoms were scanned to establish a protocol that worked to calculate T1. Then volunteers were scanned without contrast agent to determine slice positioning and other scan parameters. Finally volunteers were scanned with contrast agent to verify that the process worked.

4.4.1 Approaches to measuring T1

As noted in Chapter 2, the dGEMRIC index (or calculated T1 value) is an estimation of the concentration of GAG in the tissue. T1 is a tissue property that varies with field strength and tissue type. Thus, the same tissue will have different T1 values when imaged in a 1.5T scanner and a 3.0T scanner.

There are several ways to measure T1, each involving a series of images. T1 is also known as the spin-lattice relaxation time (units of ms). One image by itself can be said to be T1-weighted (tissues with higher T1 will be brighter), but neither T1 nor differences in T1 can be quantified. In a series of T1-weighted images, however, the signal intensity of each tissue changes according to its T1. By fitting a curve of these signal intensities versus the variable parameter in the scans, T1 may be calculated.

Two types of T1 measurement were tested. Inversion recovery (IR) has a 180 degree inversion pulse at the beginning of the sequence. It is often used to null signal with a particular T1, such as that of fat. The critical time interval is the time between the inversion pulse and the next pulse (90 degrees). Following the 180 degree pulse, the magnetization is along the z axis (where z is the direction of the $B_0$ magnetic field) with a magnitude of $-fM_0$. The z-component of the magnetization increases exponentially to $M_0$, the steady-state value. When a 90 degree pulse is applied before the magnetization is fully recovered, the magnitude of the magnetization which is flipped is $M_z$ (the amount of magnetization in the z-direction at the time of the 90 degree pulse). Thus the signal intensity relates directly to the rate of recovery (dependent on T1).

Saturation recovery (SR) involves using a series of sequences with decreasing repetition times (TR). After a 90 degree pulse, the magnetization in the z-direction is zero. It then
begins to recover exponentially along the z-axis to the steady-state value of $M_0$. When another 90 degree pulse is applied before the magnetization is fully recovered (i.e. at a short TR), the magnitude of the magnetization which is flipped is $M_z$ (less than $M_0$), so there is a declining signal response related to the T1 of the tissue.

### 4.4.2 Analysis

The analysis of dGEMRIC scans has several steps. To measure the T1 values of cartilage, a series of images were taken with one parameter varied (either inversion time or repetition time). These images were loaded into a T1-mapping software program. Curves were created for each pixel by plotting the signal intensity values against the varied parameter for the same pixel in each image. The resulting plots followed curves resembling those in Figures 4.1 and 4.3. By fitting a curve to these points, it was possible to determine the T1 value, which is a time constant for the curves. In this way we calculated a T1 value at each pixel in the image. These values for cartilage were plotted as a colour map in order to visualize local differences in T1, which is equivalent to cartilage quality. Specific pulse sequences and fit equations are described below.

#### 4.4.2.1 Inversion Recovery

We used an inversion recovery sequence to calculate T1 from a series of eight scans with different inversion times. T1 was calculated by fitting the curve with the following equation:

$$S(TI) = S_0 \left[1 - fe^{\left(\frac{TI}{TI}\right)} + e^{\left(\frac{TR}{TI}\right)}\right],$$

Equation 4.1

where $S(TI)$ is signal intensity in the image, $S_0$ is the signal as $TI$ goes to infinity, $TR$ is the repetition time (2200 ms for all IR scans), $TI$ is the inversion time, $TI$ is the spin-lattice relaxation time, and $f$ is a fit factor. $TI$ was found by the iterative fit program for each pixel of the image. See Figure 4.1 for plot.

The sequence used was an adiabatic pulse sequence. The purpose of this sequence is to ensure that the inversion pulse flip angle is 180 degrees even in the presence of inhomogeneities in the magnetic field, which is important for our application because metal hardware causes inhomogeneities. The drawback is that the magnitude of the magnetization is attenuated. Therefore a fit factor, $f$, is used to fit the curve. This fit factor was allowed to vary in value from 1 to 2, where 2 would be a non-attenuated
magnetization vector. Note that three values are varied to fit the data points to a curve described by Equation 4.1: $T_1$, $S_0$, and $f$.

The absolute value in Equation 4.1 is required due to the magnitude reconstruction of the images. The 180 degree pulse flips the magnetization vector into the anti-parallel orientation, and thus the signal intensities are negative. The scanner could only record magnitude data and not real data, so all measured values had positive signs. See Figure 4.2 for an example of a curve using real data.

![Figure 4.1: Standard inversion recovery curve.](image-url)
Figure 4.2: Inversion recovery curve using "real" data.

4.4.2.2 Saturation Recovery

We also used a saturation recovery sequence to calculate T1 from a series of eight scans with varying repetition times (TR). The data points were fit with a curve defined by the following:

\[ S(TR) = S_0 \left( 1 - e^{-\frac{TR}{T1}} \right) \]

Equation 4.2

where \( S(TR) \) is signal intensity in the image, \( S_0 \) is the signal as \( TR \) goes to infinity, \( TR \) is the repetition time, and \( T1 \) is the spin-lattice relaxation time. See Figure 4.3 for plot.

SR scans are inherently noisier than IR scans. We expect that images from the SR series will have lower image quality than the IR series.
Figures 4.1 and 4.3 illustrate another reason that the SR method is not as robust as the IR method. Since the IR curve has a very distinct point (the null point), the fitting is more robust. The SR curve, on the other hand, does not have a distinctive feature, so one erroneous point may dramatically change the T1 value calculated from the fit. This leads to higher standard deviations in the regions of interest.

4.4.2.3 Software

A custom program using IGOR (WaveMetrics, Oregon, USA) was used to analyze the image series. The images were loaded into the software in the original Philips PAR-REC format. The PAR files were checked for a scaling parameter assigned by the scanner and the inverse factor was applied to each image. A registration was performed to ensure the images were in the same position and each pixel was the same small area of tissue. The software then performed a pixel by pixel fit of the T1 curve. This T1 curve is created by plotting signal intensity for a single pixel in each image versus T1 or TR time for each image, depending on the type of sequence. Two types of sequence were used to calculate T1. Burstein et al., the group that created the original dGEMRIC protocol, have made software available to other research groups.
to calculate T1 values from dGEMRIC images. This software was inappropriate for our use as it only accepted DICOM images (a widely-used medical imaging format), but our DICOM images maintained the scaling factor applied by the Philips scanner.

4.4.2.4 Display

The T1 values calculated for each pixel were mapped with colour correspondence. The TI = 1800 ms image or TR = 2200 ms image was used to segment the cartilage and create a mask. These images were the best quality (highest signal), thus the simplest to segment. The other images were consulted in the process. The mask was then applied to the colour map so that only calculated T1 values from the cartilage were included. This cartilage colour map was then overlaid on the highest signal original image to create a composite image that is easier to interpret.

Regions of interest were identified on the images and average T1 values were calculated for those regions of interest.

The measured values of T1 in cartilage depend on field strength, presence and dose of contrast agent, and amount of GAG in the cartilage. The normal value of T1 for cartilage without contrast at 3T has been measured at 1240 (104) ms (60). The values for healthy cartilage with contrast will be lower than the value of cartilage without contrast, due to the gadolinium. The values of T1 of degraded cartilage with contrast will be even lower than healthy cartilage with contrast, as more gadolinium will be present in areas with low GAG content. There are no published values for T1 of cartilage with a double dose contrast agent at 3T. Note that the different layers or zones in cartilage have different GAG concentrations in normal, healthy cartilage (38). We expect that the thin superficial layer will have appreciably lower T1 values than the rest of the tissue.

4.4.3 Phantom Imaging

We used phantoms to develop appropriate pulse sequences to perform dGEMRIC. Phantoms are non-biological constructs used to test and optimize pulse sequences for later use with human subjects. The advantages of phantom use include allowing long scan times, homogeneity, and maintained positioning. Disadvantages include not representing complex human tissue.
4.4.3.1 Phantom Components

Phantoms for dGEMRIC testing were constructed using a MR-compatible vessel filled with Hank's Balanced Salt Solution doped with gadopentate dimeglumine (Figure 4.4). Various concentrations of gadolinium were used in different phantoms to roughly mimic the concentrations found in cartilage with contrast *in vivo* (16,82).

4.4.3.2 Imaging

Phantoms were imaged with an IR pulse sequence. They were positioned and secured on the MR couch. The coil used was the Flex-M surface coil. A wait time (approximately 10-15 minutes) was added prior to imaging to allow wave motion in the phantom to subside. This wave motion can produce dramatic artifacts in the images.

Phantoms were used to test early forms of the protocol because we wanted to minimize the use of contrast agent in volunteers for the development of the protocol (Figure 4.5). It was not possible to develop protocols on volunteers without injecting contrast agent because cartilage without contrast agent has a much higher T1 value than cartilage with contrast agent. To accurately measure T1, a TR time of five times the expected T1 value is optimal (to allow all spins to recover). T1 is a time constant for the recovery of the longitudinal magnetization vector. The following equation illustrates this concept.

\[
M_z = M_0 \left( 1 - e^{-\frac{TR}{T1}} \right), \quad \text{Equation 4.3 (66)}
\]

where \(M_z\) is the longitudinal magnetization, \(M_0\) is the longitudinal magnetization as time goes to infinity, \(TR\) is the repetition time, and \(T1\) is the spin-lattice relaxation time.

When TR equals five times T1, \(M_z\) equals 99.3% of \(M_0\), or is essentially fully recovered. If the TR is shorter, the signal to noise ratio is reduced, as fewer spins (only those fully recovered) will contribute to the signal output. The dGEMRIC protocol's TR value is about five times that of doped-cartilage, but only about two times that of undoped-cartilage. Also, without contrast agent the T1 times must be altered to span the important points on the undoped curve to obtain accurate results.

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Figure 4.4: Photo of simple phantom.

Figure 4.5: Phantom testing. Within the image, the left-hand phantom contains undoped Hank’s balanced salt solution. The right-hand phantom contains Hank’s doped with Magnevist. Note that the variation in calculated T1 in left hand bottle is due to saline having a very high T1, which could not be measured correctly with this sequence. This is analogous to cartilage without contrast agent, as mentioned above.

4.4.4 Volunteers without contrast agent

Since the knee joint is much more complex than a homogeneous bottle of doped Hank’s solution, volunteers were imaged with the IR series first without contrast agent to ensure that the in vivo images were of sufficient quality and to determine slice selection, coil positioning and FOV positioning prior to scanning with contrast. There are two reasons for doing this without contrast agent: if the scanning protocol does not work in vivo, the volunteer has not been unnecessarily injected with a drug, and if adjustments need to be made there is no imaging window to exceed. All volunteers gave informed consent.
Difficulties were encountered with file conversions from the Philips scanner format to the more common DICOM format. During analysis, it was noticed that the curves were ill-shaped, which led to the discovery of the persistent Philips scaling factor mentioned earlier. Most of these images were converted to DICOM for analysis and storage on the Radiology Department’s PACS (Picture Archiving and Communication System) and the original PAR-REC files were then deleted from the scanner. Since the value of the scaling factor was lost with the PAR-REC files, the images could not be analyzed. These scans were valuable in that we obtained this knowledge, and were also helpful in determining final slice positioning and selection.

4.4.5 Volunteers with contrast agent

The next step was to image volunteers with the IR series following a contrast agent injection. Two volunteers with no known knee pathology were scanned (one 27 year old female, one 37 year old male). At each session, the volunteer was given a double dose (0.2 mM/kg) of Magnevist contrast agent and asked to walk for ten minutes. At ninety minutes post-injection we began scanning. All volunteers gave informed consent. We chose to begin scanning at ninety minutes rather than two hours post-injection because recent work by Burstein and colleagues indicates that a shorter wait time is appropriate and allows a longer scanning window of ninety minutes (up to three hours post-injection).

The analysis of the first volunteer (female) showed abnormally high values of T1. This indicated that not enough exercise was performed, causing the concentration of contrast agent in the cartilage to be lower than normal. The protocol was adjusted to ensure supervised and timed exercise.

The second volunteer (male) underwent a dGEMRIC sequence twice, to test the protocol and to determine the scanning order. During the first session, the PF joint was scanned first, and the TF joint was scanned second. During the second session the order was reversed. The images were analyzed. It was found that when the thicker patellar cartilage was scanned first, the T1 values were higher than expected near the bone (close to values of undoped cartilage (60)). The overall T1 values for the patellar compartments were similar, but the cartilage near the bone had a higher value and the cartilage near the surface had a lower value (Figure 4.6 - top). Since cartilage is avascular and principally nourished by synovial fluid, this may indicate that the contrast
agent had not fully equilibrated. Since the lower contrast agent concentration appears as "healthier" cartilage, according to the dGEMRIC index, it was important that the diffusion be complete before imaging. When the patellar cartilage was imaged second and it had an extra 30 minutes to allow the contrast to diffuse, the T1 values were more spatially consistent (Figure 4.6 - bottom). Therefore, the protocol was adjusted such that the TF joint was scanned first and the PF joint second.
Figure 4.6: Scan order. Axial scan performed first (at 90 minutes) – top. Axial scan performed second (at 120 minutes) – bottom. Note higher T1 near bone interface and lower T1 near cartilage surface in the top image.
Figure 4.7: Scan order. The bars denote the mean of the pixel T1 values within the ROI, and the error bars indicate the standard deviation of the individual T1 pixel values within the ROI.

Figure 4.7 shows the results of reversing the scan order. The T1 values measured in each patellar compartment are similar, however it is clear that the standard deviation in these values is much smaller.
Figure 4.8: ROIs of specific areas in scan order trials. The bars denote the mean of the pixel T1 values within the ROI, and the error bars indicate the standard deviation of the individual T1 pixel values within the ROI.

When ROIs were selected in several regions of the patellar cartilage, regional differences are apparent (Figure 4.8). For the scan sequence with the axial scan first, the superficial/middle zone area of the patellar ridge showed low T1s, while the deep zone area of the medial and lateral compartments were elevated. Transient focal "lesions" have been described previously (144), and have been associated with lower wait times.

In the sequence with the axial scan second, the values in the ROIs even out to give normal T1 times for all areas of the patella. The deep cartilage is still higher than the more superficial cartilage, as expected from normal GAG distribution changes with depth.
4.5  *In vivo* dGEMRIC in subjects with implanted hardware

4.5.1 Recruitment

We recruited subjects with implanted hardware to assess dGEMRIC after HTO. Stainless steel is the predominant material used in HTO hardware. A volunteer was found locally with a stainless steel implant.

We also assessed one subject with implanted titanium hardware. Titanium implants can also be used for HTO fixation but are rarely used due to higher cost. Since titanium is more MR-compatible than stainless steel it was desirable to image a volunteer with this type of implant. I was unable to find any local patient with a titanium implant from HTO. In order to test our scans in vivo, I recruited one of seven subjects from a previous study done by Hill (73) who all had titanium implants specifically to allow MR scanning. This volunteer was flown from Ontario to British Columbia for two days of scanning to check our protocols.

4.5.2 In vivo testing

The two volunteers with metal implants in place from HTO were scanned using the standard dGEMRIC protocol to determine whether metal artifact would affect the results. Both subjects gave informed consent. The subjects were scanned at the UBC 3.0 Tesla Philips Intera scanner, using a six channel cardiac coil. This coil was used because the more appropriate Flex-M surface coil was not yet available.
Figure 4.9: Subjects with metal plates in the proximal tibia: (a) Stainless steel (b) Titanium – note the lack of visual distortion in the cartilage area (IR-TSE, TI = 1800ms).

Images from the subject with a stainless steel plate implanted in the proximal tibia could not be used for dGEMRIC analysis due to distortion from the plate (Fig. 4.9a). Images from the subject with a titanium plate implanted in the proximal tibia exhibited much less distortion (Fig. 4.9b). The cartilage area, in particular, appeared unaffected.

When the images were analyzed, however, the signal intensity versus TI time curves at a single pixel in the cartilage areas did not show the typical null point in a standard IR-curve and were often nearly flat. This resulted in severe fitting problems and therefore T1-values which were meaningless. When mapped, the calculated-T1 values showed large variations, and there was a clear demarcation in the medial tibiofemoral cartilage (Figure 4.10). These results together indicated an artifact not visible in the original images.
Figure 4.10: Subject with titanium implant – note highly variable T1 and demarcation in medial tibial cartilage which indicates an artifact.

The axial image was unaffected by the hardware, likely because the imaged cartilage was farther from the hardware than in the coronal plane image (Figure 4.11).
4.6 Artifact reduction

We assessed the effect of hardware on two different methods for measuring T1 using a phantom.

4.6.1.1 Phantom construction

A phantom was constructed using nested plastic bottles. The inner bottle was filled with a doped-saline solution with a T1 meant to resemble cartilage. The outer bottle was filled with a similar solution with a different gadolinium concentration, designed to have a T1 which resembled that of bone (16,82).

Figure 4.11: Axial image from volunteer with titanium implant. The axial T1 map is unaffected by the titanium in the proximal tibia (lateral patella T1 = 803 (201) ms; medial patella T1 = 643 (134) ms).
A titanium Puddu plate (Arthrex, USA) was mounted in styrofoam and placed in contact with the outer bottle of the phantom (Figure 4.12) during some of the scans, to imitate the location of an implant in HTO. The plate (Figure 4.13) and the screws are a titanium alloy (Ti6Al4V).
4.6.1.2 **Pulse sequences**

Both IR and SR pulse sequences were tested on the phantom. A 3D dGEMRIC sequence was tested on the 3.0T scanner as well. It is based on a gradient echo sequence with partial flip angles.

4.6.1.3 **Phantom testing**

T1 was measured and mapped in the phantom using inversion recovery and saturation recovery sequences, both with and without the titanium plate. Phantoms were scanned using the 3.0 Tesla Philips Intera at the UBC High-Field MRI Centre. The coil used was a Philips Flex-M surface coil. The phantom was also imaged on a GE 1.5 Tesla scanner using a birdcage head coil, to determine whether metal effects were related to field strength.

4.6.1.4 **Results: 3.0T**

A curved line artifact with a total signal void near the plate was evident in the phantom IR images with shorter TIs, but was not apparent in longer TI images (Figure 4.14, left and inset A). As we analyzed the inversion curves pixel by pixel from just outside the edge of the artifact toward the plate, the null point of the inversion curve appeared to shift left, implying a shorter and shorter T1 within the homogeneous phantom liquid. About nine pixels (approximately 3.5 mm) toward the plate from the boundary of the distortion, the null point shifted below 50 ms (our lowest TI value), and the curves were similar to those from the subject with titanium (Figure 4.14, right). The result on the T1 map is an area of altered and consequently inaccurate T1 values (Figure 4.15b). Note that this T1 map has used an inversion recovery fit for the entire map, and therefore the specific values in the proximity of the plate cannot be considered accurate, as the data do not obey the condition of an inversion recovery experiment.

We observed no such distortion of T1 when using the saturation recovery (SR) series on the same phantom (Figure 4.15d). However, the SR series resulted in a noisier image than the inversion recovery (IR) series (see Figure 4.15a and 4.15b) due to a lower signal-to-noise ratio (SNR) in the images and the absence of the characteristic null-point.

The phantom images of 3D sequence had too much distortion from metal to be usable.
Figure 4.14: The left image shows pixel positions and metal artifact in gadolinium-doped saline phantom (IR image at one inversion time: TI = 100 ms). Points 1 to 4 within inset A denote the ROI locations used to plot the signal intensity inversion curves depicted in the right diagram. Note the drift of the inversion point towards smaller IR times as the ROIs approach the implant, and the total disappearance of any signal changes in the vicinity of the Ti-plate.
Figure 4.15: T1 maps of phantom with (b,d) and without (a,c) titanium at 3.0 T: (a,b) IR; (c,d) SR

The gray rectangles 1 and 2 depict the location of the ROIs that were used for statistical analysis of the T1-maps (mean and standard deviation of the relaxation time T1):

- a) ROI1: (257 ± 2) ms; ROI2: (456 ± 3) ms
- b) ROI1: (256 ± 1) ms; ROI2: (423 ± 32) ms
- c) ROI1: (250 ± 9) ms; ROI2: (413 ± 18) ms
- d) ROI1: (249 ± 7) ms; ROI2: (419 ± 20) ms

In (b) and (d), the gray-shaded rectangles mark the approximate position of the titanium plate. The distortion of the T1-map is seen clearly in the area above the Ti-plate in (b).
4.6.1.5 Results: 1.5T

Images were taken of the phantom at 1.5 Tesla with and without the titanium HTO plate and using both IR and SR sequences. The distortion seen at 3.0 T was not evident at 1.5 T. See Figure 4.16.

![Figure 4.16: IR with titanium at 1.5 T (left), SR with titanium at 1.5 T (right).](image)

The green outlines in Figure 4.16 represent ROIs for the inner and outer bottles.

<table>
<thead>
<tr>
<th>Sequence at 1.5T</th>
<th>Inner bottle (T1 [ms])</th>
<th>Outer bottle (T1 [ms])</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR with titanium</td>
<td>427 (8)</td>
<td>242 (6)</td>
</tr>
<tr>
<td>SR with titanium</td>
<td>432 (15)</td>
<td>243 (29)</td>
</tr>
</tbody>
</table>

Table 4.3: T1 values for phantom at 1.5T. Mean T1 values for all pixels within the ROI are reported, as well as standard deviations of pixel T1 values within the ROI.

Table 4.3 shows the values obtained from ROIs of Figure 4.16. The standard deviations for the SR series were larger than for the IR series (as expected).

4.6.1.6 In vivo test

The SR protocol was tested on one normal volunteer (Figure 4.17). The resulting image is somewhat noisier than the axial IR image in the same volunteer (see Figure 4.6 – bottom).
4.7 Final protocol

We developed a protocol to image both the tibiofemoral and patellofemoral joints of subjects in our target population (those scheduled for HTO) using two different dGEMRIC series.

4.7.1 Contrast Agent Administration

A double dose (0.2mmol/kg or 0.4 mL/kg) of gadopentetate dimeglumine (Gd-DTPA², Magnevist, Berlex Laboratories, USA) was administered intravenously to an anticubital vein. A saline IV was inserted and checked to ensure appropriate placement and flow. The contrast agent was then injected into the saline line at a slow rate (approximately 1 minute for complete injection).

4.7.2 Exercise

Following administration of the contrast agent, the subject was asked to walk for a full 10 minutes. The IV line was maintained and the subject kept under observation while exercising to ensure no adverse reaction occurred. The IV was then removed.
4.7.3 Imaging

The subject was prepared for imaging and set up in the scanner in time to begin imaging ninety minutes following the contrast administration (this differs from the 1.5T dGEMRIC protocol paper) (82).

The subject was scanned using the 3.0 Tesla Philips Intera Gyroscan at the UBC High-Field MRI Centre. The coil used was a Philips Flex-M surface coil.

The subject was asked to lie supine on the scanner bench in a feet-first orientation. The coil (consisting of two rings) was placed with a ring on each of the anterior and posterior aspects of the knee. The coil was held in place with strapping. The lower legs had sandbags placed on either side, and a blanket was placed between the knees to reduce the possibility of phase wrapping. The legs were then strapped together at the knees to prevent motion.

The PF images were obtained using an inversion recovery fast spin echo sequence (see Table 4.4) and the TF images were obtained using a saturation recovery fast spin echo sequence (see Table 4.5).
### Table 4.4: Inversion recovery scan parameters for dGEMRIC at 3T.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix size (scan)</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Matrix size (reconstructed)</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Final in-plane resolution</td>
<td>0.39 x 0.39 mm</td>
</tr>
<tr>
<td>Field of View (FOV)</td>
<td>100 mm</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>3 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>1</td>
</tr>
<tr>
<td>TSE factor</td>
<td>9</td>
</tr>
<tr>
<td>TE (echo time)</td>
<td>15 ms</td>
</tr>
<tr>
<td>TR (shot interval)</td>
<td>2200 ms</td>
</tr>
<tr>
<td>Scan durations</td>
<td>2:05 (total 16:43)</td>
</tr>
<tr>
<td>TI (inversion times)</td>
<td>50, 100, 150, 200, 400, 700, 1200, 1800 ms</td>
</tr>
</tbody>
</table>
### Table 4.5: Saturation recovery scan parameters for dGEMRIC at 3T.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix size (scan)</td>
<td>256 x 256</td>
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<tr>
<td>Matrix size (reconstructed)</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Final in-plane resolution</td>
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</tr>
<tr>
<td>Field of View (FOV)</td>
<td>100 mm</td>
</tr>
<tr>
<td>Slice Thickness</td>
<td>3 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>1</td>
</tr>
<tr>
<td>TSE factor</td>
<td>2</td>
</tr>
<tr>
<td>TE (echo time)</td>
<td>15 ms</td>
</tr>
<tr>
<td>TR (shot intervals)</td>
<td>100, 150, 200, 400, 700, 1200, 1800, 2200 ms</td>
</tr>
<tr>
<td>Scan durations</td>
<td>0:27, 0:39, 0:52, 0:58, 1:40, 2:51, 4:15, 4:43 (total 16:25)</td>
</tr>
</tbody>
</table>

Two proton density reference images were acquired to select appropriate slices in both the axial and coronal planes.

The coronal slice was imaged first. This deliberate choice was made due to faster diffusion of the contrast agent into the thinner tibiofemoral cartilage. The slice was selected to show the highest point of the tibial spines. A screen capture image was made to assist with re-selection of the slice at follow-up. Then the slice was imaged with eight TI times (Table 4.4).

The axial scan was then performed. The axial slice was selected to show the thickest patellar cartilage. Screen capture image was made to assist with re-selection of the slice at follow-up. Then the slice was imaged with eight TR times (Table 4.5). The axial slice was imaged second. This is because the thick cartilage requires slightly more time for contrast penetration.
4.7.4 Analysis

Data was imported into a custom analysis program. Images were registered, the scaling factor applied by the Philips scanner was removed, and the curves for each pixel were fit. Calculated T1 was plotted and the cartilage was segmented. A composite image was created. Regions of interest were segmented and average values for T1 were recorded.
5 Methods: feasibility assessment

5.1 Objective
The purpose of this study was to assess the feasibility of applying the protocols we have developed for measuring knee kinematics and cartilage health in three patients who are representative of our planned study population.

5.2 Ethics and Health Canada
This protocol was reviewed and approved by the UBC Clinical Research Ethics Board. All subjects gave informed consent. See Appendix B for a copy of the ethics application.

Approval was also obtained from Health Canada to use Magnevist (gadopentatate dimeglumine) for an off-label purpose in this study. See Appendix D.

Subjects were recruited through their orthopaedic surgeon. The surgeon asked for permission to give the investigators their contact information. Each subject was mailed a letter and information package with a copy of the consent form. The subjects were then contacted by telephone. If he or she was interested, a pre-screening for the MR was done, to determine if any special approval was required to scan. A scan time was booked, and consent was asked for on the scan day.

5.3 Population
The subject population consisted of patients with medial tibiofemoral osteoarthritis and varus leg alignment. Diagnosis was made by the subject’s orthopaedic surgeon using clinical and radiographic techniques.

The group was examined within one month before high tibial osteotomy surgery.

5.3.1 Inclusion criteria
Individuals were invited to participate if they:
- Were booked for HTO surgery within one month
- Had medial osteoarthritis
- Were able to complete the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire
- Were able to give informed consent
• Passed a standard MRI screening to ensure they could be scanned safely

5.3.2 Exclusion criteria

Subjects were excluded if they had:
• Prior knee surgery on the study knee involving more than simple arthroscopy
• Prior knee injury to the study knee which required ambulatory aids other than a cane or knee brace (6)
• Symptomatic instability (e.g. patellar dislocation)
• Intra-articular corticosteroid injection to the study knee within the last three months (6)
• Any of the precautions for the MR contrast agent, Magnevist (pregnancy, breastfeeding, respiratory allergies, asthma, thrombotic syndromes, history of grand mal seizures, impaired renal or hepatic function) (1,19)
• Exclusion criteria for MRI scanning (e.g. metallic object in eye, pacemaker)

5.3.3 Population characteristics

Other information was collected to allow characterization of the population. Height and weight were measured. Age was recorded. To determine the dominant leg, subjects were asked: “Which leg would you kick a ball with?” (115)

5.4 Methodology

The testing protocol consisted of the following:
1. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire
2. Assessment of knee mechanics
3. Assessment of cartilage degeneration

The assessments outlined above took place before surgery. Due to the long scan times, delay for dGEMRIC, and limited contrast enhancement window, only the affected knee was assessed.

5.4.1 WOMAC questionnaire

Clinical severity of OA was assessed by having subjects complete the Western Ontario and McMaster University Osteoarthritis Index (WOMAC). The WOMAC questionnaire is a self-administered questionnaire which addresses issues such as knee pain, stiffness and function related to osteoarthritis. It is widely used in osteoarthritis studies and has been validated as a treatment outcome measure for the hip and knee (17).
Subjects rated their pain, stiffness, and difficulty during specific activities of daily living on a scale of 0 to 4, where 0 is no impairment and 4 is severe impairment. Each subscale is scored separately. Note that each subscale is the sum of several questions – pain (5), stiffness (2), and physical function (17).

See Appendix C for a copy of the WOMAC.

5.4.2 Assessment of knee mechanics

We used a new MRI-based method to measure three-dimensional patellofemoral and tibiofemoral kinematics during loaded flexion with a 3.0 Tesla MRI scanner at the UBC hospital.

See Chapter 3 for a complete description.

5.4.3 Assessment of cartilage degeneration

We assessed GAG concentration in the tibial, femoral and patellar cartilage using the dGEMRIC protocol.

See Chapter 4 for a complete description.
6 Results

6.1 Population

Three male subjects were recruited. All three subjects had occupations which involved heavy physical activity. Two of the three subjects’ occupations put them at risk for metal fragments in the eye, and were therefore screened with an orbital radiograph. No metal was detected in the eye.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age (yrs)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>Dominant leg</th>
<th>Surgical leg</th>
<th>Orbital</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>193</td>
<td>112</td>
<td>30</td>
<td>R</td>
<td>R</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>42</td>
<td>174</td>
<td>83</td>
<td>27</td>
<td>R</td>
<td>L</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>176</td>
<td>84</td>
<td>27</td>
<td>R</td>
<td>L</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 6.1: Subject data.

6.2 WOMAC questionnaire

We saw a wide range of WOMAC scores for pain, stiffness, and physical function. The results of the WOMAC questionnaire are presented in Table 6.2.

<table>
<thead>
<tr>
<th>Subscale (Range)</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
<th>Ave (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (0-20)</td>
<td>7</td>
<td>15</td>
<td>8</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td>Stiffness (0-8)</td>
<td>4</td>
<td>6</td>
<td>0</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Physical function (0-68)</td>
<td>24</td>
<td>49</td>
<td>20</td>
<td>31 (12.8)</td>
</tr>
</tbody>
</table>

Table 6.2: WOMAC results.

6.3 Assessment of Knee Mechanics

6.3.1 Shape-matching

Total time for shape-matches ranged between 1 hour 15 minutes and 31 hours 18 minutes per subject.
All mean shape-match errors were less than 1.6 mm, with a grand mean of 1.17 (0.20) mm.

<table>
<thead>
<tr>
<th>Flexion angles</th>
<th>Bone</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data set 1</strong></td>
<td>Patella</td>
<td>0.97</td>
<td>0.90</td>
<td>0.82</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>1.10</td>
<td>1.11</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>1.34</td>
<td>1.01</td>
<td>1.16</td>
</tr>
<tr>
<td><strong>Data set 2</strong></td>
<td>Patella</td>
<td>0.97</td>
<td>0.98</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>1.43</td>
<td>1.13</td>
<td>1.18</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>1.48</td>
<td>1.21</td>
<td>1.18</td>
</tr>
<tr>
<td><strong>Data set 3</strong></td>
<td>Patella</td>
<td>1.01</td>
<td>1.18</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>1.32</td>
<td>1.37</td>
<td>1.15</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>1.54</td>
<td>1.28</td>
<td>1.15</td>
</tr>
<tr>
<td><strong>Data set 4</strong></td>
<td>Patella</td>
<td>1.05</td>
<td>1.19</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>1.26</td>
<td>1.28</td>
<td>1.10</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>1.57</td>
<td>1.37</td>
<td>1.17</td>
</tr>
<tr>
<td><strong>Data set 5</strong></td>
<td>Patella</td>
<td>1.08</td>
<td>1.32</td>
<td>0.85</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>1.33</td>
<td>1.50</td>
<td>1.20</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>1.28</td>
<td>1.35</td>
<td>1.35</td>
</tr>
<tr>
<td><strong>Data set 6</strong></td>
<td>Patella</td>
<td>0.91</td>
<td>1.07</td>
<td>0.92</td>
</tr>
<tr>
<td></td>
<td>Femur</td>
<td>1.11</td>
<td>1.38</td>
<td>1.37</td>
</tr>
<tr>
<td></td>
<td>Tibia</td>
<td>1.08</td>
<td>1.49</td>
<td>1.18</td>
</tr>
</tbody>
</table>

Table 6.3: Mean errors in shape matching each bone of each data set (mm).
6.3.2 Kinematics

Figure 6.1: Tibial flexion v. tibial adduction

Subjects 1 and 3 had increasing tibial adduction with flexion (r = 0.96 and 0.94 respectively; Figure 6.1). There was no significant relationship between adduction and tibial flexion for Subject 2 (α = 0.05). Adduction at full extension (intercept) was within 3 degrees for all subjects. In Subject 1, the tibia adducted substantially more with flexion than it did in Subject 3.
Internal Rotation at full extension (intercept) ranged from -15 degrees to +10 degrees.

Figure 6.2: Tibial flexion v. tibial internal rotation

In Subject 2, internal rotation increased with increasing tibial flexion ($r = 0.87$; Figure 6.2). In Subjects 1 and 3 there was no significant relationship between internal rotation and tibial flexion.
The tibia translated proximally with tibial flexion in Subjects 1 and 3 (r = 0.97 and 0.84; Figure 6.3). There was no significant relationship between proximal translation and tibial flexion for Subject 2 (α = 0.05). The amount of translation per degree of flexion was quite varied, however. Proximal translation at full extension (intercept) ranged from -11 mm to -2 mm.

Figure 6.3: Tibial flexion v. tibial proximal translation.

The tibia translated proximally with tibial flexion in Subjects 1 and 3 (r = 0.97 and 0.84; Figure 6.3). There was no significant relationship between proximal translation and tibial flexion for Subject 2 (α = 0.05). The amount of translation per degree of flexion was quite varied, however. Proximal translation at full extension (intercept) ranged from -11 mm to -2 mm.
Figure 6.4: Tibial flexion v. tibial lateral translation.

While the correlations were good for the linear fits ($r = 0.78$, 0.96, and 0.81 respectively) for all three subjects, a significant relationship between tibial lateral translation and tibial flexion existed for only Subject 2 ($\alpha = 0.05$; Figure 6.4). Lateral position at full extension (intercept) ranged from -5 mm to +3 mm.
The tibia shifted posteriorly with increasing tibial flexion for all three subjects ($\alpha = 0.05$, $r = 0.97$, 0.86, and 0.89 respectively; Figure 6.5). Rates varied, and anterior positions at full extension ranged from -18 mm to -9 mm.

Figure 6.5: Tibial flexion v. tibial anterior translation.
Patellar flexion increased with increasing tibial flexion in all three subjects ($\alpha = 0.05$, $r = 0.99$, 0.94, and 0.97 respectively; Figure 6.6). The rates of flexion were very similar for all subjects. Patellar flexion at full extension for Subjects 1 and 3 are similar (around -20 degrees), but Subject 2 is quite different with a value of patellar flexion around -5 degrees at full extension.

Figure 6.6: Tibial flexion v. patellar flexion.
Figure 6.7: Tibial flexion v. patellar spin.

In all three subjects medial patellar spin was not significantly correlated with tibial flexion ($\alpha = 0.05$; Figure 6.7). Strength of association was relatively poor for all three subjects ($r = 0.69$, 0.66, and 0.40 respectively). Values of patellar spin at full extension (intercept) are close, ranging from -4 to -1 degrees.
Figure 6.8: Tibial flexion v. patellar tilt.

Patellar tilt patterns are very different for all three subjects (Figure 6.8). Tilt increased for Subject 2 with tibial flexion ($\alpha = 0.05, r = 0.90$), but was not significantly correlated in Subjects 1 and 3. Tilt at full extension varied from 9 to 19 degrees.
Figure 6.9: Tibial flexion v. patellar proximal translation.

In all three subjects, the patella translated distally with tibial flexion ($\alpha = 0.05$, $r = 0.96$, 0.99, and 0.99 respectively; Figure 6.9). The rates are similar for all three subjects. Proximal position at full extension ranged from 28 to 42 degrees.
Figure 6.10: Tibial flexion v. patellar lateral translation.

There was no significant relationship between patellar lateral translation and tibial flexion ($\alpha = 0.05$; Figure 6.10). Lateral position at full extension ranged from -4 to +2 mm.
Figure 6.11: Tibial flexion v. patellar anterior translation.

In Subjects 2, the patella translated posteriorly with tibial flexion (α = 0.05, r = 0.98; Figure 6.11). No significant relationship was found for Subjects 1 and 3. Anterior position at full extension ranged from 29 to 32 mm.
6.4 Assessment of cartilage degeneration

All subjects successfully completed the dGEMRIC scan protocols. Sample IR and SR images are shown in Figures 6.12-6.15.

6.4.1 Sample images

Figure 6.12: IR series for Subject 1 (TI = 50, 100, 150, 200 ms)
Figure 6.13: IR series for Subject 1 (TI = 400, 700, 1200, 1800 ms).
Figure 6.14: SR series for Subject 1 (TR = 100, 150, 200, 400 ms).
6.4.2 Analysis

Using their respective fit equations, both the IR and SR data from the three subjects were successfully analyzed. The highest TR scan (TR = 2200 ms) in each coronal series was discarded because SENSE (Philips' name for parallel imaging) was on for this scan to reduce scan time by about 3 minutes, and it resulted in abnormally lower signal intensities. This reduced signal intensity is detectable in the lower right image in Figure 6.15. However, for Subjects 2 and 3 additional scans were made at TR = 300 ms. This image was added to bring the total number of data points to eight for these two subjects.

Figures 6.16 to 6.18 show the T1 maps for the three subjects. Note, the pixels in the cartilage areas which are not assigned a colour either have a T1 below 200 or the
program was not able to fit the curve. This is more prevalent in the SR maps (coronal), and particularly in Subject 3. The areas which were problematic were primarily where cartilage appeared severely disrupted, with fluid in fissures in the tissue. These areas were not included in the ROIs for data summary.
Figure 6.16: dGEMRIC map for Subject 1.

T1 distribution in the patellar cartilage (top) appears normal for Subject 1. The lateral cartilage on both the tibia and the femur appears normal as well. The medial compartment cartilage for both tibia and femur appears degenerated.
In Subject 2, the medial patellar cartilage (left, top image) appears degenerated compared to the lateral patellar cartilage. There is a large volume of effusion in the axial image. The medial TF cartilage (bottom, left) is severely degenerated, and the lateral cartilage shows a lower T1 near the centre of the joint.
In Subject 3, the lateral patellar cartilage has a slightly lower T1 than the medial patellar cartilage. There is fluid visible between the PF joint surfaces on the lateral side. There is a small amount of effusion in both images. The medial TF cartilage, especially the tibial cartilage, is somewhat more degenerated than the lateral, but both appear degenerated (bottom).
Regions of interest (ROIs) were drawn in each compartment and the average T1 values and standard deviations were computed for the pixels within that ROI.

![Graph showing T1 values for different cartilage locations and subjects](image)

**Figure 6.19: dGEMRIC indices.** Note that these values are means over the number of pixels in each ROI from one dGEMRIC series per subject, and the error bars indicate the variability in the value of these pixels.

For each subject, the dGEMRIC indices for the medial TF cartilage were lower than those for both the lateral TF cartilage and the patellar cartilage (Figure 6.19). In Subjects 1 and 2, the tibial cartilage had a higher T1 than the femoral cartilage in both compartments. Subject 3 had higher T1 in femoral cartilage than tibial cartilage. Subject 3 had higher T1 in femoral cartilage than either of the other subjects, and lower T1 in tibial cartilage than either of the other subjects.

The standard deviation is markedly larger for the TF joint measures than for the patella. This relates directly to the use of the noisier SR sequence for the TF joint.
7 Discussion

The objective of this study was to develop and test methods for measuring knee kinematics and cartilage degeneration in subjects with medial tibiofemoral (TF) osteoarthritis (OA) due to varus alignment scheduled for high tibial osteotomy (HTO). The work in this thesis represents the protocol development process for both an MR-based knee kinematics protocol and a dGEMRIC cartilage health protocol on a high-field 3.0T scanner, in the target population, in the presence of surgical hardware. Three subjects with medial TF OA were imaged. The results found in this study were consistent with the literature.

7.1 Advantages of scanning at 3T

The advantages of using a high-field 3T system to perform the required scans include higher signal-to-noise ratio (SNR) in images of comparable scan duration. Alternately, the same SNR can be achieved in a shorter amount of time, when compared to 1.5T scanners. Also, 3T will likely be the next standard for clinical scanners; researchers will have more access to work at 3T, and important types of research scans will need 3T protocols as well as 1.5T protocols.

7.2 Knee kinematics protocol

The new loading rig, although designed for another scanner, performed well in the 3T Philips Intera. Due to the configuration of the scanner and couch, modifications could be made to dramatically increase the load applied to the subject, if this is deemed desirable. One limitation is that the rig was designed for a scanner with less flare at the end of the bore, and thus the design itself limited the weight that could be applied. Each subject was asked if the load was heavy or if they were having any trouble holding the position, and every subject indicated that they could successfully hold a fixed position under higher loading. This was somewhat surprising in relation to their relatively high WOMAC pain scores. In spite of subjects' perception, subject fatigue may produce tremor and associated motion artifact. Advantages of loading include ensuring that the joint surfaces are in contact.

We chose to collect sagittal images for both high and low resolution scans because previous work has shown higher registration errors occur with axial scans (48). Sagittal imaging is also advantageous because fewer slices were required to image the whole
knee, therefore scan time was kept down. Errors in patellar spin and patellar tilt are higher for sagittal scans than for axial scans, however (52).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3T</th>
<th>1.5T (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view</td>
<td>320 mm</td>
<td>260 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>46</td>
<td>38</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>512x512</td>
<td>512x256</td>
</tr>
<tr>
<td>NSA</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Scan time</td>
<td>16:18</td>
<td>14:28</td>
</tr>
</tbody>
</table>

Table 7.1: Comparison of high-resolution scan parameters with previous work.

The 3T protocol yielded high quality high-resolution images. The 3T high-resolution scans had 20% more slices and a higher matrix than the 1.5T images, with scan times that are similar to the 1.5T protocol (Table 7.1). What is not as easily quantified is the image quality. Since the scans are relatively similar, we would expect approximately twice the SNR with the 3T images, and the 3T images also have a higher in-plane resolution. The images were certainly straightforward to segment, and may well be easier to segment than the 1.5T images because of higher image quality.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3T</th>
<th>1.5T (72)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Field of view</td>
<td>320 mm</td>
<td>320 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Acquisition matrix</td>
<td>128x128</td>
<td>256x128</td>
</tr>
<tr>
<td>NSA</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Scan time</td>
<td>0:28</td>
<td>0:38</td>
</tr>
</tbody>
</table>

Table 7.2: Comparison of low-resolution scan parameters with previous work.

The low-resolution scan parameters for the 3T and 1.5T scans are similar (Table 7.2), however we expect about double the SNR from the 3T, all other things being equal. One difference is that at 3T, the acquisition matrix is smaller than it was at 1.5T. The images were reconstructed at a higher matrix, and edges were not crisp. This blurry appearance made it somewhat difficult to differentiate between bone and other bright tissues, such as the infrapatellar fat pad. This scan protocol may be improved upon in the future to allow...
for better segmentation. While achieving a short scan time is desirable to minimize motion artifact, it is vital to balance the need for fast imaging with the need for good image resolution.

Although metal artifact is increased at 3T, the kinematic analysis was successful in a subject with a surgical implant. Previous work (72) has shown that this kinematics protocol works even with titanium implants from HTO near the joint at 1.5T. In this study we demonstrated that it is possible to employ this protocol in subjects with titanium hardware near the joint at 3T. We noted in Chapter 4 that the results of the subject with titanium were consistent at 1.5T and 3T. We tested stainless steel hardware as well, and showed that the artifact was too severe to be able to segment the images. These important results indicate that subjects enrolled in any future study must receive titanium implants.

On the 3T Philips Intera, we found that shutter size was more of a constraint that bore size. We were able to achieve up to 60 degrees of flexion in one subject. To maximize the flexion range possible, we removed the scanner couch mattress, and positioned the foot such that the heel was on or just above the couch.

### 7.3 dGEMRIC protocol

<table>
<thead>
<tr>
<th>Parameters</th>
<th>3T</th>
<th>1.5T</th>
</tr>
</thead>
<tbody>
<tr>
<td>Final in-plane resolution</td>
<td>0.39 x 0.39 mm</td>
<td>0.35 x 0.4 mm</td>
</tr>
<tr>
<td>Number of images</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>3 mm</td>
<td>2 or 3 mm</td>
</tr>
<tr>
<td>Scan time</td>
<td>16:43 (IR)/16:25 (SR)</td>
<td>Around 12 minutes</td>
</tr>
</tbody>
</table>

Table 7.3: Comparison of new 3T dGEMRIC scans to 1.5T protocol.

We were able to acquire images at eight points (for both IR and SR) for dGEMRIC analysis in a time that was not substantially longer than the 1.5T protocol (Table 7.3). Our protocol includes one more point for calculating T1 than a published 1.5T protocol. While not technically necessary, more points generally yields a better curve fit and better T1
estimate. 3T images were acquired at the same in-plane resolution and slice thickness at 1.5T images.

Since T1 increases with field strength, the scan time at 3T must be relatively longer than at 1.5T to accommodate its measurement. As mentioned in Chapter 4 (Section 4.4.3.2), to ensure a correct measurement, the repetition time must be at least five times the T1 time to be measured. Since T1 is thought to increase by about 1.2 times between 1.5T and 3T (60), our scan time of 16.5 minutes is consistent with the 14.4 minutes (12 minutes (26) times 1.2) expected by this change of field strength, keeping in mind that we measured more points.

The curve fitting component of the dGEMRIC analysis requires sufficient points to accurately determine the curve shape. It is expected that the inversion times will be quite different between the 1.5T and 3T protocols, since the location of the null point varies with field strength. To obtain a good curve fit, it is desirable to have at least two points on either side of the null point of the IR curve, plus one near the null point. We found the null point to be around 400 ms, giving us four points below the null point and three points above it. We also expect TR times to be different between protocols at different field strengths. We had a much wider range of TR times (100 to 2200 ms) than the only published dGEMRIC protocol using SR at 1.5T (300 to 2000 ms). This likely indicates a better curve fit for our protocol.

Our difficulties with images at TR = 2200 ms were related to an assumption that parallel imaging (called SENSE for Philips systems) would not interfere with the analysis of these images. The high TR-value images are relatively more important to the curve fitting than the lower TR images, since a small change in these high-TR values can result in a large change in calculated T1. We were able to use images up to 1800 ms for these three subjects, and will be able to include the TR = 2200 ms without SENSE at a time cost of about three minutes.

We successfully performed dGEMRIC scans on a subject with metal near the joint, although some artifact was present in the images. Our work with MR phantoms suggests that this artifact can be eliminated by performing a saturation recovery series to image the TF joint rather than an inversion recovery series. This type of scan is noisier than the
inversion recovery series used to image the PF joint. No previously published protocol exists for dGEMRIC in the presence of a surgical implant.

Our work suggests that, while 2D dGEMRIC is feasible in the presence of surgical hardware, 3D dGEMRIC scans that provide more complete descriptions of GAG distribution across the entire joint’s cartilage are not possible in the presence of surgical hardware. One limitation of 2D dGEMRIC is the difficulty in selecting the same slice at the next exam. Screen captures were made at each exam to facilitate selection at the next session. Another limitation inherent in the 2D dGEMRIC sequence is the limited joint coverage. While 3D sequences that assess the entire joint have been developed, our test of 3D dGEMRIC with a phantom indicated that it will not work in the presence of metal. The 3D version of dGEMRIC is based on a different type of sequence (gradient recalled echo (GRE) verses turbo spin echo (TSE) for the 2D method). We found when the phantom was scanned in the presence of metal with the 3D sequence, the artifacts were too severe to allow for analysis. This result agrees with the literature, which states that the GRE sequence has a greater sensitivity to magnetic susceptibility effects than TSE (66).

7.4 Population parameters

The ages of the subjects in this study span the normal range for HTO patients. Although their BMIs indicate the subjects were overweight or obese, they all appeared very fit. As they all had jobs which involved heavy physical activity, the high BMIs likely indicate muscular physiques. These high BMIs are not surprising given the known relationship between high BMI and OA (Chapter 2, Section 2.2.7.3). Nonetheless, they are quite young to have OA.

From the WOMAC results, it is clear that although all three subjects have the same diagnosis and are scheduled for the same operative treatment, the pain, disability and stiffness caused by the disease is surprisingly different from subject to subject.
7.5 Comparison of kinematic results with literature

7.5.1 Tibial adduction

Our finding of increasing tibial adduction with increasing tibial flexion in two subjects is consistent with results in the literature (Figure 7.1). Hill reports two cases of decreasing adduction and a third case with slightly increasing adduction. The values of tibial adduction at full extension were closer to zero (±2 degrees) than those of Hill. This may be the result of different applications of the tibial coordinate system between the two studies. Our results are consistent with findings from the literature of normal kinematics (76, 87, 105, 111) as seen in Figure 7.1.

![Graph showing tibial valgus vs flexion angle]

Figure 7.1: Results from the current study for tibial valgus, or adduction, compared directly to results from previous studies in the literature (Original figure, Patel (111)).

7.5.2 Tibial internal rotation

Tibial internal rotation values from this study are consistent with those from literature (21, 76, 105, 111) as shown in Figure 7.2. Hill shows similar trends of increasing internal rotation with tibial flexion to those found in the current study, with internal rotation values at full extension which vary widely from zero to +12 degrees.
7.5.3 **Tibial proximal translation**

Our results for tibial proximal translation agree well with those Hill reports. Hill's resulting curves have similar trends and slightly lower values at full extension (-8 to -18 degrees).

7.5.4 **Tibial lateral translation**

Our results for tibial lateral translation agree fairly well with Hill's. Hill reports small increases and decreases with increasing tibial flexion, and values of lateral translation at full extension ranging from 1 to -5 mm, while all subjects in our study had small decreases in lateral translation with tibial flexion (Subject 2), or no relationship (flat curve).

7.5.5 **Tibial anterior translation**

Our results for tibial anterior translation agree very well with Hill, who reports decreasing anterior translation with increasing tibial flexion, and values at full extension ranging from -10 to -20 mm. The results of the current study are consistent with those from literature as shown in Figure 7.3.
Chapter 7 – Discussion

![Diagram](image)

Figure 7.3: Results from the current study for tibial posterior translation compared directly to results from previous studies in the literature (Original figure, Patel (111)).

7.5.6 **Patellar flexion**

The trend we found of increasing patellar flexion with increasing tibial flexion is similar to that found by both McWalter and Hill. The amount of flexion at full extension in two subjects (1 and 3) is lower than that of McWalter’s group. Hill’s subjects have similar values of patellar flexion at full extension to those in the current study.

7.5.7 **Patellar spin**

Results for patellar spin vary a great deal in the literature. McWalter indicates a slight decrease in spin with increasing tibial flexion (Figure 7.4). Hill’s subjects show both small increases and decreases of spin with increasing tibial flexion. The three subjects in this study show no significant relationship between spin and tibial flexion. The values of spin at full extension are lower than McWalter’s, closer to those of the valgus group in that study, and are similar to one of Hill’s subjects. Comparisons to other studies in patellar kinematics indicate that our results are within the broad range reported, as shown in Figure 7.4.
Chapter 7 – Discussion

Figure 7.4: Results from the current study for patellar spin compared directly to results from previous studies in the literature (Original figure Katchburian (79)).

7.5.8 Patellar tilt

Results of measurements of patellar tilt in the literature are quite varied (Figure 7.5). Our results show patellar tilt increasing or decreasing with tibial flexion. McWalter indicates that patellar tilt does not change with tibial flexion. If averaged, the subjects in the current study would produce a similar curve. Values of patellar tilt at full extension are similar to McWalter’s except for Subject 3, who has a much more tilt at full extension. Hill shows relatively little change with tibial flexion. Two of Hill’s subjects have similar initial patellar tilt values to the subjects in this study (including Subject 3). Our results are within the range of measured values from literature (Figure 7.5).

Figure 7.5: Results from the current study for patellar tilt compared directly to results from previous studies in the literature (Original figure Katchburian (79)).
Since values of patellar tilt reported in the literature are quite varied, it is difficult to compare them. Our results fit within the range of those previously reported.

7.5.9 *Patellar proximal translation*

Our finding of decreasing proximal translation with tibial flexion is consistent with the results of McWalter and Hill. The values of proximal translation at full extension are similar as well, in the 30-40 mm range.

7.5.10 *Patellar lateral translation*

Our finding of no consistent pattern in lateral translation with tibial flexion is consistent with the literature (Figure 7.6). McWalter and Hill found lateral translation to be fairly constant over the range of tibial flexion, with values of lateral position at full extension ranging from near zero to below -10 degrees, compared to -4 to +4 degrees found in the current study. Values from the literature for lateral translation are quite varied, however the current study is within the reported range (Figure 7.6).

7.5.11 *Patellar anterior translation*

Our values of anterior translation agree well with both Hill and McWalter, who reported slightly decreasing anterior translation with tibial flexion. The initial values of anterior translation are also consistent at around 30 mm.

Our measurements of kinematic parameters are consistent with values from the literature. There have been two previous studies of kinematics in subjects with varus alignment.
(similar to our subjects) using this kinematic method. Hill performed kinematic assessment on subjects before and after high tibial osteotomy (72,73). McWalter studied subjects with varus or valgus alignment who were diagnosed with OA (97,98).

Our comparison with Hill’s data will be limited to the opening-wedge osteotomy group. Hill divided his subjects into two groups: those who had closing-wedge (CW) osteotomies and those who had opening-wedge (OW) osteotomies. The choice of procedure is based upon “disease severity, desired outcomes and surgeon preference” (72). Since the criteria for each surgical decision in Hill’s study is not known, I will limit comparisons to the OW group because all subjects in the current study were to undergo OW osteotomies.

The shape-match errors reported for this study are less than those in a previous study using this method at 1.5T, which may indicate more accurate kinematic results than those from the previous method. Hill reports mean errors of 2.53 mm and 2.25 mm for closing-wedge HTO and opening-wedge HTO groups respectively, which are much higher than our mean error of 1.17 mm (72). These errors describe how well the high-resolution models and low-resolution contours matched. The low error in this study may be related to the higher quality of 3T images, or better segmentation of the images.

<table>
<thead>
<tr>
<th></th>
<th>Varus Group (McWalter)</th>
<th>Current study</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain (0-20)</td>
<td>5.6 (3.2)</td>
<td>10 (3.6)</td>
</tr>
<tr>
<td>Stiffness (0-8)</td>
<td>1.4 (0.5)</td>
<td>4 (3.3)</td>
</tr>
<tr>
<td>Difficulty performing daily tasks (0-68)</td>
<td>16.4 (8.0)</td>
<td>31 (12.8)</td>
</tr>
</tbody>
</table>

Table 7.4: WOMAC score comparison between this study and McWalter’s (97).

It is clear that the level of impairment in this study group and McWalter’s varus group is quite different (Table 7.4). The three subjects in this study are more seriously impaired, however comparison with McWalter’s group indicates similar trends in patellar flexion, patellar proximal translation, and patellar anterior translation. Patellar tilt and patellar lateral translation are similar to McWalter’s results when averaged together, but are quite varied. Note that McWalter reported only patellar kinematics and not tibiofemoral kinematics.
The results of this study are consistent with those of previous work. Differences between this study and McWalter may be ascribed to different levels of impairment.

7.6 Comparison of dGEMRIC results with literature

Our results in normal volunteers compared favorably with those reported *in vitro* by Trattnig et al. (144) at 3T. This is the only published study available for direct comparison of dGEMRIC at 3T because dGEMRIC is not commonly performed at 3T. They reported T1 values ranging from 400 to 950 ms in knee cartilage. Our values were 500 to 900 ms. They did not report T1 values for *in vivo* studies – their aim appeared to be determining appropriate delay times.

Our findings are also generally consistent with those from 1.5T studies when an appropriate adjustment for field strength is applied. A number of studies have investigated T1 values for healthy cartilage at 1.5T. Normal mean values of T1 at 1.5T have been reported at 450 to 600 ms (26). Research has shown that T1 values increase by about 20% between 1.5T and 3T (60). Thus we would expect normal cartilage to range between 540 to 720 ms at 3T. Another study in normal subjects reported values in the range of 364 to 486 ms at 1.5T with a triple dose of Magnevist (143). Results from another study indicate that T1 is relatively linearly dependent on *in vivo* Magnevist concentration (14). If we apply rough correction factors for differences in field strength (1.2) and gadolinium concentration (1.5), we end up with a range of 655 to 874 ms. These results fit well with the range we have seen in normal cartilage.

Although no study has been performed in this particular population of HTO patients, similar results to the current study have been seen in total knee arthroplasty (TKA) patients who were pre-operatively imaged with dGEMRIC. The study, performed at 1.5T, demonstrated qualitatively that the medial tibial plateau had lower GAG concentration than the lateral tibial plateau, but did not provide T1 values (16). This difference between the two TF compartments is consistent with our results. Subjects undergoing TKA may have more advanced OA than those undergoing HTO, but generally HTO surgery is used to delay TKA because of the relative youth of the patients, so the direct comparison is reasonable.

dGEMRIC studies of patients diagnosed with early OA found better cartilage than in our subjects who were scheduled to undergo HTO to treat OA, which was expected. In early
OA of one TF compartment, values of 290 to 340 ms were reported for degenerated cartilage at 1.5 T and using a triple dose of Magnevist (141). This corresponds to approximately 522 to 612 ms at 3T with a double dose of contrast using the conversion described above. We found T1 values in the medial TF compartment ranging from 370 to 525 ms, with a mean at 432 ms. Our values are somewhat lower than those reported for early OA, which is expected since our subjects should have more advanced OA.

7.7 Summary of Strengths and limitations

7.7.1 Strengths

We have developed kinematic and cartilage health imaging protocols at 3T. Imaging at 3T allows better image quality than imaging at 1.5T in a comparable scan time.

The protocol that we have developed for assessing kinematics and cartilage health is more accurate and less invasive than techniques that have been used to assess HTO in the past. Measurements of alignment using radiographs are limited in that they assess only two-dimensional positions and orientations, and only at one position of knee flexion. Biopsy for cartilage health assessment is invasive and does not allow for repeated measurements at the same location. Arthroscopy is invasive and only allows assessment of the cartilage surface. This new protocol will allow us to learn more about changes in kinematics and cartilage health, and their relationship, even following surgery.

We have demonstrated the feasibility of using these protocols in a larger study by assessing both kinematics and cartilage health in a subject with a titanium implant, a normal subject, and three subjects with medial TF OA. Our data are generally consistent with values from literature. Although imaging times are long, the subjects tolerated the scans well. The risks associated with MR scans are low, and subjects are interested in participating as they can receive detailed information about their joints and cartilage.

7.7.2 Limitations

One limitation is that we have only collected data for a few subjects. The small number of patients who receive HTO operations in British Columbia contributed to our small recruitment numbers.
Our dGEMRIC protocol has several limitations. There are few published papers to compare our data with, and even fewer report data collected at 3T. We have been able to roughly gauge equivalent T1 values at 1.5T, and our data have compared well to the available literature in both areas. Measurements of GAG concentrations using dGEMRIC are substantially lower than the actual values (15), and consequently direct comparison to other methods of evaluating GAG concentration is not possible. Comparisons between dGEMRIC scans are possible, however. Also, we have only been able to do 2D analyses with metal present in the proximal tibia, due to metal artifacts, which limits data collection to one slice in each joint.

Our kinematics protocol has a number of limitations. One limitation is the time-intensive nature of the imaging and analysis required. This limitation is not unique to this method or this study, but affects most kinematic measurement methods. Only low loads were applied while subjects lay in a horizontal position in the scanner, which does not represent a weight-bearing situation. More weight may exaggerate the tibial varus, and may change other kinematic parameters. However, the load was limited due to concerns about subject fatigue resulting in motion artifacts. We measured quasi-static rather than dynamic motion, because dynamic imaging is difficult and lower quality than static imaging. Dynamic imaging may change kinematic parameters. Knee flexion was limited to 60 degrees or less due to the closed scanner configuration, however this range is considered the most important as many common daily activities fall into this range of motion.

7.8 Future work

7.8.1 Kinematics scans

In future work, we may apply a 3D imaging protocol, which would dramatically shorten the acquisition time and/or allow better images (especially low-resolution images) in the same amount of scan time. Also, in the current images, only trabecular bone is segmented, since cortical bone appears black (along with tendon and ligament). Using a new ultra-short TE sequence, it may be possible to image the cortical bone fairly well. This may improve segmentation (especially at the shaft), and reduce differences between high and low resolution images due to partial volume effects in the trabecular bone.
Since the appearance of the low-resolution scans and the high-resolution scan are quite different, it may be useful to follow the high-resolution scan with a low-resolution scan in the same knee position. This would allow the segmenter to directly compare images in the same planes, and possibly make it easier to identify structures in the low-resolution scans.

It was found that the subjects tolerated the small load applied by the rig well. Despite having medial TF OA, all were young and presently performing physical work. It may be advantageous to increase the load to more closely mimic physiological conditions.

7.8.2 dGEMRIC scans

In future work we may attempt a IR TSE sequence with metal artifact reduction protocols (30,84,90,108). This may allow us to keep the higher SNR associated with the IR sequence and still limit the artifact to an area outside the cartilage.

To improve our limited joint coverage, we could also attempt a SE-based 3D sequence. This type of sequence should be less susceptible to magnetic inhomogeneities than the GRE-based sequence, but may require scan times which are too long to be practical.

7.9 Conclusions

1. We have developed a method for measuring three-dimensional knee kinematics with loading using MR at 3T.
2. We have determined that our method successfully measures knee kinematics in subjects without hardware and in a subject with implanted titanium surgical hardware, despite the larger metal artifact expected at a field strength of 3T compared to 1.5T. 3T and 1.5T results for this subject are comparable.
3. We have developed a method for measuring GAG concentration using MR at 3T, based on the dGEMRIC protocol.
4. We have determined that our dGEMRIC sequence yields valid maps of GAG distribution in cartilage in the presence of titanium surgical hardware. There are no prior published attempts to perform dGEMRIC scans with metal near the joint. This important development will allow us to evaluate the effect on cartilage health of
surgical changes to knee kinematics, specifically in the case of the high tibial osteotomy procedure.

5. We have tested our protocols on three subjects scheduled for high tibial osteotomy. Both kinematic and cartilage GAG concentration results are consistent with values from literature.

6. We have documented a protocol, incorporating the knee kinematics and dGEMRIC methods, that will allow us to study relationships between knee kinematics and cartilage GAG concentration changes as a result of high tibial osteotomy and other surgical procedures.
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A Magnetic Resonance Imaging

Magnetic resonance (MR) imaging is a widespread medical imaging modality. The strength of MR is its ability to image soft tissues well, and is therefore commonly used to diagnose illnesses and injuries to the brain, heart, spinal cord and abdomen. In orthopaedics, the most common uses are imaging ligaments, tendons, menisci, cartilage, and occult fractures (6).

A.1 Basic MR physics

Unlike radiographs and computed tomography (CT), MR imaging does not use radiation. An MR scanner is a large, very strong magnet. When tissue is introduced to this magnetic field, the hydrogen nuclei (which are single protons) within the tissue align with the external magnetic field and begin precessing at a frequency proportional to the strength of the field. A radiofrequency (RF) pulse is then turned on at the precession frequency and delivers energy to the protons which causes them to precess in phase and ‘flip’, or move away from the axis of the original magnetic field. Once the RF pulse is turned off, the protons start returning to their original orientation which gives off an RF pulse which is detectable and provides the signal from which the image is constructed. Using a variety of methods, the RF pulse received can be tagged in a way that allows determination of the location in three dimensions of the source of the signal (2).

Tissues are differentiated in MR not by radio-opacity, as in CT, but by tissue specific properties called relaxation times. T1 [ms] is the time constant for the protons to move from the flipped angle to the original orientation in line with the magnetic field. T2 [ms] is the time constant for the protons to dephase following the RF pulse. T1 is always greater than T2, and can be much greater. These two properties, along with proton density, can distinguish between tissues. By using different pulse sequences, images can be made to show contrast by any of these three measures (5).

Some of the basic tradeoffs in MR are that, in general, longer scans equal better images (more signal to noise (SNR)); higher field strength equals better images (more SNR); higher field equals slightly longer scan times, exclusive of adding more SNR.

A.2 Metal artifacts

The tissues of the body are diamagnetic – they have a small magnetic susceptibility. Magnetic susceptibility is a measure of how magnetized a substance will get when placed in a magnetic field. Since most tissues have similar susceptibilities, imaging works well.
When materials with very different susceptibilities are next to each other in the scanner, artifacts, called susceptibility artifacts are created (2). One example is the air-tissue boundary of the lungs. Another is the boundary between tissue and metal implants in the body. This causes difficulty when imaging patients with surgical hardware left in place.

The location and severity of metal artifacts depends on the pulse sequence and operator selection of imaging parameters (8). Metal artifact reduction for the purpose of clinical diagnosis has been studied and implemented (1, 3, 4), however these images were not intended to be used for quantitative analysis. It has been noted that stainless steel implants produce much more distortion than titanium implants (7). As a result, we chose to use a titanium osteotomy plate (Puddu plate, Arthrex) for this study.

A.3 References


B Ethics Application
1. INTRODUCTION – Invitation to participate

You have been invited to participate in this research study because you are scheduled to undergo a high tibial osteotomy operation. The purpose of this surgery is to change the alignment of your leg in order to reduce the pain in the medial (inside) compartment of your tibiofemoral joint (the joint between your shin bone and your thigh bone). You display signs of tibiofemoral osteoarthritis (break-down of cartilage). This surgery provides a unique opportunity to study the effect of changing leg alignment on living cartilage, and may provide some important information as to the cause of osteoarthritis and its progression.

2. YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary, so it is up to you to decide whether or not to take part in this study. Before you decide, it is important for you to understand what the research involves. This consent form will tell you about the study, why the research is being done, what will happen to you during the study, and the possible benefits, risks and discomforts.

If you wish to participate, you will be asked to sign this form. If you do decide to take part in this study, you are still free to withdraw at any time and without giving any reasons for your decision.

If you do not wish to participate, you do not have to provide any reason for your decision not to participate nor will you lose the benefit of any medical care to which you are entitled or are presently receiving.

Please take time to read the following information carefully and to discuss it with your family, friends, and doctor before you decide.

3. WHO IS CONDUCTING THIS STUDY?

This study is funded by the Natural Sciences and Engineering Research Council of Canada (NSERC) which is a major federal funding agency of research in Canada.

The Principal Investigator in charge of this study, Dr. David Wilson, is an Assistant Professor in the Department of Orthopaedics of the University of British Columbia. The other investigators are associated with UBC and/or Vancouver General Hospital.

4. BACKGROUND

Knee osteoarthritis is a prevalent and disabling condition that presents many treatment challenges. Osteoarthritis is a break-down in the cartilage of a joint. Cartilage is the tissue covering the end of bones at a joint which allows the joint to move with very little resistance. Painful knee osteoarthritis has been found in 6% of adults over 30 years of age, and in over 50% of adults with an average age of 80.7 years. In advanced stages of osteoarthritis, knee replacement surgery is often performed. It is usually successful but the implanted components...
often ultimately loosen or wear out, making it necessary to operate again and replace the implants. This makes joint replacement an unattractive option for younger patients.

Osteoarthritis is believed to be associated with mechanical problems in the joint, such as excessive pressure on cartilage caused by a poor leg alignment. The objective of high tibial osteotomy, a surgical realignment procedure, is to change the mechanics of the leg in an effort to reduce pain and delay cartilage loss on the medial (inner) half of the tibiofemoral joint (the joint between the shin bone (tibia) and the thigh bone (femur)). Some studies have shown that this procedure either stops cartilage break-down or leads to cartilage regeneration. It is not clear why this happens. We, the investigators, would like to try to shed some light on this question through this research study.

Discovering how cartilage behaves when the mechanics of the joint are changed is important not only for possibly improving the high tibial osteotomy procedure, but because it may lead to other treatments for osteoarthritis in other joints.

The test procedures in this study have been carried out on humans to study other relationships involving cartilage and knee movement.

5. WHAT IS THE PURPOSE OF THIS STUDY?

During this study, we, the investigators, would like to examine the relationship between how your knee moves (the mechanics of the knee joint), changes in joint mechanics and cartilage health (amount or quality of cartilage) in several areas of the knee joint. Cartilage health will be assessed in several different ways.

There are large molecule groups in cartilage called glycosaminoglycans (GAG). They are part of larger molecules called proteoglycans (PG). It has been found that in early osteoarthritis cartilage loses its PGs, which provide much of the material strength. A new magnetic resonance imaging (MRI) method (called Delayed Gadolinium Enhanced MRI of Cartilage - dGEMRIC) allows the examination of the amount of GAGs (and therefore PGs) in human cartilage without an invasive procedure. This is one of the cartilage health measures.

There is a MRI method to measure the thickness and volume of cartilage in the knee joint. As cartilage breaks down it gets thinner. This is another of the cartilage health measures.

Magnetic resonance imaging (MRI or MR) is a medical imaging method where high magnetic fields are used to obtain images. The magnetic field causes protons (sub-atomic particles) in the body to align in one direction. A second magnetic field is turned on briefly, causing the protons to rotate: as they rotate back to the original alignment, a signal is produced that can be measured and used to construct images. MRI imaging is considered very safe and there is no radiation involved in MRI scanning.

The change in joint mechanics will be a high tibial osteotomy surgery to realign the knee joint. Half of the subjects will be undergoing this surgery during the study period, and the other half will be scheduled for the surgery or for unicompartmental joint arthroplasty (partial knee replacement surgery) but will not undergo the procedure during the study period.

Please note that we will not delay surgery for any subject for the purposes of this study. The group which will not be undergoing surgery during the study period will be recruited from waiting lists, or will be persons who have delayed the surgery themselves.
The goal of the study is to relate these measures, and examine any changes in them at three points in time.

Other assessments will be made to be able to compare our results to previous studies. These include x-rays of leg alignment, a clinical knee evaluation, and an osteoarthritis questionnaire.

6. WHO CAN PARTICIPATE IN THIS STUDY?

In order to participate in the study as a surgical group member, the following statement must be true:

You must be scheduled for high tibial osteotomy which you will undergo during the study period; you have medial tibiofemoral osteoarthritis (break-down of cartilage on the inside of the joint between your shin bone and thigh bone).

7. WHO SHOULD NOT PARTICIPATE IN THIS STUDY?

You should not participate in this study if you fall into one of the following categories:
- Prior knee surgery on your study knee involving more than simple arthroscopy (insertion of a scope into the knee to examine it)
- Prior knee injury to your study knee which required ambulatory aids other than a cane or knee brace
- Symptomatic instability (e.g. dislocation of the patella (knee cap))
- Intra-articular corticosteroid injection to your study knee within the last three months (injection into the knee to relieve pain)
- Any of the precautions for the MR contrast agent, Magnevist (pregnancy, breast-feeding, respiratory allergies, asthma, thrombotic syndromes (involving blood clots obstructing blood vessels), history of grand mal seizures, impaired renal or hepatic (kidney or liver) function)

Note: Your study knee is the knee which is going to be operated on.

8. WHAT DOES THIS STUDY INVOLVE?

Overview

The study is designed to involve two groups: a surgical group and a control group. The surgical group will undergo high tibial osteotomy within the study period, and will allow us to examine the effect of a change in joint alignment. The control group will not undergo surgery within the study period, although they will be scheduled to undergo it. The reason for having a control group is to be able to tell the difference between a change caused by the operation and a normal change over time. The control group subjects are surgical candidates so that they are similar enough to the surgical group (same diagnosis) that we can say the changes in their cartilage would be the same as someone in the surgical group if they had not had an operation.

Prior to participating, you would be asked a series of standard MR screening questions. The questions ask about metallic implants (such as pacemakers) which may be disrupted or disturbed by the magnetic fields in the scanner.

You are being asked to participate in the surgical group.

Study Procedures
This study will take place over thirteen months. You will be asked to commit three and a half hours of your time three times to this study, for a total of ten and a half hours. Some of the procedures are part of normal care such that the total extra time is 9 hours for the surgical group, and 9.75 hours for the control group. (The difference is due to the control group only undergoing the pre-operative standard procedures and not the post-operative ones as well). This is outside your normal health care and is strictly voluntary. Both of your knees will be examined. Your normal health care regime will continue as usual, including your surgery.

By participating in this study you will be asked to fill out the following questionnaire:

1. Western Ontario and McMaster University Osteoarthritis Index –WOMAC questionnaire. This questionnaire will take approximately 15 minutes to complete. You will be asked questions regarding your knee pain, stiffness and function. This questionnaire will help the investigators to classify possible osteoarthritis.

By participating in this study you will be asked to undergo the following examination:

1. A clinical examination by a physician. This will be an evaluation of overall knee health and will include standard tests for joint laxity (looseness), range of motion (how far you can bend and unbend your knee), tenderness near the joint, effusion (excess fluid in the joint), crepitus (grating sensation when knee moves), patellar position (knee cap high, low, to one side), lower limb pattern (e.g. bow-legged), and clinical alignment (at what angle you may be bow-legged). Your height and weight will be measured. A standard history will be taken as well. This evaluation will take 30 minutes. This is part of standard care for high tibial osteotomy patients before and after surgery.

By participating in this study you will be asked to undergo the following four imaging sessions:

1. One full lower limb standing x-ray (from hip to ankle). This will take approximately 15 minutes to complete. This x-ray is used to determine the angle of varus or valgus at your knee joint (bow-leg or knock-knee), and is used in pre-operative planning for your high tibial osteotomy operation (part of standard care before and after surgery).

2. Assessment of patellar tracking (knee movement) using an MRI machine. One high-resolution MRI scan will be taken, this will last about 15 minutes. Six low-resolution MRI scans will be taken, each one lasting about 40 seconds. During the quick, low-resolution scans you will be asked to press on a pedal with your knee bent at different angles. You will spend about one hour in the MRI suite, which includes scanning time and leg positioning time. This process allows the investigators to study how your patella (knee-cap) moves as you bend your knee.

3. To assess cartilage health, you will undergo the following imaging sessions:
   a. One MRI scan of the knee for volume and thickness. This will take approximately half an hour including positioning and the actual MRI scan. The MRI scan itself takes approximately 8 minutes. There is a 1 hour rest time before the scan, to make sure the cartilage is not compressed. We plan to do other imaging during the wait time.
   b. One MRI scan of the knee for GAG distribution. You will be injected with a contrast agent and asked to exercise your knees for 10 minutes (by walking and/or bending and unbending your knees). This increases the amount of contrast agent that goes into the cartilage. Two hours after the injection the scan will begin. This wait time allows the contrast agent to fully penetrate the cartilage. The scan itself will take about an hour. We plan to do other imaging during the wait time.

By participating in this study you will be asked to consent to the following modification of your surgery:
1. Substitution of titanium fixation hardware for stainless steel fixation hardware (used to hold the bone together after it is cut). This modification is necessary because titanium is MR compatible while stainless steel is not (there is a great deal of distortion in the images). Both materials are widely used in implants. This will not affect the surgical procedure or your regular medical care.

9. WHAT ARE MY RESPONSIBILITIES?

You will be asked to come in three times for the testing mentioned above. These sessions will be six months apart. The testing session may be all on one day, or on more than one day. We will try to accommodate your schedule and limit the number of days involved.

Should you develop one of the conditions listed in section 7 ("Who should not participate in this study?") we ask that you inform one of the investigators. The phone numbers are included on the first page of this form.

10. WHAT ARE THE POSSIBLE HARMS AND SIDE EFFECT OF PARTICIPATING?

There is some risk associated with having x-rays taken. During x-rays you will be exposed to a small amount of radiation. The maximum radiation you will be exposed to is 3.6 mSv. To put these numbers in perspective, all individuals are exposed to 2 mSv of background radiation per year. Background radiation is the radiation we are all exposed to from sources such as the sun, the earth and other substances in our environment. The total radiation you will be exposed to by participating in this study is less than two years' worth of background radiation. Radiation can damage body cells, however at this small dose this is unlikely. Side effects due to this amount of exposure are highly unlikely.

The Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) procedure (GAG distribution; see section 8) involves intravenous administration of a MRI contrast agent called gadopentetate dimeglumine (brand name Magnevist). A small percentage of people who have this contrast agent injected have adverse reactions. The most common ones are headache (4.8%) (most transient and mild to moderate in severity), nausea (2.7%), injection site coldness/localized coldness (2.3%), and dizziness (1%). These are not life-threatening or serious. If you experience any other side effect following administration of the contrast agent, please immediately inform the study physician and seek medical care if necessary.

There is no known risk associated with MRI scans, however the MRI scanner is somewhat confined and some people experience claustrophobia when having scans. Should this occur, you will be able to signal the technologist who will assist you in leaving the scanner.

11. WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

A potential benefit from your participation in this study is the detailed examination of your knee cartilage and the information resulting from this examination. We will be able to give you detailed information regarding the progression or regression of your osteoarthritis. This may help you in deciding on treatment options with your physician.

We will be happy to provide you with copies of your imaging sessions and the final results of the study, if you wish.

We hope that the results of this study can be used in the future to benefit other people with a similar disease.
12. WHAT ARE THE ALTERNATIVES TO THE STUDY TREATMENT?

This study does not propose to treat osteoarthritis and you should continue with your normal medical care. All decisions regarding your operative care will be made by a qualified physician, and your care will not be compromised by your participation in the study. Should you choose not to participate in this study, there will be no effect on the medical care you are entitled to receive.

13. WHAT IF NEW INFORMATION BECOMES AVAILABLE THAT MAY AFFECT MY DECISION TO PARTICIPATE?

If new information becomes available which may affect your decision to participate in this study, this information will be provided to you in a timely manner by the investigators. You may choose at any time to withdraw from the study.

14. WHAT IF I CHOOSE TO WITHDRAW MY CONSENT TO PARTICIPATE?

You may choose to withdraw from the study at any time without penalty to your continuing medical care. You do not have to provide any explanation for your decision to withdraw. The investigators would retain any data collected up to the point of your withdrawal.

Once the high tibial osteotomy procedure is completed within the study with titanium fixation rather than stainless steel fixation, this substitution cannot be undone (i.e. the fixation will not be replaced with stainless steel). This substitution will not affect your regular medical care.

15. WHAT HAPPENS IF SOMETHING GOES WRONG?

In the case of a serious medical event, please report to an emergency room and inform them that you are participating in a clinical study, and that the following person can then be contacted for further information: Dr. Robert McCormack, 604 526 7885.

You do not waive any of your legal rights to compensation by signing this consent form.

16. CAN I BE ASKED TO LEAVE THE STUDY?

On receiving new information, the study doctor might consider it to be in your best interests to withdraw you from the study without your consent if they judge that it would be better for your health.

17. AFTER THE STUDY IS FINISHED

There are no additional instructions for you associated with the study testing. Your doctor may have additional instructions for you related to your surgery.

If you would like to receive a copy the final study results and findings, please let us know. These results will be available several months after the study finishes.

18. WHAT WILL THE STUDY COST ME?

Study-related expenses will be covered by the investigators. Travel expenses, including parking, incurred by participating in the study will be covered. For subjects travelling within this
city, travel expenses up to $50 per session will be covered (i.e. the cost of a taxi ride). For subjects travelling from outside Vancouver, travel expenses up to $250 per session will be covered. The amount received by the subject will be based on travel receipts.

Lunch will be provided for subjects at the hospital cafeteria. A honourarium of $50 per session will be given to subjects.

19. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

All of the personal information of subjects and data collected in this study is strictly confidential. Access to data is restricted to the investigators reported at the opening of this document only. Your name and contact information will not appear in any data files, a number assigned to you will be the only means of identification. This identification number will be associated with your name and contact information in a separate file to which only the investigators will have access.

Your confidentiality will be respected. No information that discloses your identity will be released or published without your specific consent to the disclosure. However, research records and medical records identifying you may be inspected in the presence of the Investigator or his or her designate by representatives of Health Canada and the UBC Research Ethics Board for the purpose of monitoring the research. However, no records which identify you by name or initials will be allowed to leave the Investigators' offices.

Your rights to privacy are also protected by the Freedom of Information and Protection of Privacy Act of British Columbia. This Act lays down rules for the collection, protection, and retention of your personal information by public bodies, such as the University of British Columbia and its affiliated teaching hospitals. Further details about this Act are available upon request.

20. WHO DO I CONTACT IF I HAVE QUESTIONS ABOUT THE STUDY DURING MY PARTICIPATION?

If you have any questions or desire further information about this study before or during participation, please do not hesitate to contact Dr. David Wilson at 604 875 4428; he will be more than happy to respond to all of your questions and concerns.

21. WHO DO I CONTACT IF I HAVE ANY QUESTIONS OR CONCERNS ABOUT MY RIGHTS AS A SUBJECT DURING THE STUDY?

If you have any concerns regarding your treatment or rights as a subject in the present research study please do not hesitate to contact the Research Subject Information Line of the Office of Research Services at the University of British Columbia at 604-822-8598.
22. SUBJECT CONSENT TO PARTICIPATE

I have read and understood all of the information regarding this study provided above. I understand that participation in this study is strictly voluntary and all of the measurements are in addition to my normal health care. I realize that I am not waiving my legal rights by signing this consent form. I have received a copy of this document for my personal records.

By signing this document, I consent to participate in this study.

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Protocol

Title: Effect of changes in joint alignment and loading on cartilage in humans
(Grant title: The relationship between patellar tracking, pain and cartilage degeneration in patients with patellofemoral pain syndrome)

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| Date:                  | Friday, August 29, 2003          |
Background

Knee osteoarthritis is a prevalent and disabling condition that presents many treatment challenges. Symptomatic knee osteoarthritis occurs in 6% of US adults over 30 years of age (11) and was found in over 50% of subjects with a mean age of 80.7 (18). The patella was involved in over half of these cases, with combined tibiofemoral and patellofemoral osteoarthritis found in 41% of subjects and isolated patellofemoral disease found in 11% of subjects (18). Conservative treatment with drugs and physical therapy is used at early stages of the disease, while joint arthroplasty is widely used for advanced osteoarthritis. Although joint replacement is usually successful, the prosthetic components often ultimately loosen or wear out, making revision necessary. This limits the use of joint arthroplasty in young patients. Effective repair of the damaged joint is a major objective of osteoarthritis research.

Osteoarthritic degeneration of articular cartilage is widely believed to be associated with altered joint mechanics. In the patellofemoral joint, for example, contemporary surgical and conservative treatment is based, to a large extent, on Ficat's hypothesis that pain and cartilage degeneration is caused when abnormal lateral patellar tilt produces excessive pressure on the lateral patellar facet (12). This mechanical hypothesis has been supported to some extent by evidence in the literature. Biomechanical factors such as obesity, excessive joint laxity, proprioceptive deficiency and malalignment are associated with the development of knee osteoarthritis (10). Valgus malalignment is associated with cartilage degeneration on the lateral patellar facet (8). Current surgical opinion mandates correction of joint alignment when osteochondral allografts are used to replace articular cartilage, which is based on the hypothesis that the newly implanted cartilage will not survive in the same adverse mechanical environment that produced the original damage.

The objective of high tibial osteotomy, a surgical realignment procedure performed to treat unicompartmental osteoarthritis, is to change the mechanics of the lower limb. In high tibial osteotomy, a wedge of bone from the proximal tibia is resected (closing-wedge) or added (opening-wedge) to realign the lower limb, placing more force on the lateral compartment of the knee in an effort to reduce pain and delay cartilage degeneration in the medial compartment (7). This procedure is a more desirable alternative to unicompartmental or total knee replacement for many patients (particularly the young) because it preserves bone stock and carries no risk of prosthesis loosening. High tibial osteotomy generally yields mixed success (13,24). Long-term good to excellent results are achieved in about half of all patients (23).

Although high tibial osteotomy does sometimes arrest osteoarthritic degeneration in the involved compartment, it is not clear why. Several groups have reported that high tibial osteotomy either arrests cartilage degeneration (26) or leads to cartilage regeneration (16,20) in the diseased compartment. The degree of correction of the mechanical axis does not provide a clear explanation. While one group has suggested that this arrested degeneration or regeneration is only related to overcorrection of the mechanical axis (20), another group has shown that "undercorrected" knees also regenerate cartilage (4).

These results suggest that restoring the mechanical axis to normal is not sufficient for restoring joint mechanics to normal. The mechanical axis, typically measured from a radiograph, offers a poor representation of joint alignment (21) because it is two dimensional. It is also generally only assessed at full extension, and therefore offers no description of joint alignment through the range of loaded knee flexion.

The relationships between knee kinematics and cartilage degeneration are not clear. They have not been studied extensively to date because appropriate techniques for assessing
knee kinematics and cartilage non-invasively were not available. Very few studies of three
dimensional knee kinematics have been performed in vivo, because of how difficult it is to make
accurate measurements without highly invasive procedures (17). Most studies of cartilage after
high tibial osteotomy have been performed with arthroscopy and biopsy (16,20,26), invasive
procedures that cannot be used at a number of time points after surgery. Techniques have
recently been developed for measuring three-dimensional knee movement (9), assessing
cartilage volume and thickness (25) and assessing glycosaminoglycan concentration (6) non-
invasively with magnetic resonance imaging.

Objectives

The broad question we would like to address is:

How does a change in alignment and loading affect cartilage?

The objective of this study is to answer the following research questions:

1. Does glycosaminoglycan (GAG) concentration in cartilage change with a change in knee
kinematics (due to high tibial osteotomy (HTO)) in the three compartments of the knee?
2. Does cartilage thickness/volume change with a change in knee kinematics (due to HTO)
in the three compartments of the knee?

We also aim to generate pilot data for further studies in the areas of joint mechanics and
osteoarthritis.

Hypotheses

The null hypotheses are:

2. GAG concentration will not change with a change in knee kinematics (due to HTO) in the
three compartments of the knee.
3. Cartilage thickness /volume will not change with a change in knee kinematics (due to
HTO) in the three compartments of the knee.

Design

This is to be a pilot study to assess the effect of alignment change on cartilage health through
several non-invasive emerging MR measures. The participants will be identified with the
assistance of Dr. R. McCormack. They will be individuals scheduled to undergo a high tibial
osteotomy procedure to correct varus malalignment of the lower limb and to relieve the pain of
medial tibiofemoral osteoarthritis which is associated with this malalignment. Some members of
the control group may be scheduled for unicompartmental arthroplasty instead, which is a partial
joint replacement to relieve the pain of medial tibiofemoral osteoarthritis. Forty participants will
be recruited; twenty will be scheduled for and will undergo the HTO surgery during the course of
the study; twenty will be scheduled for either surgery following the study, and will act as
controls. Preliminary results from work at Queen’s University suggest that the change in
alignment of the lower limb will be in the range of 3.5° (SD 2.2°) (9). The amount of change
expected in cartilage health parameters is not known at this juncture, however, as previous
studies have recorded visual (arthroscopic) and radiographic changes in cartilage, a change of
a similar magnitude should be detectable with our MR tools.

Inclusion Criteria
Surgical Group
Individuals booked for HTO surgery will be invited to participate. They must have medial osteoarthritis and must be able to complete the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire. All participants must be able to give informed consent. They must also pass a standard MRI screening to ensure they may be scanned safely (see Appendix E).

Control Group
Individuals booked for HTO surgery (or unicompartmental arthroplasty) for the treatment of medial osteoarthritis, but who will not undergo it during the study period, will be invited to participate. They must have medial osteoarthritis, be able to complete the WOMAC questionnaire, and be able to give informed consent. They must also pass a standard MRI screening to ensure they may be scanned safely (see Appendix E).

Exclusion Criteria
Exclusion criteria of participants from either group include:

- Prior knee surgery on the study knee involving more than simple arthroscopy
- Prior knee injury to the study knee which required ambulatory aids other than a cane or knee brace (2)
- Symptomatic instability (e.g. patellar dislocation)
- Intra-articular corticosteroid injection to the study knee within the last three months (2)
- Any of the precautions for the MR contrast agent, Magnevist (pregnancy, breastfeeding, respiratory allergies, asthma, thrombotic syndromes, history of grand mal seizures, impaired renal or hepatic function) (1)
- Exclusion criteria for MRI scanning (e.g. metallic object in eye, pacemaker) (See Appendix E)

Methodology
Participants will undergo the following:

4. Clinical Evaluation
5. Assessment of Varus-Valgus Knee Alignment
6. Assessment of Three-Dimensional Patellar Tracking
7. Assessment of Cartilage Health:
   a. Assessment of Cartilage GAG Concentration
   b. Assessment of Cartilage Thickness/Volume
8. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire
9. [Surgical only] High Tibial Osteotomy

For surgical participants, these assessments will occur once before surgery and at two follow-ups, at six months and 12 months post-operatively. Control participants will undergo the same three assessments at the same time intervals. Only the affected knee will be assessed.
A clinical evaluation will be performed by Dr. McCormack or a colleague in his group. The same physician will perform all the clinical evaluations for consistency. This assessment of overall knee health will include standard tests for joint laxity (looseness), range of motion, tenderness, effusion (excess fluid in joint), crepitus (audible/palpable grating sensation), patellar position (e.g. patella alta), lower limb pattern (varus/valgus), and clinical alignment. A standard history will be taken. Height and weight will be measured. This is part of standard care. The time to complete this evaluation is 30 minutes.

2. Assessment of Varus-Valgus Knee Alignment

One radiograph will be taken to assess the axial alignment of the lower leg. This method is the most commonly used for the assessment of varus or valgus knee angles for research purposes and is used for pre-operative planning of HTO surgery. A copy of the protocol can be found in Appendix A. To summarize this protocol, a 41” by 15” graduated-grid x-ray cassette will be used in order to visualize the lower extremity from hip to ankle. An anteroposterior view radiograph of the lower leg will be taken ensuring that the patella faces forward. A lead vest will shield the torso of the individual. The x-ray beam is centred eight feet away at a setting of 50 mAs and 70-75 kV. The radiation dose incurred by the subject is 1 mSv to the abdomen and 0.2 mSv to the legs for a total of 1.2 mSv per session, or a total of 3.6 mSv over the length of the study. Recall that background radiation is 2 mSv per year therefore the participant will be exposed to a dose equivalent to 21.6 months of background radiation. This is a small dose of radiation. Standard care calls for two radiographs (pre-operative planning, and post-operative evaluation), thus the additional dosage for surgical group participants is 1.2 mSv, or 7.2 months of background radiation and for control group participants is 2.4 mSv, or 14.4 months of background radiation.

This radiograph is necessary in order to accurately assess the malalignment of the lower extremity by measuring the angle defined by various lines on the radiograph. The relevant lines are defined by the following points:

- **A. Centre of the femoral head:** Found using Mose Circles
- **B. Anatomical centre of the knee:** Found by visually selecting the midpoint of the five following points:
  1. Centre of soft tissue at cartilaginous space
  2. Centre of tibia
  3. Centre of femoral condyles at the level of top intercondylar notch
  4. Centre of tips of tibial spines
  5. Center of femoral intercondylar notch
- **C. Center of the Ankle:** Found by visually selecting the midpoint of the three following points:
  1. Centre of soft tissue just proximal to level of cartilaginous space
  2. Centre of external surface of malleoli just proximal to level of cartilaginous space
  3. Centre of the talus

A line will be drawn connecting the centre of the femoral head to the centre of the knee which will be referred to as the mechanical axis of the femur, and another from the centre of the knee to the centre of the ankle which will be referred to as the mechanical axis of the tibia. The angle created by the intersection of the mechanical axis of the femur and the mechanical axis of the tibia determines whether the alignment is varus, valgus or neutral. An angle greater than 180° indicates a valgus alignment and an angle less than 180° indicates a varus alignment. This angle will be used to determine the degree of malalignment obtained from a standard
Clinical tool (as compared to the MR patellar tracking technique), for pre-operative planning, and for standard outcome assessment (degree of correction). This process will take approximately 15 minutes to complete including positioning time (19).

3. Assessment of Three-Dimensional Patellar Tracking

We will use a new MRI-based method to study three-dimensional patellar tracking during loaded flexion. The method relies on matching three-dimensional images of the distal femur, the proximal tibia and the patella generated with a high resolution scan to their positions in loaded flexion identified using a low-resolution scan both using a 3.0 Tesla MRI scanner at the UBC hospital.

A high resolution T1-weighted spin echo sequence MR image of each subject's knee will be taken in the fully extended position with the knee relaxed. This scan will have a slice thickness of 2 mm, slice spacing of 0 mm and a scan time of approximately 15 minutes. Geometric models of the knee bones will be developed using custom software to segment the images (identify relevant bones) and fit a mesh to the outlines of those bones. Fast, low resolution T1-weighted spin echo sequence MR images will be taken with the knee in loaded flexion at six angles between full extension and 90°. Participants will load their knees using a new device that allows them to push against a calibrated pedal in the MR scanner. The low-resolution scan slice thickness will be 2mm, the slice spacing will be 5mm and the scan time will be approximately 40 seconds. The quick low-resolution scans are carried out in order to reduce the possible fatigue of the subject.

Using custom segmentation software, the outlines of the bones on each of the low resolution images can be identified and then traced. The tracings obtained from the low resolution images will be matched to the geometric model obtained from the high resolution images using an iterative closest points algorithm. The result of this method is a three-dimensional model of the distal femur, the proximal tibia and the patella for each measure angle of flexion. By defining coordinate systems in the bones, the position and orientation of the patella and tibia with respect to the femur can be determined. The mean error of this method is 1.02 degrees for patellar spin, 0.3 degrees for patellar tilt and 0.88 mm for patellar shift. This method of assessing knee kinematics is desirable as MRI poses no known risk to the patient. The assessment of knee kinematics by this method takes one hour per participant, per session, for a total of 3 hours over the study (9).

4. Assessment of Cartilage Health:

a) Assessment of Cartilage GAG Concentration

Another indicator of cartilage health, glycosaminoglycan (GAG) concentration, will be assessed non-invasively using the dGEMRIC protocol. A copy of this protocol may be found in Appendix B. GAG’s are part of the proteoglycans (PG) in healthy cartilage which provide much of the mechanical strength (5). A loss of proteoglycans has been shown in early osteoarthritis. Both the GAG’s and the contrast agent are negatively charged, causing the contrast agent to distribute with higher concentrations in areas of GAG depletion. The participant will be intravenously injected with a dose of 0.2 mM/kg (0.4 mL/kg) of gadopentetate dimeglumine (Magnevist) contrast agent. Immediately after injection, each subject will exercise the lower extremity for ten minutes. After a delay of 2 hours to allow penetration of the
contrast agent into the cartilage, an inversion recovery turbo-spin echo T1 series of images will be acquired using the 3.0 Tesla MR machine at UBC. An anatomical (proton density) scan will also be taken to display the dGEMRIC results in a functional manner. The imaging time taken will be about 1 hour per session. Note that during the wait time we intend to complete other imaging. This is a widely used and well documented research procedure developed at the Harvard Institute of Medicine, Boston. (6)

b) Assessment of Cartilage Thickness/Volume

Cartilage thickness, surface area and volume will be assessed by an additional MR scan. Often more advanced osteoarthritis is associated with a loss of cartilage volume or thickness in certain areas. Also, regrowth cartilage does not have the same composition as normal cartilage (fewer GAGs), so the dGEMRIC scans may not sufficiently measure regeneration. A copy of this protocol may be found in Appendix C. A fat-suppressed T1-weighted 3D FLASH water excitation pulse sequence will be used. The dataset consists of sagittal images with slice thickness of 2mm, slice spacing of 0mm and an acquisition time of approximately 7 minutes. Cartilage thickness, surface area and volume will be assessed (10). There is no known risk associated with MR imaging. The machine used will be the 3.0 Tesla MR at UBC. This process will take approximately half an hour per session to complete including positioning time (14,25).

5. WOMAC questionnaire

The WOMAC questionnaire is a self-administered questionnaire which addresses issues such as knee pain, stiffness and function related to osteoarthritis. It is widely used in osteoarthritis studies. The purpose of this questionnaire will be to assess subjective functional improvement of the knee, and compare this outcome to measured knee kinematics and cartilage health measures. It takes approximately 15 minutes to complete. A copy of this questionnaire is attached in Appendix D (3).

6. [Surgical Group only] High Tibial Osteotomy

The high tibial osteotomy will be carried out in the standard manner, with the exception of using titanium hardware instead of stainless steel, since titanium is MR compatible. Both stainless steel and titanium are widely used implant materials (22). The two materials have comparable material strengths and are both inert. This change will not affect the standard of care.

High tibial osteotomy for varus malalignment may be performed in two ways: opening-wedge and closing-wedge. The choice of which procedure is preferred depends on a variety of factors including surgeon preference, degree of correction, and associated pathologies. The decision of which method is used will be made by the surgeon as part of standard care. Opening-wedge HTO involves an incision on the medial side of the knee, an osteotomy made in the proximal tibial, superior to tibial tubercle. This osteotomy is opened; a bone wedge is inserted and fixed in place with hardware. Closing-wedge HTO involves an incision on the lateral side of the knee. Two osteotomies are made in proximal tibia, to remove a bone wedge. The bone is closed together and fixed in place (15).
Statistical Considerations

The effect sizes are as yet unknown since there is very little published research regarding patellar kinematics. For the pilot study there will be 20 participants in the surgical group, and 20 participants in the control group. The size of the groups is limited by expected recruitment numbers.

A repeated-measures analysis of variance will be used to assess the repeatability of cartilage thickness/volume (from MR) and GAG concentration (from dGEMRIC) in each participant over the length of the study. A t-test will be employed to assess the differences, if any, between the subject and control groups for the same measures mentioned above.

Organization of a Study

This study will be carried out under the supervision of Dr. David R. Wilson, Assistant Professor, Orthopaedics. The data collection and analysis will be carried out by Ms. Agnes d'Entremont, graduate student. Expertise will be provided by the co-investigators. Dr. Donald Garbuz will assist in recruitment and will perform the clinical evaluations and HTO operations. Dr. Alex MacKay will provide MRI expertise.
References


### 9. Co-Investigators and Students: Use box 45 if additional space is needed.

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<th>Agnes</th>
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### 10. Provide the NAME of the funding source (see Guidance Note #10): NSERC Collaborative Health Research Projects grant

**Classify the type of funding:**
- [ ] For-profit sponsor
- [x] Grant
- [ ] Grant-in-aid
- [ ] UBC internal
- [ ] No funding
- [ ] Other

**What is the status of the funding?**
- [x] Awarded
- [ ] Pending

### 11. Has this research proposal received any independent scientific/methodological peer review? (see Guidance Note #11)
- [x] Yes
- [ ] No

If Yes, provide full details in 11a or 11b as relevant. Include the names of committees or individuals involved in the review. State whether the peer review process is ongoing or completed.

11a. External Peer Review Details:
- NSERC: CHRP, April 2003 competition. Peer review completed.

11b. Internal (UBC or hospital) Peer Review Details: N/A

11c. If No, explain why no independent scientific/methodological review has taken place: N/A

### 12. For clinical trials involving investigational drugs/devices or marketed drugs/devices outside of their indications (including positron-emitting radiopharmaceuticals (PERs)), indicate whether or not approval has been obtained from the appropriate federal regulatory agency for this purpose. (see Guidance Note #12)
- [ ] Yes
- [ ] No
- [x] Request for Approval has been submitted. (Please notify the Clinical Research Ethics Office when approval is obtained.)
- [ ] Not applicable

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Version approved: 26 March 2002 (First Revision 15 Nov 2002; Second Revision 08 April 2003; Third Revision 31 July 31 2003)
The purpose of the proposed research is to investigate relationships between knee alignment, or changes in knee alignment, and cartilage health in vivo. This is a pilot study.

2) Hypothesis:

The null hypotheses are as follows:

1. Glycosaminoglycan (GAG) concentration does not change with a change in knee kinematics (due to high tibial osteotomy (HTO)) in the three compartments of the knee.

2. Cartilage volume and/or thickness does not change with a change in knee kinematics (due to HTO) in the three compartments of the knee.

3) Justification:

Osteoarthritic degeneration of articular cartilage is widely believed to be associated with altered joint mechanics. In the patellofemoral joint, for example, contemporary surgical and conservative treatment is based, to a large extent, on Ficat's hypothesis that pain and cartilage degeneration is caused when abnormal lateral patellar tilt produces excessive pressure on the lateral patellar facet. This mechanical hypothesis has been supported to some extent by evidence in the literature. Biomechanical factors such as obesity, excessive joint laxity, proprioceptive deficiency and malalignment are associated with the development of knee osteoarthritis. Valgus malalignment is associated with cartilage degeneration on the lateral patellar facet. Current surgical opinion mandates correction of joint alignment when osteochondral allografts are used to replace articular cartilage, which is based on the hypothesis that the newly implanted cartilage will not survive in the same adverse mechanical environment that produced the original damage.

The objective of high tibial osteotomy, a surgical realignment procedure performed to treat unicompartamental osteoarthritis, is to change the mechanics of the lower limb. In high tibial osteotomy, a wedge of bone from the proximal tibia is resected (closing-wedge) or added (opening-wedge) to realign the lower limb, placing more force on the lateral compartment of the knee in an effort to reduce pain and delay cartilage degeneration in the medial compartment. This procedure is a more desirable alternative to unicompartmental or total knee replacement for many patients (particularly the young) because it preserves bone stock and carries no risk of prosthesis loosening. High tibial osteotomy generally yields mixed success. Long-term good to excellent results are achieved in about half of all patients.

Although high tibial osteotomy does sometimes arrest osteoarthritic degeneration in the involved compartment, it is not clear why. Several groups have reported that high tibial osteotomy either arrests cartilage degeneration or leads to cartilage regeneration in the diseased compartment. The degree of correction of the mechanical axis does not provide a clear explanation. While one group has suggested that this arrested degeneration or regeneration is only related to overcorrection of the mechanical axis, another group has shown that "undercorrected" knees also regenerate cartilage.

The relationships between knee kinematics and cartilage degeneration are not clear. They have not been studied extensively to date because appropriate techniques for assessing knee kinematics and cartilage non-invasively were not available. Very few studies of three dimensional knee kinematics have been performed in vivo, because of how difficult it is to make accurate measurements without highly invasive procedures. Most studies of cartilage after high tibial osteotomy have been performed with arthroscopy and biopsy, invasive procedures that cannot be used at a number of time points after surgery. Techniques have recently been developed for measuring three-dimensional knee movement, assessing cartilage volume and thickness and assessing glycosaminoglycan concentration noninvasively with magnetic resonance imaging. The knowledge gained from this research may possibly lead to insight about causes of osteoarthritis and improvement in high tibial osteotomy by applying results to computer-assisted surgery programs.

4) Objectives

The objective of this research is to generate pilot data to determine effect sizes and to study possible relationships between knee mechanics and cartilage health by addressing the hypotheses listed above.

5) Research Method

For this case-control study, we will recruit participants for two groups of twenty: a surgical group and a control group. The surgical group will be undergoing high tibial osteotomy surgery during the study period and the control group will be undergoing either high tibial osteotomy or unicompartmental arthroplasty after the end of the study period. The participants will be identified by Dr. McCormack and colleagues. A repeated-measures analysis of variance used to assess changes in measured parameters and a correlation will be carried out to examine the relationship between knee kinematics and cartilage health.
Human Subjects

14. Is this a multi-centre trial?  ☑ Yes  ☐ No

How many subjects, including controls, will be enrolled in the entire study? 40
  Of these, how many will be participating at the UBC/institution site? 40
  How many normal subjects will be enrolled in the study? 0
  Of the normal subjects, how many will be participating at the UBC/institution site? 0

15. Describe who is being selected, and the criteria for their inclusion. (see also Box 34, and Guidance Note #15)

Surgical Group

Individuals booked for HTO surgery will be invited to participate. They must have medial osteoarthritis and must be able to complete the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire. All participants must be able to give informed consent. They must also pass a standard MRI screening to ensure that they may be scanned safely.

Control Group

Individuals booked for HTO surgery or unicompartmental arthroplasty, but who will not undergo it during the study period, will be invited to participate. They must have medial osteoarthritis, be able to complete the WOMAC questionnaire, and be able to give informed consent. They must also pass a standard MRI screening to ensure that they may be scanned safely.

16. Describe which subjects will be excluded from participation. (see Guidance Note #16)

Exclusion criteria of participants from either group include:

- Prior knee surgery on the study knee involving more than simple arthroscopy
- Prior knee injury of the study knee which required ambulatory aids other than a cane or knee brace
- Symptomatic instability (e.g. patellar dislocation)
- Intra-articular corticosteroid injection in the study knee within the last three months
- Any of the precautions for the MR contrast agent, Magnevist (pregnancy, breast-feeding, respiratory allergies, asthma, thrombotic syndromes, history of grand mal seizures, impaired renal or hepatic function)
- Exclusion criteria for MRI scanning (e.g. metallic object in eye, pacemaker)

17. Describe how potential subjects will be contacted and by whom. In addition, describe how the potential subjects will be identified, including the source of the contact information (see Guidance Notes #17.1.1 and 17.1.2). Outline who originally collected the contact information and for what purpose it was originally collected. Attach copies of initial letters of contact and any other recruitment documents. Note that UBC CREB policy does not allow initial contact by phone, unless in the case of emergencies (see UBC CREB Policy #2 in Guidance Note #17.5.2). Initial contact should not be made by the subject's primary caregiver. (see Guidance Note #17.2.1)

Potential subjects will be identified by Dr. McCormack and colleagues in the course of their normal treatment. The physicians will ask for permission to pass contact information on to the investigators. Dr. Wilson will then mail out an initial contact letter and a copy of the consent form. The letter will indicate that a follow-up phone call will be made by Ms. d'Entremont.

18. Describe the selection and/or recruitment procedures for normal subjects, if these differ from the above. Attach copies of initial letters of contact and any other recruitment documents.

N/A
Description of Procedures (Must be written in the space provided):

19. Which of the following procedures are involved in this study? (Check all that apply.)

<table>
<thead>
<tr>
<th>[X] Drug administration</th>
<th>☐ Collection of blood</th>
<th>☐ Questionnaires</th>
</tr>
</thead>
<tbody>
<tr>
<td>☒ Surgical procedures</td>
<td>☐ Collection of other tissue</td>
<td>☐ Home visits</td>
</tr>
<tr>
<td>☐ Experimental medical devices</td>
<td>☐ Individual interview</td>
<td>☐ Video/Audio Recording</td>
</tr>
<tr>
<td>☐ Imaging studies (e.g., X-ray, MRI)</td>
<td>☐ Group interview</td>
<td>☐ Use of medical records</td>
</tr>
</tbody>
</table>

20. Summary of Procedures: Describe any specific manipulations: type, quantity, and route of administration of drugs and radiation, operations, tests, use of medical devices that are prototypes or altered from those in clinical use, interviews or questionnaires. Also, specify what procedures in this project involve an experimental approach, in that there may be diagnostic procedures or treatment dictated by the protocol differing from those required for standard patient care. (see Guidance Note #20)

The following procedures will be repeated three times at six month intervals, the first session being prior to surgery for the surgical group participants.

1. Clinical Evaluation (part of standard care - before and after surgery)
   Time: 30 minutes
   Location: Physician's office
   Procedure: Standard history taken, assessment of knee health performed.

2. Assessment of Varus/Valgus Knee Alignment (part of standard care - before and after surgery)
   Time: 15 minutes
   Location: UBC Hospital Radiology Department or Vancouver General Hospital Radiology Department
   Procedure: Standing radiograph of lower extremity including ankle and hip
   Radiation exposure: 0.2 mSv to leg, 1.0 mSv to abdomen; total exposure 1.2 mSv per session, 3.6 mSv total for study

3. Assessment of Three-Dimensional Patellar Tracking
   Time: 1 hour
   Location: UBC High Field Magnetic Resonance Imaging Centre, 3.0 T scanner
   Procedure: High resolution relaxed scan, then low resolution weight-bearing scans at six angles of flexion

4. Assessment of Cartilage Health:
   a) Assessment of Cartilage GAG Concentration
      Time: 1 hour (wait time 2 hours post-injection - other imaging/testing to be done during wait time)
      Location: UBC High Field Magnetic Resonance Imaging Centre, 3.0 T scanner
      Procedure: Inversion recovery turbo-spin echo T1 scan according to dGEMRIC protocol
      Drug administration: "Double dose" (0.2mM/kg or 0.4 mL/kg) of gadopentetate dimeglumine (Magnevist) contrast agent intravenously 2 hrs prior to scanning
   b) Assessment of Cartilage Thickness/Volume
      Time: 30 minutes (wait time 1 hour - other imaging/testing to be done during wait time)
      Location: UBC High Field Magnetic Resonance Imaging Centre, 3.0 Tesla
      Procedure: Fat-suppressed T1-weighted 3D FLASH water excitation pulse sequence

5. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)
   Time: 15 minutes
   Location: Physician's office or UBC High Field MRI Centre (during wait time)

6. [Surgical Only] High Tibial Osteotomy (part of standard care)
   Alteration to normal procedure: Titanium fixation (MR compatible)

21. Does the study involve research to be carried out in physician's private offices? ☒ Yes ☐ No
22a. How much time (i.e., how many minutes/hours over how many weeks/months) will a subject be asked to dedicate to the project beyond that needed for normal care?

Three and a half hours, three times over thirteen months, for a total of 10.5 hours. Some of the procedures are part of normal care such that the extra time is 9 hours for the surgical group, and 8.75 hours for the control group. The difference is due to the control group having only pre-operative procedures during the study, and not post-operative as well.

22b. How much time (i.e., how many minutes/hours over how many weeks/months) will a normal volunteer (if any) be asked to dedicate to the project?

N/A

23. Describe what is known about the risks of the proposed research. Include any information about discomfort or incapacity that the subjects are likely to endure as a result of the experimental procedure, along with the details of any known side effects which may result from the experimental treatment. (see Guidance Note #23)

The subject will be exposed to a small radiation dose for each of the radiographs. The maximum radiation dose is 3.6 mSv. One year of background radiation is 2 mSv, so the exposure here is equivalent to 21.6 months of background radiation. Risks associated with radiation exposure include cellular damage and changes in blood content at levels of 0.25 Sv (Statkiewicz, Sherer, et al., Radiation Protection in Medical Radiography, 2002, p 10). Note that the subject will be exposed to 3.6 mSv, or 0.0036 Sv, which is much lower than the level where blood changes occur. The dose of radiation proposed here is very small and side effects as a result of these radiographs are highly unlikely.

The dGEMRIC protocol uses gadopentetate dimeglumine (Magnevist), a MR contrast agent. Common adverse reactions noted were headache (4.8%) (majority transient, and mild to moderate severity), nausea (2.7%), injection site coldness/localized coldness (2.3%), and dizziness (1%). There are no contraindications, however participants with the precautions listed in the package insert will be excluded.

There are no known risks involved with MR scans. The MR scanner is confined, however, and some subjects may feel claustrophobic. Should this occur, they will be able to signal the technologist and leave the scanner.

24. Describe the benefits to the subject that would arise from his or her participation in the proposed research. (see Guidance Note #24)

The participants in the study will benefit from possible early detection of osteoarthritic changes. This is beneficial as steps can then be taken to slow down the progression of the disease. A more detailed and sensitive assessment of cartilage health is carried out here than in standard clinical assessment.

The participants will be given copies on compact disc of all the imaging done during the study, if they wish. Also, they will be able to receive the results of the study once the analysis is complete.

25. Describe any reimbursement for expenses or payments/gifts-in-kind (e.g. honoraria, gifts, prizes, credits) to be offered to the subjects. Provide full details of the amounts, payment schedules, and value of gifts-in-kind. (see Guidance Note #25)

Travel expenses incurred by participating in the study will be covered, including parking. For participants travelling within the city, travel expenses up to $50 per session will be covered (i.e. the cost of a taxi ride). For participants travelling from outside Vancouver, travel expenses up to $250 per session will be covered. The amount received by the participant will be based on travel receipts. Lunch will be provided to participants at the hospital cafeteria up to a maximum amount of $15 per day. An honourarium of $50 per session will be given to participants.

A small gift, value not to exceed $10 before taxes, will be given to participants at the completion of the study. Participants will not know about this in advance.

Version approved: 26 March 2002 (First Revision 15 Nov 2002; Second Revision 08 April 2003; Third Revision 31 July 31 2003)
### Monitoring and Data Analysis

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>26. Describe the provisions made to break the code of a double-blind study in an emergency situation, and indicate who has the code. (see Guidance Note #26)</td>
<td>N/A</td>
</tr>
<tr>
<td>27. Describe data monitoring procedures while the research is ongoing. Include details of planned interim analyses, Data and Safety Monitoring Board, or other monitoring systems. (see Guidance Note #27)</td>
<td>N/A</td>
</tr>
<tr>
<td>28. Describe the circumstances under which the study could be stopped early. Should this occur, describe what provisions would be put in place to ensure that the subjects are fully informed of the reasons for stopping the study.</td>
<td>As this is a pilot study, we do not know effect sizes for some of the tests. Should the results from the first follow-up be adequate to answer our research questions, the second follow-up will be cancelled. If this should occur, participants will be informed by letter of the reason.</td>
</tr>
<tr>
<td>29. Describe how the identity of the subjects will be protected both during and after the research study. (see Guidance Note #29)</td>
<td>Data and results will be identified by subject number only. Subjects will be assigned numbers 01 - 40. The contact information and identity of subjects will be available only to investigators, and will be kept separate from data and results.</td>
</tr>
<tr>
<td>30. Explain who will have access to the data at each stage of processing and analysis, and what steps will be taken to safeguard the confidentiality of the data at each stage. (see Guidance Note #30)</td>
<td>Imaging: Investigators and Imaging Technicians. At least one investigator will be present to ensure all necessary data is collected. Imaging technicians will be present to operate the equipment and position the subject. They will observe the data to ensure it is complete and free of defects. Analysis: Investigators. Dr. Wilson and Ms. d'Entremont will be involved in all steps of the data analysis. The images taken as part of standard care will be used in the surgical procedures, and confidentiality will be protected as with any other patient's data.</td>
</tr>
<tr>
<td>31. Describe what will happen to the data at the end of the study, and what plans there are for future use of the data.</td>
<td>As per the UBC guidelines, all data will be retained for at least five years after the publication of any results. The data associated with the use of the gadopentetate dimeglumine (Magnevist) will be retained for twenty-five years, as required by Health Canada. There are no current plans to use the data further.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Question</th>
<th>Answer</th>
</tr>
</thead>
<tbody>
<tr>
<td>32. Describe the consent process. Who will ask for consent? Where, and under what circumstances? (see Guidance Note 32)</td>
<td></td>
</tr>
<tr>
<td>The potential participants will be contacted by letter and will receive a consent form at that time. They will have the opportunity to review the form at their leisure and to contact Ms. d’Entremont to answer any questions they may have. If an individual agrees to participate, they will be asked by Ms. d’Entremont to sign the consent form at their first meeting, likely prior to the first test session. Due to unknown scheduling at this time, the location may be at one of the hospitals, or at the physician’s office prior to clinical evaluation. The physician will not participate in asking for consent.</td>
<td></td>
</tr>
<tr>
<td>33. How long will the subject have to decide whether or not to participate? If this will be less than twenty-four hours, provide an explanation. (see Guidance Note 17.3)</td>
<td></td>
</tr>
<tr>
<td>Subjects will have three weeks from the receipt of the initial contact letter to decide if they would like to participate.</td>
<td></td>
</tr>
<tr>
<td>34. Will every subject be competent to give fully informed consent on his/her own behalf? (see Guidance Note #34)</td>
<td>Yes</td>
</tr>
<tr>
<td>If Yes, skip to box 37. If No, provide details of the nature of the incompetence (for instance, young age, mental or physical condition).</td>
<td></td>
</tr>
<tr>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>35. If a subject is not competent to give fully informed consent, who will consent on his/her behalf?</td>
<td>N/A</td>
</tr>
<tr>
<td>36. If a subject is not competent to give fully informed consent, will he/she be able to give assent to participate? Explain how assent will be sought. Attach copies of the assent form as necessary. (see Guidance Note #34.1)</td>
<td>No</td>
</tr>
<tr>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>37. Describe any situation in this research in which the renewal of consent might be appropriate, and how this would take place. (see Guidance Note #37)</td>
<td>N/A</td>
</tr>
<tr>
<td>38. What provisions are planned for subjects, or those consenting on a subject’s behalf, to have special assistance, if needed, during the consent process (e.g., consent forms in Braille, or in languages other than English)? (see Guidance Note #38) Since the study is small, translation will be made available as necessary.</td>
<td></td>
</tr>
</tbody>
</table>
**Consent Forms**

39. UBC CREB policy requires written consent in all cases. All of the following information must be included in the consent form and not fragmented into information sheets. Please check off items in the following list to show that these items have been incorporated into all consent forms. (See Guidance Note #39) Note that a separate tissue/DNA banking consent form is required when consent to bank tissue (including blood/DNA) is requested but is independent from the subject’s participation in the study (i.e., when the subject may refuse banking, but still participate in the study). Refer to Guidance Note 39.6.1.3).

- Consent forms prepared on institutional letterhead (UBC department or hospital) or a facsimile.
- The title of the project.
- The identity of the Principal Investigator and the co-investigators, and the name and telephone number of a contact person.
- A contact telephone number for emergencies, and an explicit statement that it operates 24 hours a day, seven days a week, when appropriate.
- Second-person pronouns (you/your child) when referring to subjects. Be consistent throughout all consent forms.
- A clear explanation of why the subject has been invited to participate in the study.
- An offer to answer any inquiries concerning the procedures, to ensure that they are fully understood by the subject.
- An explanation of who is sponsoring the study.
- A brief but complete description in lay language of the purpose of the study and of all research procedures. (Terms such as Phase 1, Phase II, Phase III, random assignment, placebo, double-blind, etc. must be explained in lay language.)
- A statement of the total amount of time for participating in the research required of a subject, beyond that normally needed for standard care.
- A description of which subjects must be excluded from the study, to allow the subject to self-select out of the study. This list should be limited to exclusions which the potential subject is likely to be aware of themselves.
- A statement of all known side effects, with either an estimate of the probability of their occurrences or a summary of the available data (e.g., “has been tested in 50 normal volunteers; 5 experienced nausea and vomiting”).
- A statement describing what alternatives to participating in the research project are available to the subject (i.e., what other treatment options are available outside of the study).
- A statement describing the timely disclosure to subjects of information related to their continuing participation.
- Assurance that the identity of the subject will be protected, and a description of how this will be accomplished. (See Guidance Note #39.7.1)
- Assurance that the information collected will be kept confidential, an explanation of how this will be done, and a statement of who will have access to it. (See Guidance Note #39.7.1 and UBC CREB Policy #11)
- Details of payment for expenses and/or any other remuneration to be offered to the subjects, if any.
- A statement that subjects do not waive any of their legal rights by signing the consent form. (See Guidance Note #39.7.5)
- A statement of any actual or potential conflict of interest on the part of the researchers or sponsor.
- An unambiguous statement that the subject may decline to enter, or withdraw from, the experiment at any time without any consequences to continuing medical care. (See Guidance Note #39.7.8)
- A statement that if the subject has any concerns about his/her treatment or rights as a research subject, he/she may telephone the Director, Office of Research Services at the University of British Columbia, at 604-822-8598. (See Guidance Note #39.7.6)
- A statement acknowledging receipt of a copy of the consent form, including all attachments.
- A statement that the subject is consenting to participate (by signing).
- The signature and printed name of the subject consenting to participate in the research project, investigation, or study, the date of the signature.
- The signature and printed name of a witness, and the date of signature. (See Guidance Note #39.8.3)
- The signature and printed name of the P. I. (or qualified designated representative), and the date of the signature. (See Guidance Note #39.8.4)
- Page numbers (“page 1 of 3,” “page 2 of 3,” etc.).
- The version number and date of the consent form, as a footer at the bottom of each page.
### Potential Conflict of Interest

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>40. Describe any restrictions regarding the disclosure of information to research subjects (during or at the end of the study) that the sponsor has placed on investigators, including those related to the publication of results. (see Guidance Note #40.1)</td>
<td>N/A</td>
</tr>
<tr>
<td>41. Describe any personal benefits that the investigators and/or their partners/immediate family members will receive, connected to this research study. In addition, include details of all remuneration associated with the project that the investigator(s) or research organization will receive, i.e. fees and/or honoraria directly related to this study, such as those for subject recruitment, advice on study design, presentation of results, or conference expenses. (see UBC Policy#16 in Guidance Note #40.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>42. Describe any current or recent (within the last two years) consultancy or other contractual agreements with the sponsor held by the investigators. (include amounts.) (see Guidance Note #40.3)</td>
<td>N/A</td>
</tr>
<tr>
<td>43. Give details, if any of the investigators and/or their partners/immediate family members have direct financial involvement with the sponsor via ownership of stock, stock options, or membership on a Board. (see Guidance Note #40)</td>
<td>N/A</td>
</tr>
<tr>
<td>44. Give details, if any of the investigators and/or their partners/immediate family members hold patent rights or intellectual property rights linked in any way to this study or its sponsor. (see Guidance Note #40)</td>
<td>N/A</td>
</tr>
</tbody>
</table>
45. Use this space to provide information which you feel will be helpful to the CREB, or to continue any item for which sufficient space was not available. The group that developed the dGEMRIC protocol for GAG distribution has agreed to train Ms. d'Entremont in the use of this protocol. A letter to this effect has been included on the following page.
Instructions

In Sections A, B and C of Part 2, questions will be asked in the following format and you should give your answers by putting an "X" in one of the boxes.

NOTE:

1. If you put your "X" in the left-hand box, for example:

None  Mild  Moderate  Severe  Extreme  
\[ \text{None} \quad \text{Mild} \quad \text{Moderate} \quad \text{Severe} \quad \text{Extreme} \]

then you are indicating that you have no pain.

2. If you put your "X" in the right-hand box, for example:

None  Mild  Moderate  Severe  Extreme  
\[ \quad \text{None} \quad \text{Mild} \quad \text{Moderate} \quad \text{Severe} \quad \text{Extreme} \]

then you are indicating that your pain is extreme.

3. Please note:
   a) that the further to the right you place your "X" the more pain you are experiencing.
   b) that the further to the left you place your "X" the less pain you are experiencing.
   c) please do not place your "X" outside the box.

You will be asked to indicate on this type of scale the amount of pain, stiffness or disability you have experienced in the last 48 hours.

Remember the further you place your "X" to the right, the more pain, stiffness or disability you are indicating that you experienced. Finally, please note that you are to complete the questionnaire with respect to your study knee. You should think about your study knee when answering the questionnaire, that is, you should indicate the severity of your pain, stiffness and physical disability that you feel is caused by arthritis in your study knee. Your study knee has been identified for you by your health care professional. If you are unsure which knee is your study knee, please ask before completing the questionnaire.
**Section A**

**Instructions**

The following questions concern the amount of pain you have experienced due to arthritis in your study knee. For each situation please enter the amount of pain experienced in the last 48 hours (Please mark you answers with an “X”.)

**QUESTION: How much pain do you have?**

1. **Walking on a flat surface.**
   - None
   - Mild
   - Moderate
   - Severe
   - Extreme

2. **Going up or down stairs.**
   - None
   - Mild
   - Moderate
   - Severe
   - Extreme

3. **At night while in bed.**
   - None
   - Mild
   - Moderate
   - Severe
   - Extreme

4. **Sitting or lying.**
   - None
   - Mild
   - Moderate
   - Severe
   - Extreme

5. **Standing upright.**
   - None
   - Mild
   - Moderate
   - Severe
   - Extreme

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Section B

Instructions

The following questions concern the amount of joint stiffness (not pain) you have experienced in the last 48 hours in your study knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your joints. (Please mark your answers with an “X”.)

6. How severe is your stiffness after first wakening in the morning?

None    Mild    Moderate    Severe    Extreme
□        □        □          □        □

7. How severe is your stiffness after sitting, lying or resting later in the day?

None    Mild    Moderate    Severe    Extreme
□        □        □          □        □

Section C

Instructions

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities, please indicate the degree of difficulty you have experienced in the last 48 hours due to arthritis in your study knee. (Please mark your answers with an “X”.)

QUESTION: What degree of difficulty do you have?

8. Going down stairs.

None    Mild    Moderate    Severe    Extreme
□        □        □          □        □

9. Going up stairs

None    Mild    Moderate    Severe    Extreme
□        □        □          □        □

10. Standing up from sitting.

None    Mild    Moderate    Severe    Extreme
□        □        □          □        □

11. Standing.

None    Mild    Moderate    Severe    Extreme
□        □        □          □        □
<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>12. Bending to the floor.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>13. Walking on a flat surface.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>14. Getting in/out of a car.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>15. Going shopping.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>16. Putting on socks/stockings.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>17. Rising from bed.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>18. Taking off socks/stockings</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>19. Lying in bed.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
<td></td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>20. Getting in/out of bath.</td>
<td>None</td>
<td>Mild</td>
<td>Moderate</td>
<td>Severe</td>
</tr>
<tr>
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<td>Extreme</td>
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22. **Getting on/off toilet.**

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23. **Heavy domestic duties.**

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24. **Light domestic duties.**

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D Health Canada application
### Part 1

**Related Submissions (referred to in this submission):**

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*Reason for Submission:*

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*Reason for Submission:*

Attach separate sheets (same format) if necessary. Number of pages attached: ______

### Part 2 - Drug Product Formulation Information

**DIN 01989987**

54. Proposed Shelf Life ______ years ______ months at ______ °C.

55. Medicinal (Active) Ingredient(s)

<table>
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<th>Units</th>
<th>Per</th>
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Attach separate sheets (same format) if necessary. Number of pages attached: ______

56. Non-medicinal Ingredient(s) (include colouring agents)

**A) Preservative(s)**

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**B) Colouring Agents**

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</table>

**C) Other**

<table>
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<th>Strength</th>
<th>Units</th>
<th>Per</th>
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Attach separate sheets (same format) if necessary. Number of pages attached: ______

**D) For Biological drugs (human) containing non-medicinal ingredients of biological origin, indicate on a separate sheet the manufacturer and product name for each non-medicinal ingredient of biological origin.**

57. Dosage Form

58. Container Type | Package Size

59. Therapeutic/Pharmacological Classification

60. Route(s) of Administration
## E Kinematic curve slopes and intercepts

<table>
<thead>
<tr>
<th>Motion</th>
<th>Subject 1</th>
<th>Subject 2</th>
<th>Subject 3</th>
</tr>
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<tbody>
<tr>
<td><a href="#">Tibial abduction</a></td>
<td>Slope</td>
<td>Intercept</td>
<td>Slope</td>
</tr>
<tr>
<td></td>
<td>0.108315</td>
<td>-1.78047</td>
<td>0.042868</td>
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<tr>
<td><a href="#">Tibial internal rotation</a></td>
<td>Slope</td>
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<td>Slope</td>
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<tr>
<td></td>
<td>0.119403</td>
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<td><a href="#">Tibial proximal translation</a></td>
<td>Slope</td>
<td>Intercept</td>
<td>Slope</td>
</tr>
<tr>
<td></td>
<td>0.275481</td>
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<td>Intercept</td>
<td>Slope</td>
</tr>
<tr>
<td></td>
<td>-0.05582</td>
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<tr>
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<td>-0.60171</td>
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<td>Intercept</td>
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<td>0.150204</td>
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<td><a href="#">Patellar tilt</a></td>
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<td>Intercept</td>
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<td></td>
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<td>-0.10587</td>
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</tbody>
</table>

Table E.4: Kinematic curve parameters.
F Planned protocol

This chapter describes the recommended protocol for a study to investigate the effect of changes in joint mechanics on cartilage health. Recommendations are based on our findings during the development of the dGEMRIC and kinematic protocols and in their application in three subjects.

In the first instance, we will perform a pilot study to determine the effect size of changes in kinematics and cartilage health following high tibial osteotomy (HTO).

F.1 Objectives

The broad question we would like to address is:

How does a change in alignment and loading affect cartilage?

The objective of the pilot study is to determine the sample size required to answer the following research questions:

3. Do any of the twelve parameters of knee kinematics change with HTO?
4. Does glycosaminoglycan (GAG) concentration in cartilage change in any of the compartments of the knee with HTO?
5. Are changes in GAG concentration and changes in kinematics correlated?

F.2 Hypotheses

1. Knee kinematics will change following HTO.
2. Cartilage GAG concentration will change in some compartments (lateral), and remain the same in some compartments (medial and patellar) following HTO.
3. Changes in GAG concentration and changes in kinematics will be correlated.

F.3 Population

Participants will be identified with the assistance of orthopaedic surgeons who perform HTO, and will be scheduled to undergo a high tibial osteotomy procedure to correct varus malalignment of the lower limb and to relieve the pain of medial tibiofemoral osteoarthritis which is associated with this malalignment.

Forty participants will be recruited; twenty will be scheduled for and will undergo HTO surgery during the course of the study; twenty will be scheduled for either HTO or
unicompartamental arthroplasty (another surgical treatment) following the study, and will act as controls.

F.3.1 Inclusion Criteria

Participants in the surgical group must:

- Be scheduled for HTO surgery
- Have medial TF osteoarthritis
- Be able to complete the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index questionnaire
- Be able to give informed consent
- Pass a standard MRI screening to ensure they may be scanned safely

Participants in the control group must:

- Be scheduled for HTO surgery or unicompartamental arthroplasty for the treatment of medial osteoarthritis, but will not have surgery during the study period
- Have medial TF osteoarthritis
- Be able to complete the WOMAC questionnaire
- Be able to give informed consent
- Pass a standard MRI screening to ensure they may be scanned safely.

F.3.2 Exclusion Criteria

Exclusion criteria of participants from either group include:

- Prior knee surgery on the study knee involving more than simple arthroscopy
- Prior knee injury to the study knee which required ambulatory aids other than a cane or knee brace
- Symptomatic instability (e.g. patellar dislocation)
- Intra-articular corticosteroid injection to the study knee within the last three months
- Any of the precautions for the MR contrast agent, Magnevist (pregnancy, breast-feeding, respiratory allergies, asthma, thrombotic syndromes, history of grand mal seizures, impaired renal or hepatic function)
- Exclusion criteria for MRI scanning (e.g. metallic object in eye, pacemaker)
F.4 Methodology

Subjects and controls will undergo the same set of testing three times. The procedures for each session are:

1. Western Ontario and McMaster University Osteoarthritis Index (WOMAC) questionnaire
2. Assessment of knee kinematics
3. Assessment of cartilage degeneration
4. Standard assessment of varus-valgus angle

For surgical participants, these assessments will occur once before surgery and at two follow-ups, at six months and 12 months post-operatively. Control participants will undergo the same three assessments at the same time intervals. Only the knee requiring surgery will be assessed.

F.4.1 WOMAC questionnaire

All participants will complete the WOMAC assessment of OA severity. The WOMAC questionnaire is a self-administered questionnaire which addresses issues such as knee pain, stiffness and function related to osteoarthritis. It is widely used in osteoarthritis studies. The purpose of this questionnaire will be to assess subjective functional improvement of the knee. It takes approximately 15 minutes to complete.

F.4.2 Assessment of knee kinematics

Tibiofemoral and patellofemoral kinematics in loaded flexion will be assessed using the protocol developed in Chapter 3. The general method for measuring knee kinematics involves taking one high-resolution scan and six low-resolution, loaded scans at flexion angles ranging from 0 degrees to 60 degrees. These high- and low-resolution scans are then segmented and shape-matched. The transformations between the bones for each low-resolution data set will be calculated.

All subjects will be scanned using the 3.0 Tesla Philips Intera Gyroscan at the UBC High-Field MRI Centre. The coil used will be a Philips body coil.

F.4.2.1 High-Resolution Imaging

Subjects will undergo a high-resolution MR scan to obtain a very accurate model of the bones of the knee. The subject will lie supine on the scanner bench in a feet-first
orientation with legs relaxed. A soft strap will encircle the legs and a blanket will be placed between the knees to keep them apart in order to reduce the possibility of phase wrapping. The field of view (FOV) will be positioned so that the joint will be approximately centred in the image. The images will be obtained using a multi-slice T1-weighted fast spin echo sequence (Table F.1).

<table>
<thead>
<tr>
<th>Matrix size (scan)</th>
<th>512 x 512</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matrix size (reconstructed)</td>
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</tr>
<tr>
<td>Final in-plane resolution</td>
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<td>Field of View (FOV)</td>
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<td>Slice Thickness</td>
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<tr>
<td>Slice gap</td>
<td>0 mm</td>
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<tr>
<td>Number of slices</td>
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<tr>
<td>TSE factor</td>
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<tr>
<td>TE (echo time)</td>
<td>10 ms</td>
</tr>
<tr>
<td>TR (shot interval)</td>
<td>700 ms</td>
</tr>
<tr>
<td>Scan duration</td>
<td>16 minutes 18 seconds</td>
</tr>
</tbody>
</table>

**Table F.1: High-resolution scan parameters.**

**F.4.2.2 Low-Resolution Imaging**

Subjects will undergo low-resolution scanning during simulated loaded activity at various angles of flexion. A custom-built MR-compatible rig will be used to load the leg while the subject lies supine in the scanner. The subject will be positioned with the foot of the study leg on the pedal of the loading device. The tibiofemoral (TF) joint line will be marked on the subjects’ skin and TF flexion angles will be estimated with a goniometer. The leg will be supported in the correct position with foam wedges, and the subject will be moved into the scanner on the couch.
Upon completion of the preparatory scans, the technologist will signal an investigator in
the scanner suite to remove a block within the loading device which causes the load to be applied. The subject will maintain his/her knee position by pressing on the pedal against the weight. A signal will then be given to the technologist who runs the scan sequence. During the scanning, the investigator will observe coincident markings on the loading device for any movement during the scan. When the scan is complete, the investigator will reinsert the block and remove the weight from the subject. The subject will then be moved out of the scanner and repositioned for the next flexion angle.

The optimal sequence is a multi-slice T1-weighted fast spin echo sequence (Table F.2). Each scan will last 28 seconds.

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<td>Final in-plane resolution</td>
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<td>Field of View (FOV)</td>
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<td>Slice Thickness</td>
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<tr>
<td>Slice gap</td>
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<tr>
<td>Number of slices</td>
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<td>TR (shot interval)</td>
<td>700 ms</td>
</tr>
<tr>
<td>Scan duration</td>
<td>28 seconds</td>
</tr>
</tbody>
</table>

Table F.2: Low-resolution scan parameters.

Flexion angle range is limited by the size of the scanner bore, and also the "shutter size", or usable imaging area inside the scanner. We will attempt to image at every ten
degrees from 0 to 60 degrees. However, if the flexion limit is reached before six low-resolution scans are completed, the remaining images will be taken at five degree intervals between already acquired images.

F.4.2.3 Segmentation of images

To create the three-dimensional high-resolution model point cloud and the low-resolution data contours, all three bones will be segmented in each slice of the scans. Using medical image processing software (Analyze, Mayo Clinic, USA), a spline will be manually created following the edge of the cancellous bone in each image. Adjustments will be done by hand, and finally the outline will be saved in an object map.

For the high-resolution images each of the bones (femur, tibia, patella) will be saved as separate surface point clouds, using Analyze. Low-resolution contours of each bone will be saved.

F.4.2.4 Coordinate system application

To calculate transformations between the three bones of the knee, we will use the point selection convention defined by Fellows and Hill (48,72) to select specific anatomical points. These points will be used to systematically create anatomical coordinate systems fixed to each bone model. The specific points chosen are listed in Chapter 3. In order to select the points, the high-resolution images (without segmentation) will be re-loaded and interpolated to create cubic voxels and will be viewed in orthogonal planes using Analyze, which allows us to page through slices quickly and easily. Points will be selected with a mouse pointer and the values recorded. The coordinate axes and origin were defined in a Matlab program.

F.4.2.5 Shape-matching

We will shape-match the high resolution models of the bones and their associated coordinate systems to the low-resolution contours that describe their positions in loaded flexion.

The segmented bone shapes will be loaded into custom software written in Matlab. A preliminary inexact coincidence will be achieved by eye as a starting position for the algorithm. The investigator will input rotations and translations, and will check a plot
showing the match of the models (high-resolution) to the data (low-resolution). This is necessary to avoid divergent solutions when the shape-matching algorithm is started.

If either the model set or the data set for a particular bone shows more of the shaft than the corresponding data or model set, it will be truncated to the length of the shorter bone.

A shape-matching procedure will be performed to match each of the high-resolution bone models to each of the low-resolution segmented images. The shape-matching algorithm is the iterative closest points method. This method minimizes the sum of the distance between the points of the model cloud and the data contours. The shape-match will be done in a custom Matlab program.

F.4.2.6 Representation of kinematic patterns
Following the shape matching procedure, transformations between the bone coordinate systems will be calculated for each angle of flexion. This will result in twelve kinematic parameters (rotations and translations for both patella and tibia) at each of six flexion angles for each subject. The parameters will be plotted against flexion angle to obtain motion curves for the tibia and patella relative to the femur.

F.4.3 Assessment of cartilage degeneration (dGEMRIC)
We will assess cartilage degeneration using the method whose development is described in Chapter 4.

F.4.3.1 Contrast Agent Administration
A double dose (0.2mM/kg or 0.4 mL/kg) of gadopentetate dimeglumine (Gd-DTPA2-, Magnevist, Berlex Laboratories, USA) will be administered intravenously to an anticubital vein. A saline IV will be inserted and checked to ensure appropriate placement and flow. The contrast agent will then be injected into the saline line at a slow rate (approximately 1 minute for complete injection).

F.4.3.2 Exercise
Following administration of the contrast agent, the subject will asked to walk for a full 10 minutes. The IV line will be maintained and the subject will be kept under observation while exercising to ensure no adverse reaction occurs. The IV will then be removed.
F.4.3.3 Imaging

The subject will be prepared for imaging and set up in the scanner in time to begin imaging ninety minutes following the contrast administration. The subject will be scanned using the 3.0 Tesla Philips Intera Gyroscan at the UBC High-Field MRI Centre, using a Philips Flex-M surface coil. The subjects will lie supine on the scanner bench in a feet-first orientation. The coil (consisting of two rings) will be placed with a ring on each of the anterior and posterior aspects of the knee. The coil will be held in place with strapping. The lower legs will have sandbags placed on either side, and a blanket will be placed between the knees to reduce the possibility of phase wrapping. The legs will then be strapped together at the knees to prevent motion. The PF images will be obtained using an inversion recovery fast spin echo sequence (see Table 8.3) and the TF images will be obtained using a saturation recovery fast spin echo sequence (see Table 8.4).

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<th>Matrix size (scan)</th>
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<tbody>
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<tr>
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<td>Slice Thickness</td>
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<td>Number of slices</td>
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<td>TR (shot interval)</td>
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<td>Scan durations</td>
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<tr>
<td>TI (inversion times)</td>
<td>50, 100, 150, 200, 400, 700, 1200, 1800 ms</td>
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</tbody>
</table>

Table F.3: Inversion recovery scan parameters for dGEMRIC.
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Matrix size (reconstructed) & 256 x 256 \\
Final in-plane resolution & 0.39 x 0.39 mm \\
Field of View (FOV) & 100 mm \\
Slice Thickness & 3 mm \\
Number of slices & 1 \\
TSE factor & 2 \\
TE (echo time) & 15 ms \\
TR (shot intervals) & 100, 150, 200, 400, 700, 1200, 1800, 2200 ms \\
Scan durations & 0:27, 0:39, 0:52, 0:58, 1:40, 2:51, 4:15, 4:43 (total 16:25) \\

| Table F.4: Saturation recovery scan parameters for dGEMRIC. |
|-----------------------------------------------------------------
| Two proton density reference images will be acquired to select appropriate slices in both the axial and coronal planes. The coronal slice will be imaged first. The slice will be selected to show the highest point of the tibial spines. A screen capture image will be made to assist with re-selection of the slice at follow-up. Then the slice will be imaged with eight T1 times. The axial slice will be imaged second. The axial slice will be selected to show the thickest patellar cartilage. A screen capture image will be made to assist with re-selection of the slice at follow-up. The slice will then be imaged with eight TR times. This is because the thick cartilage requires slightly more time for contrast penetration. |

F.4.3.4 Analysis

Data will be imported into an in-house analysis program to calculate the T1 map. Images will be registered, the scaling factor applied by the Philips scanner will be removed, and the curves for each pixel will be fit. Calculated-T1 will be plotted and the cartilage segmented. A composite image will be created. Regions of interest will be segmented and average values for T1 recorded.

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F.4.4 Standard assessment of varus-valgus angle

A standing leg-length radiograph will be taken to assess the axial alignment of the lower leg. This method is the most commonly used for the assessment of varus or valgus knee angles for research purposes and is used for pre-operative planning of HTO surgery.

A graduated computed radiography cassette will be used to capture the data, so that the both the hip and the ankle will be imaged clearly. Standard x-ray safety protocols will be taken. Subjects will be positioned such that the patellae are facing forward.

The femoral head will be found using Mose circles (101). The centre of the knee joint will be the visually-identified mid-point of five anatomic landmarks: the centre of the soft tissue at the level of the cartilage, the centre of the tibia, the centre of the femoral condyles at the level of the top of the intercondylar notch, the centre of the tips of the tibial spines, and the centre of the femoral intercondylar notch. The centre of the ankle will be the visually-identified mid-point of three selected points: the centre of the soft tissue just proximal to the level of the cartilage, the centre of the external surface of the malleoli just proximal to the level of the cartilage, and the centre of the talus (99).

The line between the femoral head and the centre of the knee is the mechanical axis of the femur. The line between the centre of the knee and the centre of the ankle is the mechanical axis of the tibia. The line between the centre of the femoral head and the centre of the ankle is the mechanical axis of the leg. Important values are the angle between the mechanical axes of the femur and tibia, and the perpendicular distance between the mechanical axis of the leg and the centre of the knee joint. The angular measurements will be compared to measurements made using MR imaging.

F.4.5 Timing

The timing of the follow-up visits are based upon research which indicates that regeneration of cartilage ("repair" cartilage, usually fibrocartilage) occurs within two years post-HTO (18,57). Also, with osteochondral injuries, repair tissue can form in six to eight weeks following injury, and failure of the repair tissue for large defects can occur within one year (23). A dGEMRIC case study has indicated that changes in cartilage GAG content can be detected within four weeks of an injury (150). These studies
indicate that changes in cartilage following a mechanical change or event (such as HTO) may be seen within one year.

**F.4.6 High tibial osteotomy [Surgical subjects only]**

The high tibial osteotomy will be carried out in the standard manner (either opening-wedge or closing-wedge, the surgeon's choice), with the exception of using titanium hardware instead of stainless steel, since titanium is more MR compatible. Both stainless steel and titanium are widely used implant materials (109). The two materials have comparable material strengths and are both biocompatible. This change will not affect the standard of care.

**F.5 Analysis**

Longitudinal dGEMRIC data will be compared using a repeated-measures analysis of variance (ANOVA) for each cartilage location (i.e. medial femur, or lateral patella).

Longitudinal kinematics data will be compared using a repeated-measures analysis of variance for each kinematic parameter (i.e. patellar spin, or tibial anterior translation).

Correlations between changes in kinematics and changes in dGEMRIC will be assessed using a linear random effects model. The linear random effects model is a hierarchical model which is appropriate because the subjects are measured at different angles of knee flexion, so we need to compare values between data points (97).