ABSTRACT

Osteoarthritis (OA) is a prevalent disease with mechanical risk factors. One risk factor, varus knee alignment, is associated with medial tibiofemoral (TF) OA. High tibial osteotomy (HTO) is a surgical treatment for younger patients with varus malalignment that aims to reduce medial TF loading by realigning the mechanical axis.

Post-HTO MR investigation of cartilage health is complicated by metal artifact from surgical implants. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is a validated assessment of cartilage health sensitive to early OA. Techniques to reduce metal artifact in dGEMRIC were tested in phantom and in vivo. Saturation recovery reduced the extent of metal artifact, allowing dGEMRIC measurement near metal.

The mechanical change caused by HTO may increase lateral TF or patellofemoral (PF) loads, which may damage cartilage. Fourteen knees were examined before and after HTO using dGEMRIC. No significant differences were found between pre-operative and either 6- or 12-month results (TF or PF). These results indicate that cartilage may not be degenerating in the short term with HTO.

Clinical measures of mechanical changes with HTO are often frontal radiographs obtained in one joint position. Three-dimensional kinematic changes associated with HTO are unknown. Using a validated MR kinematics method, fourteen knees were examined before and after HTO. Seven of 11 kinematic parameters (TF and PF) showed significant differences between pre-operative and both 6- and 12-month follow-ups. These 3D changes may relate to clinical success; identifying these relationships may lead to improvements in HTO.

Knee kinematics are often assessed from a series of static positions. However, differences may exist between kinematics estimated from static poses and those from movement. A new dynamic method was developed to evaluate differences between static and dynamic kinematics in normal knees (n = 10). Eight of 11 kinematic parameters showed significant differences between dynamic and static kinematics. Dynamic 3D kinematics are often different from static results, and may provide information not obtainable from static scans.
In conclusion, numerous changes in knee joint kinematics and no apparent changes in cartilage health are associated with HTO within one year. Methods developed may help answer important questions about other orthopaedic disorders.
PREFACE

Parts of Chapter 2 have been published as a review paper [Agnes G. d’Entremont, David R. Wilson, “Joint Mechanics Measurement Using Magnetic Resonance Imaging”, Topics in Magnetic Resonance Imaging (2011) 21(5): 325-334]. I was responsible for researching and writing sections on MR kinematics and joint mechanics, providing some research for meniscal movement section, and editing the manuscript. Dr. David Wilson researched and wrote sections on cartilage strain and meniscal movement (not included in this thesis), and edited the manuscript.

I was the lead investigator for the project described in Chapter 3 where I was responsible for study concept and design, phantom design and construction, data collection, programming for data analysis, data analysis (segmentation, curve-fitting), noise simulation, statistical programming and analysis, and manuscript writing and editing. Dr. David Wilson provided supervision, and edited the manuscript. Dr. Alex MacKay provided supervision, advised on study concept and design, advised on sequence design, advised on phantom design, advised on curve fitting and noise simulation, and edited the manuscript. Dr. Shannon Kolind programmed the MARS patch and edited the manuscript. Dr. Burkhard Maedler advised on study concept and design, advised on sequence design, advised on curve fitting and noise simulation, and edited the manuscript. A version of this chapter has been submitted for publication as: Agnes G. d’Entremont, Shannon H. Kolind, Burkhard Maedler, David R. Wilson, Alexander L. MacKay, “Using the dGEMRIC technique to evaluate cartilage health in the presence of surgical hardware at 3T: comparison of inversion recovery and saturation recovery approaches”.

I was the lead investigator for the projects described in Chapter 4 and Chapter 5, where my responsibilities were study concept and design, data collection, programming for data analysis (curve fitting), data analysis (segmentation), statistical programming and analysis, and manuscript writing and editing. Dr. David Wilson advised on study concept and design, provided supervision, and edited the manuscripts. Kenard Agbanlog wrote code to assist in manual registration, performed the registration and curve fitting, and wrote code to facilitate segmentation for Chapter 4. Dr. Robert McCormack advised on study concept and design, provided
clinical advice and recruitment, wrote the surgical procedures sections and edited the manuscript. Drs. Trevor Stone, Mojieb Manzary, and Simon Horlick provided assistance with recruitment and clinical advice.

A version of Chapter 6 has been published [Agnes G. d'Entremont, Jurek A. Nordmeyer-Massner, Clemens Bos, David R. Wilson, Klaas P. Pruessmann, “Do dynamic-based MR knee kinematics methods produce the same results as static methods?” Magnetic Resonance in Medicine (2013) 69(6): 1634-44]. I was lead investigator on this project, and my responsibilities consisted of study concept and design, design and some construction of loading rig, data collection, data analysis (segmentation, kinematic calculations), statistical programming and analysis, and manuscript writing and editing. Dr. David Wilson provided assistance with study concept and design, provided supervision and substantially edited the final manuscript. Dr. Clemens Bos created the MRI sequences and edited the final manuscript. Dr. Jurek Nordmeyer-Massner created the stretchable knee coil, provided technical support for the coil use, contributed to data collection and recruitment, and edited the final manuscript. Dr. Klaas Pruessmann provided assistance with recruitment, provided supervision and edited the final manuscript. Doug Tran constructed the fiberglass base of the loading rig.

The projects in Chapter 3, Chapter 4 and Chapter 5 were reviewed and approved by the UBC Clinical Ethics Review Board [certificate numbers: C03-0432, H03-70432, H12-01776]. The project in Chapter 6 was approved under institutional ethics at ETH Zurich.
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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2D</td>
<td>Two dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three dimensional</td>
</tr>
<tr>
<td>ACL</td>
<td>Anterior cruciate ligament</td>
</tr>
<tr>
<td>ADC</td>
<td>Analog to digital converter</td>
</tr>
<tr>
<td>CP</td>
<td>Carr-Purcell sequence</td>
</tr>
<tr>
<td>CPMG</td>
<td>Carr-Purcell-Meiboom-Gill sequence</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebro-spinal fluid</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>DESS</td>
<td>Double-echo in steady state</td>
</tr>
<tr>
<td>dGEMRIC</td>
<td>Delayed gadolinium-enhanced MRI of cartilage</td>
</tr>
<tr>
<td>FCD</td>
<td>Fixed charge density</td>
</tr>
<tr>
<td>FID</td>
<td>Free induction decay</td>
</tr>
<tr>
<td>FLASH</td>
<td>Fast low angle shot</td>
</tr>
<tr>
<td>FOV</td>
<td>Field of view</td>
</tr>
<tr>
<td>FSE</td>
<td>Fast spin echo</td>
</tr>
<tr>
<td>GAG</td>
<td>Glycosaminoglycans</td>
</tr>
<tr>
<td>Gd</td>
<td>Gadolinium</td>
</tr>
<tr>
<td>Gd-DTPA&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Gadopentetate dimeglumine (trade name Magnevist)</td>
</tr>
<tr>
<td>GRE</td>
<td>Gradient recalled echo</td>
</tr>
<tr>
<td>HTO</td>
<td>High tibial osteotomy</td>
</tr>
<tr>
<td>IR</td>
<td>Inversion recovery</td>
</tr>
<tr>
<td>IR-MARS</td>
<td>Inversion recovery with metal artifact reduction sequence</td>
</tr>
<tr>
<td>MARS</td>
<td>Metal artifact reduction sequence</td>
</tr>
<tr>
<td>MR</td>
<td>Magnetic resonance</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic resonance imaging</td>
</tr>
<tr>
<td>OA</td>
<td>Osteoarthritis</td>
</tr>
<tr>
<td>PCL</td>
<td>Posterior cruciate ligament</td>
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<tr>
<td>PF</td>
<td>Patellofemoral</td>
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<tr>
<td>PG</td>
<td>Proteoglycans</td>
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<td>ppm</td>
<td>Parts per million</td>
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<td>qMRI</td>
<td>Quantitative MRI</td>
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<tr>
<td>RF</td>
<td>Radiofrequency</td>
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<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
<td>ROI</td>
<td>Region of interest</td>
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<tr>
<td>RSA</td>
<td>Roentgen stereophotogrammetric analysis</td>
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<tr>
<td>SD</td>
<td>Standard deviation</td>
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<td>SEMAC</td>
<td>Slice encoding for metal artifact correction</td>
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<td>SENSE</td>
<td>Sensitivity encoding</td>
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<td>SNR</td>
<td>Signal-to-noise ratio</td>
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<td>SR-MARS</td>
<td>Saturation recovery with metal artifact reduction sequence</td>
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<td>TE</td>
<td>Echo time</td>
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<td>TF</td>
<td>Tibiofemoral</td>
</tr>
<tr>
<td>TI</td>
<td>Inversion time</td>
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<tr>
<td>TKA</td>
<td>Total knee arthroplasty</td>
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<tr>
<td>TMJ</td>
<td>Temporomandibular joint</td>
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<td>TR</td>
<td>Relaxation time</td>
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<td>TSE</td>
<td>Turbo spin echo</td>
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<tr>
<td>TSL</td>
<td>Spin-locking time</td>
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<tr>
<td>UTE</td>
<td>Ultrashort TE (echo time)</td>
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<tr>
<td>VAT</td>
<td>View angle tilting</td>
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## LIST OF SYMBOLS

<table>
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<tr>
<th>Symbol</th>
<th>Description</th>
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<tbody>
<tr>
<td>( \alpha )</td>
<td>Adjusted alpha for multiple comparisons using Bonferroni</td>
</tr>
<tr>
<td>( B_0 )</td>
<td>Main magnetic field</td>
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<tr>
<td>( B_1 )</td>
<td>RF excitation magnetic field</td>
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<td>( d )</td>
<td>Blurring distance</td>
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<td>( f_{IR} )</td>
<td>Fit factor for imperfect inversion</td>
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<td>( G_{phase} )</td>
<td>Phase encoding gradient (also ( G_y ))</td>
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<td>( G_{read} )</td>
<td>Frequency encoding gradient (also ( G_x ))</td>
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<td>( G_{slice} )</td>
<td>Slice selection gradient (also ( G_z ))</td>
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<td>( G_y )</td>
<td>Phase encoding gradient (also ( G_{phase} ))</td>
</tr>
<tr>
<td>( G_z )</td>
<td>Slice selection gradient (also ( G_{slice} ))</td>
</tr>
<tr>
<td>( i )</td>
<td>Timepoint or Condition = 1, 2, or 3</td>
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<tr>
<td>( j )</td>
<td>Individual = 1 to 10</td>
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<tr>
<td>( M(t) )</td>
<td>Precessing magnetization</td>
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<td>Equilibrium magnetization</td>
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<td>Longitudinal magnetization</td>
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<td>( M_T )</td>
<td>Transverse magnetization</td>
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<td>Equilibrium magnetization signal</td>
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<td>( S_{0,initial} )</td>
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<td>Signal intensity</td>
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<td>( SI_{min} )</td>
<td>Lowest signal intesity</td>
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<td>( t )</td>
<td>Slice thickness</td>
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<td>Spin-lattice relaxation time</td>
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<td>Spin-lattice (T1) relaxation time in the rotating frame (rho = rotating)</td>
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<tr>
<td>( T_{1p} )</td>
<td>Spin-lattice (T1) relaxation time in the rotating frame (rho = rotating)</td>
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<td>( T_2 )</td>
<td>Spin-spin relaxation time</td>
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<td>( T_2^* )</td>
<td>Spin-spin and field inhomogeneity transverse relaxation time</td>
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<tr>
<td>( T_{1max} )</td>
<td>Highest inversion time</td>
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\( TR_{\text{max}} \quad \text{Highest repetition time} \\
u \quad \text{Individual deviation from group mean, a component of } \beta \\
x \quad \text{Cartesian coordinate} \\
y \quad \text{Cartesian coordinate, or dependent parameter in model equation} \\
z \quad \text{Cartesian coordinate} \\
\beta \quad \text{Coefficient in statistical mixed linear model} \\
\gamma \quad \text{Gyromagnetic ratio, or group mean, a component of } \beta \\
\theta \quad \text{Tilted view angle} \\
\omega_0 \quad \text{Larmor frequency}
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I would like to sincerely thank my supervisors for their understanding and guidance throughout my degree. Dr. David Wilson has been invaluably supportive to my training and development. Dr. Alex MacKay has been both knowledgeable and endlessly positive. Thanks also to my clinical collaborators, especially Dr. Robert McCormack, for supporting this work.

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Finally, I want to thank the friends who helped me through it all.
Chapter 1. Introduction

Knee osteoarthritis is a prevalent and debilitating condition that affects 6% of US adults over the age of thirty\textsuperscript{1}. Treatments are limited, both in range and ability to alter the disease course. Treatments with moderate or better effects in terms of pain and function, such as total knee arthroplasty (TKA), often only address the end stages of the disease and have other limitations, such as both a finite lifespan and difficulty in revision with TKA.

Mechanical factors play a key role in the incidence and progression of knee osteoarthritis, yet the idea of mechanical “wear and tear” of tissues is limited, because cartilage is a living and adaptable tissue\textsuperscript{2,3}. Correction of mechanical abnormalities can permit cartilage healing\textsuperscript{4}, however little is known about which specific mechanical changes lead to cartilage healing. Knee mechanics and changes in mechanics are complex, due to the array of connections between joint structures.

The overall theme of this research is to develop and apply magnetic resonance (MR) imaging tools to examine knee osteoarthritis and knee mechanics, with a particular focus on one surgical treatment called high tibial osteotomy.

High tibial osteotomy (HTO) is a treatment for medial knee osteoarthritis associated with varus malalignment (bow-legs)\textsuperscript{5}. The surgery realigns the knee joint to unload the damaged compartment. While the intent of the procedure is to change knee mechanics to protect cartilage, it is not clear what effect the surgery may have on overall joint kinematics and cartilage health.

HTO provides a unique opportunity to examine the effect of a distinct mechanical change on human cartilage \textit{in vivo}. Evidence of both the progression of cartilage degeneration with varus malalignment\textsuperscript{6} and cartilage regrowth following HTO\textsuperscript{4,7-10} highlight the linkages between cartilage health and joint mechanics, but it is not clear what specific mechanical factors lead to degeneration versus regeneration.

Cartilage changes can extend over decades, so it is critical to develop non-invasive, low risk measurement tools that are capable of evaluating kinematics and cartilage health \textit{in vivo}. Magnetic resonance (MR) imaging can be used effectively to assess both joint kinematics and cartilage health. The limitations in MR joint evaluation include the image disturbances caused
by the metal surgical implants frequently used in orthopaedic treatment, and the static and supine nature of typical scanning, which is inconsistent with the activities of daily living. Developing methods to reduce metal artifact in images and enhancing the ability to experimentally approximate typical joint usage (through loading/weightbearing and motion) are fundamental to obtaining credible post-operative MR evaluations of joint kinematics and cartilage health in a variety of clinical conditions.

1.1.1. Outline and research questions
The goal of this research was to develop and evaluate new tools for measuring knee kinematics with motion and cartilage health near metal implants using MR imaging, and obtain kinematics and cartilage health results in a group of patients undergoing HTO.

The following sections will outline four related projects.

In Chapter 3, an assessment of a particular cartilage health measure (delayed gadolinium-enhanced MRI of cartilage, dGEMRIC) near metal implants is presented. Metal causes disruptions in the magnetic fields that are integral to MR imaging, however metal implants are commonly used in surgical treatments of both osteoarthritis and injuries associated with the development of osteoarthritis, including HTO.

Research questions:
- Can we use dGEMRIC near metal implants, such as the implant used for HTO?
- How do specific metal artifact reduction strategies affect the extent of metal artifact and the results of the dGEMRIC testing?

In Chapter 4, I describe applying dGEMRIC to study the effect of HTO surgery on patellofemoral and tibiofemoral cartilage. Subjects were imaged before surgery and at 6- and 12-month follow-ups, using dGEMRIC and strategies developed from Chapter 3 to limit the effect of metal artifact on the results.

Research questions:
- How does HTO affect cartilage health (as assessed using the dGEMRIC index) at the patellofemoral joint?
- How does HTO affect cartilage health (as assessed using the dGEMRIC index) at the tibiofemoral joint?
In Chapter 5, I examine the effect of HTO on three-dimensional (3D) joint kinematics in a population of patients. Subjects were imaged before surgery and at 6- and 12-month follow-ups, using an MR-based kinematics method and loaded static scans. Kinematics of both the patella and tibia with respect to the femur were measured. A widely-used clinical questionnaire on pain, stiffness, and joint function (the Western Ontario McMaster Osteoarthritis Index, or WOMAC) was also administered.

**Research questions:**
- How does HTO affect 3D patellofemoral joint kinematics?
- How does HTO affect 3D tibiofemoral joint kinematics?
- What changes occur in WOMAC score with HTO?

In Chapter 6, I present a study comparing kinematics results from a series of loaded, static MR scans to 3D kinematics of a moving knee. Ideally, measurements of joint kinematics would be captured during weightbearing daily activities, since these are the situations where joint dysfunction may limit a patient’s quality of life. The MR scanner, however, constrains motion, position, and loading. I developed a method of measuring 3D joint kinematics based on rapid, dynamic scans of a moving knee, and applied them to a population of normal, healthy subjects.

**Research questions:**
- Are static joint kinematics measurements changed by the use of a fast sequence?
- Are the joint kinematics measured using a series of static poses the same as those measured during movement?

The work in this thesis presents a set of tools and data on the effect of HTO on joint mechanics and cartilage.
Chapter 2. Literature review

2.1. Knee joint anatomy

Joints bear load and allow movement. The knee joint is the largest synovial joint in the body, and is comprised of two individual articulations, the patellofemoral (PF) joint (between the patella and femur) and the tibiofemoral (TF) joint (between the tibia and femur). The tibiofemoral joint consists of two compartments, medial and lateral. The motion of the knee is primarily in the sagittal plane, and the active range of motion of the knee joint is large, typically around 145-150 degrees.

There are four major ligaments in the knee (Figure 2.1). The anterior cruciate ligament (ACL) and the posterior cruciate ligament (PCL) connect the tibia and femur. The ACL primarily resists anterior translation of the tibia and the PCL primarily resists posterior translation of the tibia. The cruciate ligaments are located between the two compartments of the tibiofemoral joint. The medial and lateral collateral ligaments stabilize the tibiofemoral joint and connect the tibia and femur on either side of the joint.

There are three major muscle groups that cross the knee: the quadriceps, the hamstrings and the gastrocnemius. The quadriceps (‘four heads’, for the four muscles that comprise them) act to extend the knee through the patella and patellar tendon, as well as assisting in hip flexion (Figure 2.1). The hamstrings (consisting of three muscles) act to flex the knee as well as extend the hip. The gastrocnemius acts to flex the knee, as well as to plantarflex the foot.

Other important structures within the knee joint include the medial and lateral menisci, fibrocartilaginous c-shaped structures that improve the conformance between tibia and femur, and are partially mobile within the tibiofemoral joint.

2.1. Mechanics

The function of human joints is primarily biomechanical. Joint biomechanics is studied to understand the functional anatomy of joints, to assess the effect of pathology, and to evaluate treatments for diseased and injured joints. Much of our understanding of human
Joint biomechanics is based on measures in cadaver specimens loaded to simulate biomechanics, which are limited by the difficulty in replicating physiological loads, and mathematical models, which are limited by the simplifications that are required and the difficulties in validating these methods. Some direct measurements of biomechanical quantities have been made in living humans, but have substantial limitations. Measurements of segment movement and external loads using motion analysis systems can be used to predict forces in the joint, but are limited by skin motion relative to the bones and by the assumptions that must be made to estimate forces. Joint forces and force distributions have been measured using instrumented prostheses, but these studies only provide post-operative data in a relatively small group of individuals. Because of these limitations, the need for direct measurements of joint mechanics in healthy, diseased, injured and treated human joints has remained strong.

![Diagram of knee joint anatomy](Image in public domain, from National Institute of Arthritis and Musculoskeletal and Skin Diseases. Questions and Answers about Knee Problems [Internet]. 2010)

Joint reaction forces are high (relative to bodyweight) in the knee. Maximum joint reaction forces in the tibiofemoral joint have been determined to range from 2 to 4 times body weight for normal walking\textsuperscript{14}. Joint reaction forces in the patellofemoral joint have been calculated to range from 0.5 times body weight in walking to 3.3 times body weight in stair climbing\textsuperscript{15}.
2.1.1. Mechanical axis
The mechanical axis of the lower limb is typically defined as the line connecting the center of the hip joint to the center of the ankle joint. Hip-knee-ankle (HKA) angle, also referred to as mechanical alignment, is one measure used to define coronal plane alignment. HKA is defined as the angle between the line connecting the hip joint centre and knee joint centre and the line connecting the knee joint centre and ankle joint centre. This definition is somewhat different from the anatomical tibiofemoral angle, which is typically defined as the angle between the shafts of the femur and tibia (Figure 2.2). Clinically, both measures are widely used. They are typically measured from anterior-posterior radiographs. The anatomical tibiofemoral angle is more often used, because it is a simpler measure and does not require radiating the hip joint centre, which results in the highest gonadal dose of radiation for males and leads to risk of heritable effects. Comparison between the two measures has shown strong correlation, however the anatomical axis results tend to have higher valgus angular values than equivalent measures of HKA angle.

A knee is in valgus alignment (knock-knees) when the center of the knee joint is medial to the mechanical axis (hip to ankle line), and in varus alignment (bow-legs) when the center of the knee joint is lateral to the mechanical axis (hip to ankle line).

While load distribution is not possible to measure in vivo, models of the knee joint based on kinematic and force plate measures during gait have shown that a higher proportion of the total joint load passes through the medial compartment (about 70% of total load during stance).

2.1. Cartilage
Healthy articulating surfaces of the knee joint are covered in articular cartilage. Knee cartilage varies in thickness from 0.16 to 6.25 mm, and has a low coefficient of friction which facilitates movement.

2.1.1. Anatomy and morphology
Cartilage is composed of an extracellular matrix and a sparse population of chondrocytes (cartilage cells). The extracellular matrix is primarily composed of water, held in place by the ionic charge of large macromolecules called proteoglycans. The side chains on proteoglycans are called glycosaminoglycans, are negatively charged. The other component of the extracellular matrix is collagen II fibers (20% of cartilage wet weight). Collagen fibre orientation varies depending on the layer of cartilage (deep, middle or superficial).
The deep layer has collagen that is oriented normal to the bony surface, the middle layer is a transition layer, and the superficial layer has collagen fibers oriented parallel to the surface (Figure 2.3).

**Figure 2.2: Methods of measuring knee alignment.**
(a) shows the hip-knee-ankle (HKA) angle of the leg, a measure obtainable from leg-length radiograph, as well as the axis from hip to ankle (typically what is meant by mechanical axis) which should pass through the centre of the knee joint in neutral alignment (dashed line). (b) shows the femorotibial angle (or anatomical axis), a measure obtainable from a radiograph with a smaller field of view, or a fluoroscopic image. Assembled from Gray’s Anatomy 1918, copyright expired.

Proteoglycans (PG) are cartilage proteins that have large negatively-charged side chains of glycosaminoglycans (GAG) that provide the fixed charge density (FCD) in cartilage. This FCD attracts water and limits the mobility of this water through the cartilage; these osmotic properties provide the stiffness required by cartilage in daily function. The loss of proteoglycans has been associated with early cartilage degeneration, prior to joint space loss.

Mature articular cartilage cells (chondrocytes) are not able to divide, and they receive nutrition through diffusion from synovial fluid (the tissue being avascular), so the repair potential of cartilage is limited and healing very difficult.
Figure 2.3: Schematic of healthy articular cartilage. (A) Cellular organization, (B) collagen organization. Cartilage zones (superficial transitional zone (STZ), middle, deep, and calcified) and subchondral bone indicated. Used with permission from SAGE Publications, Fox et al, “The basic science of articular cartilage: structure, composition, and function”, Sports Health. 2009, 1(6): 461-825.

2.1.2. Osteoarthritis (OA)

Osteoarthritis is a degenerative disease of cartilage and other joint tissues, including subchondral bone. Clinical signs include pain and swelling of joints. Radiographically, signs include loss of joint space (an indication of loss of cartilage thickness), osteophytes (bone spurs), and bony sclerosis (thickening of the subchondral bone). Radiographic OA does not always correlate well with clinical OA. In one cross-sectional study of the prevalence of tibiofemoral OA, 37.4% of all subjects had radiographic OA while only 12.1% had symptomatic radiographic OA, and only symptomatic radiographic OA was associated with activity limitations28.

Among US adults 30 years of age or older, 6% have symptomatic knee OA1. One study showed that 47.8% of women in a community cohort exhibited radiographic knee OA at a median age of 68, an increase from a 13.4% prevalence at baseline 15 years earlier29.

The economic impact of OA is staggering. Direct medical costs and indirect economic and wage loss effects combined were estimated at $128 billion per year in the US in 200330. Working-age people with knee OA have almost a two-fold increased risk of sick leave, and a 40-50% increased risk of disability pension compared to the general population, with nearly 2% of all sick leave days attributable to knee OA31.
2.1.2.1. **Risk factors**

Osteoarthritis has a number of risk factors, many of which are biomechanical in nature: joint injury through trauma, joint injury through repetitive use (e.g. in particular sports or occupations), obesity, joint deformity or malalignment, and muscle weakness\(^1\). Systemic risk factors for OA include age, sex, genetic predisposition, and bone density\(^1\).

2.1.2.2. **Assessment of degeneration**

In clinical practice, knee OA is often assessed using radiographs\(^32\). Radiographs are also widely used in population-based research studies\(^32\). Radiographic OA is often graded using a system and atlas of sample images (e.g. Kellgren-Lawrence, or Ahlback for the knee), and the grade is based on the presence and severity of various radiographic features (osteophytes, joint space loss, bony sclerosis, pseudocysts, and altered shape of bone ends)\(^32\). Radiographs do not image cartilage well, therefore the evaluation is primarily of bone and joint space instead of cartilage and cartilage thickness. Radiographic measures detect OA quite late in its progression (Figure 2.4).

Arthroscopy permits direct visualization and palpation of the cartilage, and can be graded much like radiographic results (Noyes scale)\(^33\). The results of radiographic assessment are not always well correlated with arthroscopy; cartilage that has apparent degeneration during arthroscopy may have no apparent degeneration radiographically\(^33\).

Biopsy and histology provide biochemical and structural information about the cartilage. This is a necessarily invasive procedure. Early histological changes include “fraying or fibrillation of the superficial zone of articular cartilage, reduced staining for proteoglycans, violation of the tidemark by blood vessels and nerves and subchondral bone remodeling”\(^34\).

Computed tomography (CT) imaging can also be used to assess cartilage defects, both through CT arthrography (intraarticular injection of contrast agent to delineate the cartilage surface)\(^35\) and contrast-enhanced CT (injection of ionic contrast agent which distributes relative to charged GAG side chains)\(^36\). CT methods allow fast, high-resolution images of the whole knee, but have the drawbacks of ionizing radiation and the requirement for injecting large amounts of contrast agent in contrast-enhanced CT to differentiate regions based on X-ray attenuation\(^36\).
A number of MR-based methods have been developed to assess cartilage health and osteoarthritis, including semi-quantitative grading systems analogous to radiographic grading (Whole Organ Magnetic Resonance Imaging Score (WORMS), the Knee Osteoarthritis Scoring System (KOSS), and the Boston-Leeds Osteoarthritis Knee Score (BLOKS))\textsuperscript{37}. MR arthrography (intraarticular injection of contrast agent followed by MR imaging) permits better delineation of cartilage surface and characterization of cartilage lesions compared to unenhanced MR, and may be used in conjunction with grading systems\textsuperscript{35}. Advanced MR imaging methods of cartilage morphology and biochemical markers, including quantitative MRI (qMRI), $T_2$ and $T_{1\rho}$ mapping, and delayed Gadolinium-enhanced MRI of cartilage (dGEMRIC), are described in Section 2.5. Advantages of MR methods over other assessment methods include their non-invasive nature, the lack of ionizing radiation, full thickness evaluation, and the characterization of biochemical or structural qualities of the cartilage.
2.1.2.1. Treatment options

Conservative treatments of osteoarthritis include ultrasound, arthroscopic debridement/lavage, acetaminophen, non-steroidal anti-inflammatory drugs, knee strengthening exercises, and intra-articular hyaluronic acid injections\(^{38}\). Except for the moderate short-term relief offered by intra-articular injections, the other conservative options provide only small treatment effects and do not alter the course of the disease\(^{38}\). Knee braces, opioids, and the controversially ineffective glucosamine and chondroitin sulfate supplements\(^{39}\) are other conservative treatment options\(^{40}\). Weight loss may be suggested for overweight or obese patients\(^{41}\), and has been shown to be effective in increasing function in obese patients with knee OA\(^{42}\).

Surgical treatment options include total knee arthroplasty (knee replacement), a widely used surgery that produces effective pain relief for many patients, with 73 to 92% of patients having favorable or uncertain pain outcomes within 5 years\(^{43}\). This surgery involves the removal of the joint surfaces, which reduces future treatment options, and may require revision after 10-15 years (recent 15 year survival rates have been reported as 77 to 90%, depending on hardware design\(^{44}\)). The mean age of patients is around 70 years\(^{43,44}\).

2.1.3. Medial tibiofemoral OA

Osteoarthritis of the medial tibiofemoral compartment is associated with varus malalignment (bow-legs)\(^{45}\). It is believed that the medial cartilage is under abnormally high loads due to the malalignment, which leads to breakdown of the cartilage\(^{45}\). Evidence links varus malalignment to progression of OA\(^{6}\), however the role of malalignment in the incidence of OA has recently been debated\(^{46,47}\). The prevalence of medial TF radiographic OA in an elderly (mean age 70 years) North American population is 14%, compared to a prevalence of 2% for lateral TF radiographic OA\(^{48}\).

Conservative treatments include neoprene sleeves, valgus braces, orthotics and wedged insoles all used to modify the malalignment of the knee\(^{40}\).

There are two established surgical treatments for medial tibiofemoral osteoarthritis: high tibial osteotomy (HTO) and unicompartmental knee arthroplasty (partial knee replacement) (UKA)\(^{49}\). Research has indicated that survival rates and long-term clinical outcomes are similar, however HTO is recommended for younger, active patients and UKA is recommended for older patients with reduced physical activity\(^{49}\).
2.2. High tibial osteotomy (HTO)

High Tibial Osteotomy (HTO) is a procedure indicated for patients with medial tibiofemoral osteoarthritis related to varus malalignment, and often is performed on active patients who are considered too young for total knee arthroplasty (TKA) due to that operation’s finite lifespan and need for complex revision, typically those 60 years of age or younger\textsuperscript{50,51}.

The purpose of high tibial osteotomy is to realign the knee such that the damaged medial compartment transmits less load and the lateral compartment transmits more load\textsuperscript{5}. The clinical purpose is pain relief (from medial compartment OA) and to ‘buy time’ before TKA. Suggested ranges for post-operative alignment are defined as either hip-knee-ankle (HKA) angles or anatomical alignment angles (see Section 2.1.1). Amendola and Panarella suggest the aim should be 8 to 10 degrees of anatomical valgus, the equivalent of 2 to 4 degrees of HKA valgus\textsuperscript{52}. Various other objectives suggested include 8 to 16 degrees valgus (anatomical)\textsuperscript{53}, 15 degrees valgus (anatomical)\textsuperscript{54}, 6 to 10 degrees valgus (HKA angle)\textsuperscript{55}, and 3 to 6 degrees valgus (HKA angle)\textsuperscript{7}, with objectives based on both surgical expertise and long-term outcomes. (Note that there are two types of measures reported for alignment aim, and that valgus HKA angles are equivalent to slightly larger valgus anatomical axis angles\textsuperscript{18}.) Other clinicians state the correction in terms of the mechanical axis passing through a percentage location on the tibial plateau (such as at 62\% of the plateau width, passing through the lateral compartment)\textsuperscript{56}.

There are two general methods for HTO: opening-wedge and closing-wedge. The opening-wedge operation involves cutting into the proximal tibia above the tibial tubercle from the medial side, leaving only a small bony hinge in the lateral cortex. The cut is then opened to an appropriate degree for correction of the alignment and bone graft (usually iliac crest autograft) is packed into the open wedge. A small plate and screws are used to secure the cut in the desired position (Figure 2.5 (a)).

The clinical results of opening-wedge high tibial osteotomy surgery have been moderately good, with ten year survival rates of between 45\% and 80\%, where survival is defined by conversion to TKA or an unacceptable clinical metric, such as a pain or function score\textsuperscript{7,16,50,53,54,57-60}.

The closing-wedge operation involves two bone cuts in the lateral proximal tibia (again above the tibial tubercle), and through the fibula. The wedge of bone created by these two cuts is
removed (leaving a small bony hinge in the medial cortex) and the wedge is closed and secured with hardware (Figure 2.5 (b)).

The opening wedge method is less technically difficult because the angle of alignment can be adjusted accurately after the cut, there is no loss of bone stock\(^{61}\), and there is minimal risk to the peroneal nerve due to the lack of lateral dissection\(^{62}\), but there is additional risk of hardware failure and a delayed time to post-operative full weight-bearing\(^{61}\). The closing-wedge method provides a stable construct that permits early weight-bearing\(^{63}\) and bony apposition for good healing potential\(^{64}\), but requires two precise cuts, a fibular osteotomy, and there is difficulty in making fine angular adjustments\(^{64}\). No difference in clinical outcomes has been seen between the two methods\(^{65,66}\).

![Figure 2.5: Two types of high tibial osteotomy.](image)

(a) Opening-wedge high tibial osteotomy radiograph. Visible are the Puddu plate and four screws, and osteotomy packed with iliac crest bone graft. (b) Closing-wedge high tibial osteotomy radiograph. Visible are the two staples stabilizing the closed osteotomy. Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery: Brouwer RW, Bierma-Zeinstra SMA, van Raaij TM, Verhaar JAN. Osteotomy for medial compartment arthritis of the knee using a closing wedge or an opening wedge controlled by a Puddu plate: a one-year, randomised, controlled study. J Bone Joint Surg [Br] 2006;8-B:1454-1459\(^{67}\).

Some studies have found statistical links between range of corrected angular alignment (measured from standing frontal radiograph) and outcomes\(^{53,54}\), and some have found no
association\textsuperscript{16,68}. It is important to note that this single metric of varus-valgus angulation is a limited measure of what may be a complex change in three-dimensions.

The effects of HTO surgery on cartilage have been studied, typically using arthroscopy, biopsy and histology, and radiographic measures. Evidence of cartilage repair in the medial compartment has been found\textsuperscript{4,7-10}. Evidence of degradation of lateral compartment and patellar cartilage has also been found in some subjects\textsuperscript{4,7}.

Clinical studies have demonstrated that HTO produces changes in addition to the intended valgus angulation post-operatively. Distal translation of the patella in opening-wedge osteotomy has been observed in vivo using radiographs\textsuperscript{65,69-75}, however no significant relationship has been found between patellar height and functional outcomes of the osteotomy\textsuperscript{73}. Lateral patellar tilt has been found to be decreased in vivo following HTO in two-dimensional radiographic work\textsuperscript{74}.

2.2.1. Tibial slope in high tibial osteotomy
Change in tibial slope has been of interest in high tibial osteotomy, and opening-wedge osteotomy tends to produce an increase in tibial slope (anterior edge of tibial plateau elevated relative to posterior edge)\textsuperscript{65,74-77}. Due to the geometry of the tibia below the plateau, the osteotomy is performed along the anteriomedial aspect of the shaft, and a wedge opened to equal height at the anterior and posterior ends of the osteotomy would result in a change in the slope of the tibial plateau (in the sagittal plane)\textsuperscript{78}(Figure 2.6). It has been estimated that each error of a 1 mm increase from the ideal anterior edge height results in a 2 degree change in tibial slope\textsuperscript{78}.

The direction of tibial slope change depends on the type of osteotomy performed; closing-wedge HTO tends to decrease posterior tibial slope\textsuperscript{16,76}, while opening-wedge osteotomy tends to increase posterior tibial slope\textsuperscript{76,77,79} (Figure 2.7). Onset of pain by 4 years follow-up in closing-wedge HTO was associated with a decreased tibial slope (-4.64° versus group with no pain at 4 years)\textsuperscript{16}. Increases in tibial slope (mean 3.5°) during opening-wedge osteotomy have been associated with more anteriorly placed hardware\textsuperscript{77}. Biomechanics studies have suggested that changes in tibial slope change the tibiofemoral contact pattern\textsuperscript{80}, and cause anterior translation of the tibia with respect to the femur\textsuperscript{81}. It has been suggested that intentional changes in slope could be protective in cruciate ligament deficient knees\textsuperscript{81}. 

Figure 2.7: Measurement of posterior tibial slope. Tibial slope is defined as the angle between the tangent to the medial tibial plateau and the line perpendicular to the axis of the tibial, typically on a radiograph.
2.2.2. Mechanical changes in high tibial osteotomy
A number of ex vivo biomechanical studies have been performed that have shown the following: a decrease in medial compartment force and an increase in lateral compartment force with HTO\textsuperscript{82}, a decrease in medial compartment pressure with lateralization of mechanical axis\textsuperscript{83}, higher peak pressure in the lateral compartment after osteotomy\textsuperscript{80}, higher peak pressure in the medial compartment after osteotomy before medial collateral ligament (MCL) release (and a reduction to below pre-operative pressure after MCL release)\textsuperscript{83}, higher pressure at the patellar cartilage surface with opening-wedge osteotomy\textsuperscript{84}, and changes in patellar kinematics with opening-wedge osteotomy, including lowered height, increased medial tilt, and decreased medial spin\textsuperscript{85}. Anterior placement of the plate is associated with increase in tibial slope compared to both pre-operative slope and slope with posterior plate placement\textsuperscript{80}, and increases in tibial slope are associated with anterior positioning of the tibia with respect to the femur\textsuperscript{81} and more posterior contact on the tibial plateau\textsuperscript{80}. Limitations of these studies include starting with knee with normal alignment rather than varus alignment, no muscle forces, limited assessment of position (often 2D measures), and limited joint positions (in some cases).

Three-dimensional in vivo kinematics have been measured for the closing-wedge and opening-wedge kinematics for four subjects each\textsuperscript{86}, however a larger study of three-dimensional kinematics has not been performed for opening-wedge high tibial osteotomy.

2.3. Magnetic resonance (MR) imaging
Magnetic resonance (MR) imaging is a widely used medical imaging modality that produces varied image contrasts and images soft tissue well. This section will briefly describe image production using MR.

2.3.1. Basics of magnetic resonance
Protons, specifically the nuclei of hydrogen atoms in water molecules, are magnetic dipoles. When placed in a strong magnetic field, they align with the field, much like a small magnet, resulting in a net magnetization of the tissue ($M_0$) made up of the individual dipole spins. This net magnetization precesses about the direction of the main magnetic field ($B_0$) at a specific frequency, called the Larmor frequency ($\omega_0$), which is a function of field strength and a nuclei characteristic called the gyromagnetic ratio ($\gamma$) (see Equation 2.1).
\[ \omega_0 = \gamma B_0 \]

Equation 2.1

The magnetization can be tipped out of alignment with the main magnetic field \(B_0\) using a radiofrequency (RF) pulse at the Larmor frequency of the spins, often referred to as the \(B_1\) field. As the net magnetization, \(M(t)\), relaxes back into alignment with the \(B_0\) field, a receiver placed on an axis perpendicular to the \(B_0\) field can capture an induction signal from the moving magnetization.

By common convention, the \(B_0\) field direction is the physical \(z\)-direction, and magnetization along this axis is called longitudinal magnetization, while magnetization in the plane orthogonal to the \(B_0\) field direction (\(x\)-\(y\) plane) is called transverse magnetization.

RF pulses applied to tip the net magnetization into the transverse plane are known as 90° pulses (Figure 2.8), and RF pulses that tip magnetization into the \(-z\)-direction are known as 180° pulses.

![Figure 2.8: 90° excitation pulse.](image)

RF pulse causing 90° rotation of net magnetization (small black vector) from the \(z\)-direction to the transverse plane.

2.3.2. Relaxation and contrast

Contrast between different tissues in MR imaging can be based on proton density, but can also be adjusted by exploiting some fundamental properties of protons in magnetic fields, known as \(T_1\) and \(T_2\) relaxation. When the net magnetization aligned with the main magnetic field, \(M_0\), is flipped 90° into the transverse plane, the longitudinal magnetization, \(M_L\), is zero, and the transverse magnetization, \(M_T\), equals \(M_0\). Over time, the magnetization, \(M(t)\), relaxes back to alignment with \(B_0\) and to the equilibrium value \(M_0\), and this relaxation is characterized by the spin-lattice relaxation time, \(T_1\).
As spins spend time in the transverse plane, they dephase due to small variations in magnetic field and spin-spin interaction. The dephasing of spins results in an eventual reduction of net magnetization to zero in the transverse plane. This combination of dephasing effects is called $T_{2}^*$, with the non-reversible dephasing component called $T_2$ relaxation (or spin-spin relaxation).

Contrast in images is formed by the relative differences in the relaxation times. The values of $T_1$ and $T_2$ depend on field strength and tissue. For example, from musculoskeletal tissues, $T_1$ relaxation times for cartilage are 1060 ms at 1.5 T and 1240 ms at 3 T, while for marrow fat $T_1$ is 288 ms at 1.5 T and 365 ms at 3 T. $T_2$ relaxation times for cartilage are 42.1 ms (1.5 T) and 36.9 ms (3 T), while for marrow fat the $T_2$ times are 165 ms (1.5 T) and 133 ms (3 T). By adjusting the timing of when magnetic fields are applied and when signals are acquired from the tissue, differences in tissues become highlighted because of slower or faster relaxation and consequent variation in signal intensity (Figure 2.9).

Figure 2.9: Comparison of the $T_1$ relaxation curve for tissues in brain. $T_1$ curves for white matter, grey matter, and cerebro-spinal fluid (CSF). White matter has the lowest $T_1$, and CSF has the highest $T_1$. Appropriate selection of signal acquisition time (along the horizontal axis) will provide greater contrast between fluids (with signal intensity being related to longitudinal magnetization, along the vertical axis). Used with permission from Pooley, “AAPM/RSNA Physics tutorial for residents: fundamental physics of MR imaging”, Radiographics. 2005, 25:1087-99, RSNA.

2.3.3. Localization of signal
To create images, signal from net magnetization must be localized to particular spatial areas. Localization is accomplished using gradient magnetic fields that modify the strength of the main magnetic field in a predictable way, typically linearly with position. Three orthogonal gradients are used, and while they are named based on the logical coordinate system (x, y, and z), they can be applied independent of actual direction of the main magnetic field.
In 2D imaging (single or multi-slice), the slice selection gradient \((G_z)\) alters the Larmor frequency in the slice selection direction \((z)\), so that only spins in a particular slice are at the correct frequency to be excited by the RF pulse. This gradient is typically only applied during the RF pulses (Figure 2.10).

The phase-encoding gradient \((G_y)\) is applied for a finite period following excitation. While \(G_y\) is active, the spins along the \(y\)-direction have variable frequencies, however the purpose of phase-encoding is to change the relative phase of the spins in the \(y\)-direction. Once the relative phase change has been achieved, the gradient is turned off and the spins resume their original frequencies but have phases related to the position along the \(y\)-direction, and when the signal is acquired the spins can be localized. This procedure must be repeated over a range of relative phase changes to obtain the desired \(y\)-direction resolution.

The frequency-encoding gradient \((G_x)\) is applied after excitation, and alters the frequency of the precession of the spins along the \(x\)-direction so that when the signal is acquired the spins can be localized based on frequency.

After the application of both phase- and frequency-encoding gradients (all phase-encoding steps), each voxel in the slice may be localized by the phase/frequency combinations.

### 2.3.4. Signal acquisition

Typically, the induction signal emitted immediately following excitation, called free induction decay, is not captured directly after the RF pulse. Rather, the spins are rephased to form an echo, and this echo is the captured signal. Because the dephasing of the spins after excitation with the 90° pulse is partly related to magnetic field inhomogeneities, by applying a 180° pulse and causing the spins to flip either along the rotating \(x\)-axis (CP, or Carr-Purcell sequence\(^{89}\)) or the rotating \(y\)-axis (CPMG, or Carr-Purcell-Meiboom-Gill sequence\(^{90}\)), they continue to have the relative phase shift caused by inhomogeneities but now move toward coherence again, resulting in an echo (Figure 2.10). These sequences are both types of spin-echo sequences, to distinguish them from other methods of forming echos.

### 2.3.1. Image creation

The complex signal obtained from the echo includes information on spatial localization encoded by frequency and phase. This signal is acquired in Fourier space, or \(k\)-space, and contains the same information as the MR image; the image can be reconstructed by a two-dimensional Fourier transformation.
2.3.2.  \( T_1 \) measurement

In measuring \( T_1 \), there are two basic and common methods: saturation recovery (SR) and inversion recovery (IR).

![Spin-echo pulse sequence diagram]

**Figure 2.10:** A spin-echo pulse sequence diagram.

“RF” shows RF pulses (90° excitation pulse, and 180° refocusing pulse). “Signal” shows the free induction decay with the 90° pulse and the echo at TE (echo time) from the initial excitation. Slice selection gradient \( G_z \) is active during RF pulses; frequency encoding gradient \( G_x \) is active during phase encoding and readout of the signal; and phase encoding gradient \( G_y \) is represented by a series of amplitudes, indicating that at each repetition of the sequence (defined by the next 90° excitation pulse spaced at the repetition time, TR) a different \( G_y \) is applied.

2.3.2.1.  **Inversion recovery (IR)**

Inversion recovery sequences are often used for nulling the signal from fat in an image (that is, making it appear black on the image). An inversion recovery sequence, as described by the diagram in Figure 2.11, involves an initial 180° inversion pulse before excitation. The spins start to recover according to \( T_1 \) relaxation, and at a particular time, the inversion time \( TI \), the 90° excitation pulse is applied.

When the 90° excitation pulse is applied, only spins that are not in the transverse plane will be excited. All spins in the transverse plane will continue relaxing and will not contribute to the echo. Selection of the inversion time such that the \( T_1 \) curve of a particular tissue has zero longitudinal magnetization means that tissue will be nulled in the image (Figure 2.12).
Figure 2.11: Inversion recovery pulse sequence.
A $180^\circ$ pulse is applied at a time, TI before the $90^\circ$ excitation pulse.

Figure 2.12: Signal in inversion recovery.
Note that the inversion time, TI, was selected here to obtain nulling of signal from fat. Used with permission from RSNA, Pooley, “AAPM/RSNA Physics tutorial for residents: fundamental physics of MR imaging”, Radiographics. 2005, 25:1087-99.

By obtaining a series of images with a range of inversion times, the contrast of the image changes, with each tissue following its $T_1$ relaxation curve (Figure 2.13).
By fitting a curve through the signal values at each pixel, based on Equation 2.2, the value of $T_1$ may be calculated (Figure 2.14).

\[
SI = \left| M_0 \left(1 - f_{IR} e^{-\frac{TI}{T_1}}\right) \right|
\]

Equation 2.2

Where $SI$ is the signal intensity, $M_0$ is the magnetization at equilibrium, $f_{IR}$ is a fit factor to account for imperfect 180° pulses (ideal inversion: $f_{IR} = 2$), and TI is inversion time.

**Figure 2.13: A series of inversion recovery images.**
The largest inversion time is at the top left. Different tissues, such as bone, cartilage, and synovial fluid, exhibit nulling at different TI times.

**Figure 2.14: Example inversion recovery data and curve fit.**
2.3.2.2. **Saturation recovery (SR)**

Saturation recovery is similar to inversion recovery in that a series of images are taken and a curve is fit through the signal values at each pixel, based on Equation 2.3, to obtain $T_1$ (Figure 2.15). In this case, TR is varied. When the new 90° pulse is applied, the spins that are recovered get excited again, while the spins that are still in the transverse plane do not get excited, leading to varying contrasts over the range of TR times.

$$SI = M_0 \left(1 - f_{SR} e^{-\frac{TR}{T_1}}\right)$$

Equation 2.3

Where $SI$ is the signal intensity, $M_0$ is the magnetization at equilibrium, $f_{SR}$ is a fit factor to account for imperfect 90° pulses (ideal excitation: $f_{SR} = 1$), and TR is repetition time.

![Figure 2.15: Example saturation recovery data and curve fit.](image)

2.3.3. **MR imaging for musculoskeletal applications**

MR imaging is widely used for neurological and visceral applications, due to its good differentiation of soft tissue. Musculoskeletal imaging using MR also has a number of advantages over x-ray based methods, such as computed tomography (CT) and radiographs. There is no ionizing radiation involved, which means that longitudinal imaging and multiple scans are not associated with long-term risk, and MR provides good soft tissue imaging, which is useful for cartilage, muscle, and other structures. Some disadvantages of MR compared to other modalities include limited signal from dense tissue, such as cortical bone, and metal orthopaedic hardware, if present, causes artifact in the images.
2.4. Metal artifact in MR

Metal artifact in MR results from mis-mapping (disrupted spatial encoding) due to magnetic field disruption caused by differences in magnetic susceptibility and eddy currents within conductive materials caused by switching radiofrequency (RF) energy\textsuperscript{91-93}. These cause both in-plane distortion and through-plane distortion\textsuperscript{94}.

There is interest in imaging near orthopaedic implants, including unicompartmental knee replacements\textsuperscript{95}, total knee replacements\textsuperscript{96-101}, ACL repairs\textsuperscript{98}, hip arthroplasty\textsuperscript{96-98,101-108}, shoulder arthroplasty\textsuperscript{96,97}, spinal implants\textsuperscript{98,101,109-114}, ankle hardware\textsuperscript{100,107}, and various other screws, plates and staples\textsuperscript{98,110,115,116}. Even when hardware is removed, metal artifact can still affect images due to metallic particles left behind\textsuperscript{117}.

This section will discuss factors that can modify metal artifact in MR.

2.4.1. Field strength

Metal artifact severity increases with the strength of the main magnetic field\textsuperscript{91}, in a roughly linear way\textsuperscript{93}. Figure 2.16 shows an example of 1.5 T and 3 T images of the same knee, with a larger artifact at 3T.

![Figure 2.16: Comparison of field strength.](image)

(a) Image taken at 1.5 T and (b) image taken at 3 T, with larger artifact at 3 T. Used with permission from RSNA, Lee et al., “Overcoming artifacts from metallic orthopedic implants at high-field strength MR imaging and multi-detector CT”, Radiographics. 2007, 27:791-803\textsuperscript{118}. 


Parameter adjustment to best enable imaging of patients with metal artifact may not be available on low-field scanners. On high-field scanners, such as 3T, artifact reduction by bandwidth increase may be limited by gradient hardware and energy deposition limits. One study in porcine tissue has suggested that sequences well optimized for metal artifact reduction result in qualitatively better images for visualizing tissue near orthopaedic hardware at 3 T than at 1.5 T.

2.4.2. Type of metal
Magnetic susceptibility is a material property that describes the tendency of a material to become magnetized in the presence of a magnetic field. It also indicates the amount of perturbation of the background static magnetic field caused by the material, since this relates to susceptibility in a roughly linear way. The homogeneity of the background field in MR is around 1.5 ppm. Natural magnetic susceptibility boundaries in the body can affect the homogeneity of the field: for example, air has a susceptibility of 0.3 ppm and tissue/bone has a susceptibility of -10 ppm. Susceptibilities of implant materials are much higher; examples include titanium (182 ppm), cobalt chromium (900 ppm), and stainless steel (3000-5000 ppm). Differences at tissue/implant boundaries can be hundreds or thousands of ppm.

Orthopaedic materials that tend to produce larger artifacts include stainless steel, cobalt chromium and nickel. Materials that produce smaller artifacts include titanium, zirconium oxide, tantalum, magnesium, and carbon fibre. That stainless steel produces more artifact than titanium is clear from Figure 2.17.

2.4.1. Alignment of metal relative to $B_0$ field
The main magnetic field, or $B_0$ field, is typically oriented along the axis of the scanner for superconducting magnets, which is typically also the superior-inferior axis of the human patient.

The orientation of metal within the main magnetic field affects the size and shape of the artifact (Figure 2.18).

In many cases, the orientation of the metal implant cannot be modified very much because of the limitations of positioning the patient in the scanner. For example, it is virtually impossible to position a hip replacement stem, located within a patient’s femur, across the main magnetic field in a conventional scanner.
Figure 2.17: Comparison of type of metal and type of sequence.
(a) Schematic of three screws (titanium and stainless steel) in phantom, (b) gradient-recalled echo (GRE) scan of phantom (arrow indicates frequency encoding direction), (c) spin echo scan of phantom. Used with permission from RSNA, Lee et al., “Overcoming artifacts from metallic orthopedic implants at high-field strength MR imaging and multi-detector CT”, Radiographics. 2007, 27:791-803118.

2.4.1. Frequency and phase directions
The directions of the frequency and phase encoding can be switched, and often are switched to avoid phase wrap (aliasing of tissue outside the field of view to the opposite side of the image) or artifacts due to physiological motion or pulsatile flow falling along the direction of interest. Direction of frequency and phase can also have an effect on metal artifact, as the mis-mapping occurs in the direction of frequency encoding91. By switching the direction of phase and frequency encoding, the orientation of the artifact is changed which may allow visualization of previously distorted anatomy91,115,123.

2.4.1. Bandwidth
With frequency encoding, the strength of the gradient determines the change in Larmor frequency that occurs within the space of the field of view. This range of frequency change is known as the bandwidth91.

Metal artifact causes mis-mapping due to changes in the local magnetic field. Given a particular amount of frequency mis-map, the spatial extent of the artifact depends on the
spatial frequency in the image, or the bandwidth\textsuperscript{91}. With a lower bandwidth, each pixel is close in frequency to the next, and a particular frequency change caused by metal will extend further in the image. With a higher bandwidth, the frequency in each pixel is further from the next, and the frequency change caused by the metal is a smaller percentage of the total spatial frequency change, therefore the artifact will extend less far\textsuperscript{91,93,114,119}.

Figure 2.18: Effect of orientation in $B_0$ field on metal artifact. (a) Schematics of the orientation of a screw with respect to the main magnetic field, and (b) the corresponding fast spin echo images. Used with permission from RSNA, Lee et al., “Overcoming artifacts from metallic orthopedic implants at high-field strength MR imaging and multi-detector CT”, Radiographics. 2007, 27:791-803\textsuperscript{118}.

The disadvantage of increased bandwidth is a loss in signal-to-noise ratio\textsuperscript{92}. Gradients must be very strong to utilize high bandwidths and maintain the balance of field of view and matrix size\textsuperscript{92}.

### 2.4.2. Voxel size
Metal artifact tends to extend along the frequency encoding direction\textsuperscript{92}. Increasing the matrix size in the frequency direction, which amounts to decreasing the size of the pixels for a given field of view, means that the boundary of the artifact is more precisely defined and appears to affect less area in the image\textsuperscript{91,92,118}. Similarly, a smaller field of view with the same matrix size produces a smaller artifact (Figure 2.19)\textsuperscript{115,118}. The increase in matrix size/decrease in pixel size is limited by the amount of signal available and will reduce the signal-to-noise ratio of the image.
Slice thickness can also be minimized to reduce artifact propagation between slices\textsuperscript{92,93,118}. In practical terms, the minimum slice thickness is limited by the amount of signal available\textsuperscript{92}.

**Figure 2.19: Comparison of field of view (FOV).**
(a) Image taken with a 14 cm FOV, and (b) image taken with a 24 cm FOV (cropped to show the same extent of tissue). The image in (a) has a smaller extent of artifact, due to the smaller pixel size associated with a smaller FOV at the same matrix. The image in (b) has lower resolution due to larger pixels associated with the larger FOV; the tradeoff for reducing FOV/increasing resolution may be an increase in imaging time to maintain signal-to-noise ratio. Used with permission from RSNA, Lee et al., “Overcoming artifacts from metallic orthopedic implants at high-field strength MR imaging and multi-detector CT”, Radiographics. 2007, 27:791-803\textsuperscript{118}.

### 2.4.1. Adiabatic pulses

It is desirable to excite or invert the magnetization uniformly in the tissue, however this relies on spatial homogeneity of the $B_1$ field, which can be difficult to achieve even without metal present. The inhomogeneity in the $B_1$ field causes a spatial variation in flip angles. Adiabatic pulses are a class of RF pulses that vary amplitude and modulation frequency during the pulse. The ultimate effect is that instead of having the magnetization rotate about a static $B_1$ field, the magnetization precesses about an effective field (combination of $B_1$ and $B_0$) that rotates from the original orientation of the magnetization to the correct flip angle (based on a principle called the adiabatic passage principle) and thus draws the magnetization into the correct flip angle regardless of the local magnetic field strength variations (Figure 2.20). Adiabatic pulses require relatively long pulse width and high $B_1$ amplitude. These pulses are often employed in inversion recovery sequences to obtain more accurate (uniform) 180 degree inversions, especially when using surface coils, where the $B_1$...
field is highly non-uniform\textsuperscript{124}. Adiabatic pulses have been employed in the presence of metal artifact\textsuperscript{116,125}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{adiabatic_pulses.png}
\caption{Adiabatic inversion pulses. Adiabatic inversion pulse (a to e), and non-adiabatic inversion pulse (f). During the adiabatic inversion, the magnetization precesses about the effective field. Used with permission from Elsevier, Bernstein et al., “Handbook of MRI Pulse Sequences”, 2004\textsuperscript{124}.}
\end{figure}

2.4.1. Type of sequence

There are many types of sequences for many purposes, so it is challenging to examine the effect of metal on all of them, however there are a few basic and general differences that are important to discuss.

Sequences that are sensitive to susceptibility artifacts, such as gradient recalled echo (GRE) or chemical saturation pulses (such as inversion pulses for fat saturation), generally have more severe artifact\textsuperscript{91,92}. More extensive artifact has been observed in GRE as compared to spin-echo sequences\textsuperscript{115,118,123} (Figure 2.17).

Short TE sequences and short interecho spacing in fast- or turbo-spin echo (versus regular spin echo) show less artifact because there is less time for intravoxel signal dephasing caused by hardware\textsuperscript{92,117,118,123} (Figure 2.21).

More recently, ultrashort TE (UTE) sequences have also been utilized to reduce metal artifact\textsuperscript{108,126}. UTE sequences are typically used to image tissues with short T\textsubscript{2} components,
like bone, tendons and ligaments, and can have echo times in the range of 1-2 ms rather than the 8-10 ms of conventional spin echo\textsuperscript{127}.

Figure 2.21: Effect of echo spacing.
For the same echo train duration, these images were obtained with echo train lengths of (a) 4, (b) 10, and (c) 20. The effect of increasing echo train length is to reduce the time between echoes and the resulting dephasing, leading to less metal artifact. Used with permission from RSNA, Lee et al., “Overcoming artifacts from metallic orthopedic implants at high-field strength MR imaging and multi-detector CT”, Radiographics. 2007, 27:791-803\textsuperscript{118}.

2.4.2. View angle tilting (VAT)
View angle tilting (VAT) is a method for reducing the mis-mapping of in-plane signal from susceptibility-induced field inhomogeneities near metal artifact\textsuperscript{128}. The method does this by adding a gradient on the slice-select axis during readout equal in magnitude to the slice-select gradient\textsuperscript{94,128} (Figure 2.22).

VAT helps correct in-plane distortions, but still suffers from through plane distortions\textsuperscript{129}.

\[
\theta = \tan^{-1}\frac{G_z}{G_x}
\]

Equation 2.4

The tilted view angle is described by Equation 2.4, where \(G_z\) is the slice select gradient magnitude, \(G_x\) is the readout (frequency-encoding) gradient magnitude, and \(\theta\) is the tilting of the view angle.

VAT causes blurring: pixel edges overlap when the slice is viewed at an angle causing partial volume effects\textsuperscript{128}. The distance of blurring is described by Equation 2.5, where \(d\) is distance of blur, \(t\) is slice thickness, and \(\theta\) is tilted view angle, which equals the ratio of \(G_z\) (slice selection gradient) and \(G_x\) (readout or frequency-encoding gradient).
\[ d = t \ast \tan \theta = t \ast \frac{G_z}{G_x} \]

Equation 2.5

Blurring also comes from slice profile modulation, where the path in k-space angles across the slice direction sinc function at the tilted view angle rather than following the peak. Thus view-angle tilting acts as a low-pass filter, and the attenuation of high frequency signal leads to blurring.

Figure 2.22: View angle tilting pulse sequence.
Conventional spin echo sequence with VAT added, showing in black the added gradients. RF = radio frequency, \( G_z \) = slice selection gradient, \( G_y \) = phase-encoding gradient, \( G_x \) = frequency-encoding gradient. Used with permission from RSNA, Olsen et al., “Metal artifact reduction sequence: early clinical applications”, Radiographics. 2000, 20:699-712.

2.4.2.1. VAT combinations
Blurring can be reduced by using a high bandwidth, which also reduces extent of mis-mapping and reduces signal-to-noise ratio (see 2.4.1). This combination of VAT and high bandwidth has been called the Metal Artifact Reduction Sequence (MARS) and applied in a number of orthopaedic imaging situations including hip, knee, wrist and spine. Addition of MARS has been shown to reduce the volume of artifact in \( T_1 \)-weighted spin echo imaging at 1.5 T.

Butts et al. used multiple high-bandwidth readouts in place of a single high-bandwidth readout to reduce blurring while increasing signal-to-noise in VAT.

Bos et al. used a different amplitude of the additional compensation gradient \( G_z \) than the typical amplitude (equal to that of the slice selection gradient) to suppress off-resonance signal in VAT.
Slice encoding for metal artifact correction (SEMAC) is a recently developed method for reducing the effect of metal-induced field inhomogeneities on MR images\textsuperscript{110}. This method uses VAT to reduce the in-plane distortion, and adds an additional slice selection phase encoding step to capture signal from out-of-plane distortions. Once this signal is captured for a number of z-phase encoding steps (for example, 16 steps used in the images in Figure 2.23) from a single slice excitation, this signal that has been mis-mapped to other slices is corrected to actual slice location (Figure 2.23). The disadvantage is the extra time required to collect the data, though acceleration techniques are being employed\textsuperscript{125}.

![Figure 2.23: SEMAC versus spin echo and VAT results in the knee. Used with permission from John Wiley and Sons, Lu et al., “SEMAC: Slice encoding for metal artifact correction in MRI”, Magn Reson Med. 2009, 62(1): 66-76\textsuperscript{110}.

This method has been used in a variety of applications, including hip arthroplasty\textsuperscript{102}, spinal implants\textsuperscript{109}, knee implants\textsuperscript{99,100}, and ankle hardware\textsuperscript{100}. It has also been enhanced with improved reconstruction\textsuperscript{131} and acceleration techniques\textsuperscript{125}, and hybridized with other metal artifact methods\textsuperscript{107}.  

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2.4.3. Quantifying image distortion
Several authors have quantified image distortion due to metal artifact from orthopaedic materials\textsuperscript{100,101,105,106,116,132,133}. Often this quantification is based on images from phantoms (made of water\textsuperscript{105,106,133}, contrast-doped water\textsuperscript{116}, agarose gel\textsuperscript{100}, or margarine\textsuperscript{115}), one with metal hardware, and the other with no metal or a non-metal replica obtained under the same imaging conditions, however a wide range of analyses have been performed. Some of these include: energy analysis of images (image, noise, artifact and blur energy terms) with metal hip implant and replica\textsuperscript{105}; segmentation of artifact area in phantom images, manually or with the aid of no-metal condition signal profile \textsuperscript{100,101,106}; linear distance between screw location (based on plastic grid in image) and the edge of the void/pile-up boundary in the frequency direction\textsuperscript{116}; distance between the edges of the middle and lateral lobes of cloverleaf artifact\textsuperscript{115}; relative difference in spatial location of physical grid nodes with and without metal screw in area adjacent to metal artifact\textsuperscript{132}; and subregional analysis of absolute displacement of physical grid points in images with and without metal bar\textsuperscript{133}.

2.5. MR of cartilage
The standard clinical measure of osteoarthritic progression is obtained via radiographs, from which joint space (as a surrogate for cartilage thickness) is measured. MR imaging allows for non-invasive direct measurement of cartilage, including full thickness assessment and biochemical assessment of degeneration. There are a number of types of MR measures of cartilage, including cartilage morphology measures (quantitative MRI, or qMRI\textsuperscript{134}), and mapping of cartilage based on magnetic properties - \(T_2\) mapping and \(T_1p\) mapping\textsuperscript{135} - which have been shown to be related to a mixture of collagen structure orientation and integrity, and cartilage hydration status. One method that has been well validated to relate to early degeneration is the delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) method\textsuperscript{136}.

2.5.1. Quantitative MRI (qMRI)
Cartilage thickness loss is a well-known symptom of OA, however clinical radiographs have many limitations in assessing cartilage thickness. Radiographs are projection images, dependent on exact joint orientation, and radiographs cannot distinguish between tibial and femoral cartilage loss or detect changes throughout the joint surface\textsuperscript{134}. Quantitative MRI (qMRI) is a three-dimensional measure of cartilage morphology using MR imaging\textsuperscript{134}. qMRI involves obtaining high-resolution three-dimensional images of the cartilage using a sequence designed for cartilage, such as a spoiled 3D gradient-echo sequence (fast low angle shot, FLASH) with selective water excitation or double echo in steady-state (DESS) sequence\textsuperscript{137}. Manual\textsuperscript{137} or semi-automated\textsuperscript{134} segmentation of the cartilage surface and subchondral bone
are performed, and cartilage surface area, volume, and thickness (total, or for specified regions of cartilage) are calculated.

2.5.2. \textbf{T}_2 mapping
\textit{T}_2 relaxation (section 2.3.2) in cartilage is associated with tissue hydration and collagen content, but has not been found to be correlated with proteoglycan content\textsuperscript{36}. \textit{T}_2 mapping is accomplished by obtaining a series of \textit{T}_2-weighted scans with different echo times (TE) and fitting a curve to obtain \textit{T}_2 at each pixel.

2.5.3. \textbf{T}_1\rho mapping
\textit{T}_1\rho (also written as \textit{T}_{1\rho}) is a measurement of the spin-lattice (\textit{T}_1) relaxation time in the rotating frame (\textit{rho} = rotating). It is differentiated using a procedure known as spin-locking. In typical sequences, \textit{B}_1 pulses are static RF pulses meant to flip the net magnetization (section 2.3.1); one exception is the adiabatic pulse (section 2.4.1). Spin-locking involves applying a rotating RF (\textit{B}_1) pulse (spin-locking pulse), which is activated after a 90 degree pulse, and its effect is to keep the net magnetization in the transverse plane and allow it to relax under effectively a \textit{B}_1 field strength rather than a \textit{B}_0 field strength\textsuperscript{138}. The relaxation of bound water (such as that in cartilage extracellular matrix) is sensitive to the locking field strength, but free water relaxation is not\textsuperscript{138}. To produce a \textit{T}_1\rho map, a series of images are obtained, each with a different spin locking time (TSL), and then a curve is fit to obtain \textit{T}_1\rho\textsuperscript{139}.

When the extracellular matrix of cartilage is disrupted (specifically when GAG is lost), there is more water motion, which leads to longer \textit{T}_1\rho times\textsuperscript{36}.

2.5.4. \textbf{dGEMRIC}
Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC) is a method for assessing the content of proteoglycans in cartilage. Proteoglycans (PG) are cartilage proteins that have large negatively-charged side chains of glycosaminoglycans (GAG) that provide the fixed charge density (FCD) in cartilage\textsuperscript{23}. This FCD attracts water, which provides the resistance to compression required by cartilage in daily function\textsuperscript{23}. The loss of proteoglycans has been associated with early cartilage degeneration, prior to joint space loss\textsuperscript{24}.

Briefly, the method involves intravenous injection of an ionic gadolinium-based MR contrast agent (typically gadopentetate dimeglumine (Gd-DTPA\textsuperscript{-2}), trade name Magnevist\textsuperscript{140}). This is followed by exercise of the joint and a wait time to allow the avascular cartilage to uptake
the contrast agent. Then a $T_1$ measurement is made, usually by inversion recovery (Figure 2.24)\textsuperscript{141}. [See Chapter 3 and Chapter 4 for specific methods].

![Diagram](image)

**Figure 2.24: Diagram of cartilage in the presence of ionic contrast agents.** Proteoglycans, with their glycosaminoglycan side chains, are in black. Negative charges associated with GAG indicated by yellow fixed negative ions. Pink mobile negative ions represent gadolinium contrast agent with negative charge, and green mobile positive ions represent sodium with positive charge. The negative and positive mobile ions distribute relative to the fixed negative ions, with the negative mobile ions being repelled and the positive mobile ions being attracted. Used with permission from Wolters Kluwer Health, Burstein et al., “MRI techniques in early stages of cartilage disease”, Invest Radiol. 2000, 35(10): 622-38\textsuperscript{158}.

dGEMRIC was validated both with histological measures of GAG concentration, and with sodium MR imaging (another nucleus that can be imaged using magnetic resonance techniques) in bovine cartilage explants\textsuperscript{142}, was compared with histology in human cartilage explants \textsuperscript{136}, and was compared with histology in vivo human cartilage after removal during joint replacement \textsuperscript{136}.

dGEMRIC has been used to evaluate cartilage in vivo in osteoarthritis (OA)\textsuperscript{143-145}, posterior cruciate ligament (PCL) injury\textsuperscript{146}, anterior cruciate ligament (ACL) injury\textsuperscript{147,148}, total knee
arthroplasty (patellar cartilage)\textsuperscript{149}, high tibial osteotomy (HTO)\textsuperscript{150,151}, autologous chondrocyte transplantation\textsuperscript{152-154}, microfracturing\textsuperscript{154}, meniscectomy\textsuperscript{147,155}, hip cam deformity\textsuperscript{156}, and hip joint dysplasia\textsuperscript{157}.

It has also been used to evaluate the effect of an exercise intervention in early OA\textsuperscript{159}, the effect of physical activity level on cartilage GAG content in healthy knee joints\textsuperscript{3}, and dGEMRIC findings have been associated with future knee osteoarthritis\textsuperscript{144}.

2.6. MR kinematics

Kinematics describes bone position and orientation (and how they change), which directly affect the lines of action of muscles and ligaments, and the relative positions of contact surfaces. Changes in kinematics can therefore reflect changes in contact force direction and distribution in the joint. Kinematics measures (also referred to as tracking) are quite different from the widely-used measures of joint alignment at a single position. At the patellofemoral joint, for example, even three-dimensional measures of alignment at one joint position cannot provide a useful surrogate for kinematics over the range of motion\textsuperscript{160}. Measuring these joint forces in vivo would provide a more complete picture of joint mechanics, however this type of measurement is an invasive procedure typically limited to surgical situations\textsuperscript{161}. Measurements of kinematics are therefore useful, although indirectly, in the study of many disorders, such as osteoarthritis\textsuperscript{162} and patellofemoral pain\textsuperscript{163}, which are believed to be associated with abnormal forces in the joint. Similarly, measurements of kinematics are useful for studying interventions, such as osteotomies\textsuperscript{164} and braces\textsuperscript{165}, that are developed to alter these loading patterns.

The advantages of MR in kinematics research on living humans include its non-invasive nature (in contrast to bone pins or implanted fiducial markers), its ability to obtain measures for soft tissue structures, the ability to extract information beyond anatomy, and its lack of ionizing radiation, which allows for extensive and longitudinal studies.

MR kinematics measures have been applied to study healthy joints (patellofemoral (PF)\textsuperscript{166-174}, tibiofemoral (TF)\textsuperscript{171,175-179}, hip\textsuperscript{180}, ankle complex\textsuperscript{181-186}, shoulder\textsuperscript{187-192}, elbow\textsuperscript{193}, wrist\textsuperscript{194,195} and temporomandibular joint (TMJ)\textsuperscript{196}); pathological joints (patellar maltracking\textsuperscript{163,197,198}, patellar dislocation or subluxation\textsuperscript{199,200}, patellofemoral pain syndrome\textsuperscript{165,201-210}, osteoarthritis\textsuperscript{211-214}, shoulder instability\textsuperscript{215}, TMJ arthrosis\textsuperscript{196}, ACL injury and deficiency\textsuperscript{216-224}, PCL injury\textsuperscript{225},
malalignment\textsuperscript{212,213}, and congenital abnormalities and conditions\textsuperscript{183,226,227}; and interventions (braces\textsuperscript{165,200,206}, taping\textsuperscript{201,228}, ACL repair\textsuperscript{220,224,229-232}, and total knee replacement\textsuperscript{233-235}). There are several common elements to most procedures for measuring joint kinematics using MRI, and these are important considerations in the validity and utility of the procedure that directly influence the kinematic measurements. They include: a) loading and movement of the joint; b) imaging procedure; c) definition of bone coordinate systems; and d) calculation of kinematics.

2.6.1. Loading and movement of the joint
Joints move and transmit load, and ideally we would measure kinematics during physiological loading and motion. Scanner geometry and limits to image acquisition, such as length of scans, make this very difficult in most joints. Most MR scanners are oriented horizontally, therefore gravitational forces are different from typical activities and axial loading is limited compared to weightbearing in the lower limb. Direction of motion (e.g. flexion-extension or abduction-adduction) and range of motion are important considerations. Some pathologies are expected to affect kinematics in particular ways, for example patellar subluxation is associated with lateral translation of the patella in the first 20 degrees of knee flexion\textsuperscript{208}. For joints such as the hip and shoulder, imaging in a closed bore scanner severely limits the available motions and ranges compared to the full range possible for normal joints. The increasing availability of open scanners, both vertical and horizontal, allow for a wider range of joint positions. A few studies have employed vertically oriented open scanners which allow for weight-bearing in the lower limb and superior-inferior gravitational forces\textsuperscript{192,202,208,219}.

Many different loading configurations have been used in MR studies of joint kinematics: no applied loading (gravitational forces only)\textsuperscript{171,191}, isometric muscle contraction without externally applied load\textsuperscript{167,210}, applied moment or torque (also called open kinetic chain)\textsuperscript{218}, applied axial force (closed kinetic chain)\textsuperscript{169}, and weightbearing (also closed kinetic chain)\textsuperscript{202} (Figure 2.25). Many studies comparing load magnitudes and types have found significant differences in several kinematic parameters with changes in loading\textsuperscript{167,169,202,208,210,212,218,234}, while a few have not found differences\textsuperscript{178,214,222}.
Designing devices to load joints presents a substantial challenge for kinematic MR imaging. These devices must be made of MR compatible materials, fit within the scanner, and apply a known load over a range of motion (known loads are important for comparisons between studies). There are three general types: free hanging weights applied with either pulley and cable\textsuperscript{186,218,229} or pendulum system\textsuperscript{169} (requiring muscle activation); elastic material providing a spring force\textsuperscript{236} (requiring muscle activation); and positioning systems that apply torque to the joint which is resisted by connective tissue\textsuperscript{175,182} (typically with no voluntary muscle activation) (Figure 2.26). Free hanging weights can be simple in terms of determining magnitude of force, but applying the force in a consistent direction over a range of motion can present a design challenge. The magnitude of applied force (spring force) in elastic material-based devices depends on the amount of deformation applied by the subject (the force-deformation relationship may not be linear), and calibrations must be performed in advance. Devices applying torque to the joint require measurement of the applied torque for each individual subject because the load-deformation relationship is dependent on the
subject’s own connective tissue. An applied force or torque may have to be applied outside the scanner room, involving the transportation of the device and the subject, because load cells and strain measurement equipment may not be permitted in the vicinity of the magnetic field[182]. Weightbearing and/or upright studies with gravity loading often utilize devices to assist subjects in maintaining a position for the duration of the scan[189,192], or stabilizing the subject during dynamic scanning[165,230]. Some studies of unloaded joints use a positioning device[179,181,191]. Some loading devices function as positioning devices as well, but many require external positioning.

2.6.1. Imaging procedure

2.6.1.1. Measurement type (planar (2D) or spatial (3D) kinematics)

Planar, or two-dimensional, kinematics data are obtained from a series of single images over a range of motion[165-167,189,196,200,202,204-209,228,233,237,238] (Figure 2.27). Changes in kinematics measured between two-dimensional images often assume that the objects have not translated or rotated out of the image plane, which is typically not the case and is a source of error in these measurements. Often manual scan plane placement at each static pose is done using a scout or survey scan. Some protocols use scan plane tracking to maintain a constant imaging plane with respect to one of the bones[176,219,225,230]. Other protocols utilize automatic and/or manual rotation/translation of scan plane while dynamic scanning[165,166,202], however anticipating bone movement correctly may be challenging, especially in pathology. Several methods have been developed to determine 2D kinematic parameters in more than one slice at the same joint position, often the measurement of anterior-posterior translation in both the mid-medial and mid-lateral sagittal slices through the tibiofemoral joint[176,178,214,219-221,225,230-232] (Figure 2.28). While providing more than typical planar information (by obtaining an estimate for one out-of-plane rotation), they do not provide other out-of-plane information, and ensuring images are taken through a consistent anatomical plane remains a challenge.
Figure 2.26: Types of loading devices in MR kinematics measurement. (a) Free weights with pulley and cable\textsuperscript{229}, (b) elastic material providing a spring force\textsuperscript{239}, (c) applied torque resisted by connective tissue (with no muscle activation)\textsuperscript{182}. Used with permission from: (a) Elsevier, Carpenter et al., “Magnetic Resonance Imaging of 3-Dimensional In Vivo Tibiofemoral Kinematics in Anterior Cruciate Ligament-Reconstructed Knees”, Arthroscopy. 2009, 22(7):760-6; (b) John Wiley and Sons, Fellows et al., “Repeatability of a novel technique for in vivo measurement of three-dimensional patellar tracking using magnetic resonance imaging”, J Magn Reson Imag. 2005, 22(1):145-53; (c) Elsevier, Siegler et al., “Mechanics of the ankle and subtalar joints revealed through a 3D quasi-static stress MRI technique”, J Biomech. 2005, 38(3):567-78.
Spatial, or three-dimensional, kinematics generally require either an imaged volume or information about the instantaneous pixel velocity (as in phase contrast imaging) at each pose. In general, volume methods do not require exact scan plane placement, since out-of-plane transformations can be measured, but since image resolution is typically higher in-plane, slices are typically oriented such that the primary movement of interest and/or the major joint movement is in the plane. The techniques to obtain data from the images are typically more complex than 2D methods.

2.6.1.2. Movement and range of motion

Many methods for quantifying kinematics using MR estimate movement from a sequence of static poses, for either planar (2D) or spatial (3D) measurements. Static imaging typically allows for higher quality images, especially at lower field strengths. It may use simpler sequences and loading devices, and can provide information about kinematic differences between groups. Static imaging does not, however, reflect typical use of the joint in daily activities, and differences in kinematics have been measured between static and dynamic imaging.

Dynamic imaging of a joint better represents physiological joint activity, but is technically challenging. Several approaches to imaging a moving joint have been developed, including cine phase contrast (cine-PC or fast-PC) imaging to capture 3D velocity measures, and sequences that are sufficiently rapid to capture images from a moving joint. The latter have been applied to scan a single 2D slice, to scan slices in orthogonal planes and register 3D bone models to obtain spatial kinematics, and to scan multiple slices at each joint position in one cycle to obtain spatial kinematics.

2.6.2. Definition of bone coordinate systems

Measurements of kinematics are influenced directly by the definition of coordinate systems in the bones whose relative motion is of interest. Bone is often first identified through segmentation (manual or automated) or visualized directly (in the case of several 2D techniques). Cine-PC/fast-PC methods image a single plane to capture velocity values for each pixel during movement of the joint over a number of cycles. Because the velocity is based on a pixel rather than a volume of tissue, this velocity data must then be integrated in a step-wise fashion to obtain rigid body poses for each time interval.

The bone coordinate system is then defined, often based on bony landmarks (found manually, by geometrical fitting, or by semi-automated landmark tracking) (Figure 2.31). The International Society of Biomechanics has published standards for each joint based on the joint coordinate system of non-orthogonal floating axes originally proposed for the knee by Grood and Suntay. However, many different coordinate systems continue to be used in MR kinematics, partly due to limited bony features visible in the images obtained. This can make comparing kinematic results between studies difficult, as results can be highly sensitive to coordinate system definition.
The coordinate system must be applied to the bones in the same way for each pose, and this can be accomplished either by rigorously choosing the same landmark points in different images (manually or semi-automatically) or by registering one model with an attached coordinate system to the other poses based on surface or voxel (intensity) information, or a combination of those with phase contrast data.

Figure 2.29: Segmentation and registration for subsequent calculation of relative translations and rotations. (a) Segmentation of images at different joint positions, (b) resulting 3D models, (c) registration of one of the two bones (tibia, in this case), to allow calculation of relative movement of femur. Used with permission from Elsevier, Carpenter et al., “Magnetic Resonance Imaging of 3-Dimensional In Vivo Tibiofemoral Kinematics in Anterior Cruciate Ligament-Reconstructed Knees”, Arthroscopy. 2009, 22(7):760-6.

2.6.1. Calculation of kinematics

Kinematics describes change in position, and the fundamental quantities from which these measurements are made are often measures of position. In planar (2D) kinematics, the relative position of two objects can be described with three parameters (three degrees of freedom), typically two translations and one rotation. Methods often employ direct measurement of one or more of these parameters between two bones on the image, and can be similar to standard clinical measurements of alignment (Figure 2.27, Figure 2.32). Limitations include the previously mentioned assumption that there is no out-of-plane motion, possible subjectivity in manually fitting shapes and visually finding contact points, and the typical use of only a few landmark points rather than entire bony outlines in the measurements.
Figure 2.30: Sample results from cine-PC imaging of the knee.
Magnitude images (leftmost column), and velocity images for each of three orthogonal directions, at each of four temporal frames. In the velocity images, velocity component values (both positive and negative) are indicated by the grey scale at the bottom of the figure. Used with permission from John Wiley and Sons, Barrance et al., “Altered knee kinematics in ACL-deficient non-copers: A comparison using dynamic MRI”, J Orthop Res. 2006, 24(2):132-40.

Figure 2.31: Examples of spatial (3D) bone coordinate system creation.
(a) Bony landmarks used to create origins and axes, and (b) geometrical fitting and bony landmarks used to create origin and axes. Used with permission from: (a) Elsevier, Sheehan, “The finite helical axis of the knee joint (a non-invasive in vivo study using fast-PC MRI)”, J
In spatial (3D) kinematics, the relative position of two objects is fully described by six parameters (six degrees of freedom). Often, these are three translations and three rotations. The values of these parameters can differ for the exact same relative bone positions and coordinate systems when different methods are used to decompose the relative positions into translations and rotations. This can make comparing kinematics results between studies difficult. The International Society of Biomechanics has published standards for each joint based on the joint coordinate system of non-orthogonal floating axes originally proposed for the knee by Grood and Suntay\textsuperscript{245} (Figure 2.33). Unlike the 2D case, the value of rotation about each axis in an orthogonal system depends on the order of those rotations (e.g. Euler angles (zyz rotation order)\textsuperscript{181,192,194,242} or Cardan angles (xyz rotation order)\textsuperscript{226}). The Grood and Suntay joint coordinate system creates rotations that are independent of each other and permit descriptions similar to clinical movements\textsuperscript{160,168,169,175,182,213,216,217,224,236}.

An alternative approach, the helical axis (also called a screw axis) can be used to represent position and orientation\textsuperscript{181,182,185,186,190,193,247}. The six parameters in this case are: an axis (vector defining angular velocity in three space); the position of axis in mid-sagittal plane

\begin{figure}
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\includegraphics[width=0.5\textwidth]{figure232}
\caption{Sample results from multi-slice planar (2D) kinematics. Healthy controls shown as solid lines, symptomatic osteoarthritic knees as dotted lines). Used with permission from Elsevier, Scarvell et al., “Magnetic Resonance Imaging Analysis of Kinematics in Osteoarthritic Knees”, J Arthroplasty. 2007, 22(3):383-93\textsuperscript{214}.}
\end{figure}
(two coordinates); and a rotation (angle) about the axis. Advantages include having no singularities (no gimbal lock), but the results can be more difficult to interpret clinically.

Figure 2.33: Example of a joint coordinate system (JCS) for the patellofemoral joint. JCS uses the flexion axis of the proximal bone (e1), the long (or superior-inferior) axis of the distal bone (e3), and a third axis which is the cross product of the first two (e2). Used with permission from Elsevier, McWalter et al., “The effect of load magnitude on three-dimensional patellar kinematics in vivo”, J Biomech. 2010, 43(10):1890-1897.

Kinematic parameters are frequently reported as a function of a measure of overall joint motion, such as knee flexion angle. These angles may be measured externally, set as part of a positioning device, interpolated to convenient intervals, estimated from the division of a range of motion or time interval, and/or binned/grouped. Only in some studies have the actual measured angles for each subject been used. In 2D methods, it may not be possible to measure actual angles, and in a number of reports it is not clear which approach has been taken. This may introduce errors in the results.

2.6.2. Conclusion
There has been substantial progress on methods for measuring joint kinematics using MRI in the last decade. Kinematic results can be directly influenced by a number of imaging and analysis factors, and these should all be considered carefully when evaluating the value of studies in the literature and when designing new studies. There is substantial promise for further improvement of these methods as MR technology improves and for broader application of these methods to more joints and more pathology.
Chapter 3. Using the dGEMRIC technique to evaluate cartilage health in the presence of surgical hardware at 3T: comparison of inversion recovery and saturation recovery approaches

3.1. Introduction

Osteoarthritis (OA), or injury associated with development of OA such as a ligament tear, is sometimes treated with surgery with the objective of slowing, arresting, or preventing cartilage degeneration. Sensitive, non-invasive evaluations of cartilage degeneration are important for making objective assessments of how effectively surgical treatments achieve these objectives.

Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) is a non-invasive imaging method that measures a surrogate for glycosaminoglycan (GAG) concentration in articular cartilage. GAG is a macromolecule whose concentration is directly related to the mechanical stiffness of cartilage. Prior to the development of dGEMRIC, GAG could only be assessed histologically. To perform the dGEMRIC procedure, anionic gadolinium contrast agent (Gd-DTPA) is first injected intravenously or intraarticularly and then allowed to diffuse into the cartilage during a prescribed wait time. The contrast agent distributes in inverse proportion to the GAG content due to Coulomb interaction (because both are negatively charged), and causes a local change in $T_1$. The concentration of GAG in cartilage can then be estimated by calculating the reduction of the longitudinal relaxation time $T_1$ after Gd-administration from appropriate MR images of the cartilage. dGEMRIC has been validated and used at the knee to study several populations cross-sectionally including patients with autologous chondrocyte transplants, subjects with differing physical activity levels, subjects with knee malalignment, subjects with ACL injury and/or subsequent repair, and subjects with OA or OA risk factors. Only a few studies and case reports have followed subjects longitudinally.

While there are a number of potential applications for dGEMRIC imaging near surgical hardware, it is not clear to what extent implanted surgical hardware affects the $T_1$ relaxation time in the cartilage.

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2 A version of this chapter (which comprises the unedited, pre-publication draft) has been published as: Agnes G. d’Entremont, Shannon H. Kolind, Burkhard Maedler, David R. Wilson, Alexander L. MacKay. “Using the dGEMRIC technique to evaluate cartilage health in the presence of surgical hardware at 3T: comparison of inversion recovery and saturation recovery approaches”. Skeletal Radiology. 43:331–344. DOI: 10.1007/s00256-013-1777-2 The final publication is available at www.springerlink.com.
measurements that are used to infer GAG concentration in dGEMRIC imaging. One study of high tibial osteotomy used dGEMRIC with substantial surgical hardware in place, and these authors did not address the effect of metal artifact on their results\textsuperscript{253}. Another group recommended that implants be removed prior to dGEMRIC imaging, however that requirement may significantly limit applications in regions where hardware removal is not standard clinical practice\textsuperscript{150}, or where it is not possible. The effect of metal on T\textsubscript{1} measurements is of particular concern in high-field MR systems (3T), which offer a superior signal-to-noise ratio with increased spatial resolution and are therefore preferable to investigate thin structures like knee cartilage, but produce higher static field (B\textsubscript{0}) and radio frequency field (B\textsubscript{1}) inhomogeneity artifacts in the presence of metal implants. Several types of metal artifact reduction techniques exist: one such approach for B\textsubscript{0} artifacts is the Metal Artifact Reduction Sequence (MARS). MARS has been developed and utilized for clinical applications\textsuperscript{98,105,106,112}, but its effect on a quantitative imaging method such as dGEMRIC has not been determined.

Our objectives for this study were to assess and optimize the dGEMRIC procedure in the presence of surgical hardware for high-field (3T) clinical MR systems. The following questions are addressed in this study: Can the conventional dGEMRIC method using inversion recovery (IR) be used near stainless steel and/or titanium implants without modification? What are the effects on T\textsubscript{1} maps of using IR, saturation recovery (SR) and/or MARS in a phantom with and without metal? What are the effects of using IR, SR and/or MARS \textit{in vivo}?

3.2. Methods

Initial testing was done \textit{in vivo} to determine whether high tibial osteotomy plates of different materials caused artifact through the cartilage. Then, the extent of this artifact and the effects of techniques to reduce it were explored using a gadolinium-doped phantom. These techniques were assessed \textit{in vivo} in human subjects with implanted high tibial osteotomy plates. Finally, simulations were used to further explore the effect of changes in signal-to-noise ratio (SNR) on the results.

3.2.1. Initial \textit{in vivo} testing

To initially, qualitatively assess the presence and severity of artifact in images and T\textsubscript{1} maps due to titanium and stainless steel high tibial osteotomy plates, we performed dGEMRIC scans following a procedure based on a published, established protocol\textsuperscript{1} on the knee joint cartilage of two human subjects with implanted metal plates. One subject (female, age 49, 4 months post-op) had a stainless steel Puddu plate (Arthrex, Naples, Florida) in the proximal tibia from a high tibial osteotomy operation and the other subject (female, age 40, 14 months post-op)
had a titanium Small Fragment plate (Synthes, West Chester, Pennsylvania) from a high tibial osteotomy. In both cases, the indication for surgery was medial tibiofemoral OA caused by varus knee malalignment. The study received approval by our Clinical Research Ethics Board and informed consent was obtained.

Each subject was injected with an intravenous double dose (0.2 mmol/kg) of gadopentatate dimeglumine (Gd-DTPA\textsuperscript{2}, Magnevist, Berlex Laboratories, USA). Subjects performed ten minutes of brisk walking following the injection and scanning began 90 minutes post-injection. We performed a series of single-slice inversion recovery fast spin-echo (FSE) scans (IR) on each subject’s operated knee (tibiofemoral (TF) joint, coronal plane) using a Philips 3T Achieva scanner, with two surface coils (SENSE Flex-M, Philips, Best, Netherlands) positioned with one on either side of the joint (Table 3.1). The inversion preparation was achieved with a commercially available hyperbolic secant adiabatic pulse (amplitude and frequency modulated) which was designed to produce accurate inversion pulses even in presence of radiofrequency field (B\textsubscript{1}) inhomogeneities\textsuperscript{254}.

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<th>Table 3.1: MRI sequence parameters for all sequences.</th>
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<td><strong>IR</strong></td>
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3.2.2. Phantom studies

Next, we tested two strategies to reduce metal artifacts in phantoms: 1) using saturation recovery fast spin-echo (SR) instead of IR and 2) applying the Metal Artifact Reduction
Sequence (MARS) to both types of series (IR and SR). SR sequences have been used with dGEMRIC in the literature\textsuperscript{157,248}, though less frequently than IR sequences which have a wider dynamic range\textsuperscript{136}. MARS is based upon view-angle tilting (VAT)\textsuperscript{128} with an increased read bandwidth (from +/- 26.9 kHz to +/- 46.0 kHz) to combat the blurring associated with VAT. The same IR and SR series were used with and without the addition of MARS (no change in imaging time; Table 3.1).

These strategies were first tested on two gadolinium-doped phantoms designed to simulate $T_1$ values of cartilage containing contrast agent. One phantom included a titanium HTO plate and four screws (Arthrex Puddu plate, Ti6Al4V, approximately 5 cm x 1.5 cm) placed inside the container with an orientation in the $B_0$ field similar to that of an implanted plate imaged \textit{in vivo}. Each phantom consisted of a plastic container, filled with 1% agarose gel (Bio Rad, Hercules, CA; prepared with distilled water) doped with 0.3 mM Gd-DTPA\textsuperscript{2-} (Figure 3.1(a)). This concentration was chosen to obtain a $T_1$ value for the phantom of around 500 ms at 3T.

We scanned the phantom using the standard dGEMRIC protocol described above (IR) as well as with a modified protocol using a single-slice saturation recovery (SR) sequence in the coronal plane (Table 3.1). The SR method was chosen for its easy implementation and relative insensitivity to $B_0$ and $B_1$ inhomogeneities as compared to faster spoiled gradient echo methods with variable flip angle for $T_1$ measurement. MARS was applied to each series (IR and SR), and all four protocols (IR, SR, IR-MARS, SR-MARS) were used to image the phantom (Table 3.1).

Agarose gel was chosen as a phantom material because there appeared to be vibration artifacts in the SR images when saline was used. A saline-based phantom was also imaged with the same scan parameters. Although the analysis will not be presented, we have included an image to show differences in artifact with phantom material (Figure 3.1(c)).
Figure 3.1: Photo, image, and ROI definition in phantom.
Photo of phantom (a), with arrow indicating direction of \( B_0 \) field and head direction, and (b) definition of ROIs on a TI = 50 ms image, where each rectangle is an ROI containing 900 pixels, labeled with the ROI name. (c) TI = 50 ms image and inset photo of saline phantom showing different pattern of artifact in image compared to agarose gel phantom, using same sequence parameters.
3.2.3. In vivo studies
The effect of different pulse sequences on metal artifact in dGEMRIC scans was assessed in vivo. To assess the effect of SR versus IR on artifact reduction in vivo, one subject (male, age 60, 6 months post-op) with a titanium Arthrex Puddu plate from a high tibial osteotomy surgery was scanned at both the patellofemoral (PF) and tibiofemoral (TF) joints (axial and coronal slices, respectively) using SR and IR at each joint (Table 3.1). Clinical Research Ethics Board approval for the study and informed consent were obtained. Since the patellofemoral joint was far enough away from the implant to have no visible artifact, this joint was used to directly compare the two sequences in vivo. Scanning was performed over two sessions two days apart, because the contrast dwell time in cartilage following injection was not long enough to complete all four scans in one session. Selection of imaging planes was made with reference to previous scans. Because contrast agent diffuses more quickly into thinner cartilage, at each session the thinner cartilage of the tibiofemoral joint was imaged first, followed by the thicker patellofemoral cartilage. Sequences were identical to those used in the previous in vivo and phantom scanning.

To assess the effect of MARS on artifact reduction in vivo, the same subject was scanned at the tibiofemoral joint (coronal slice) with and without MARS and using an SR series (SR and SR-MARS). This scanning was performed eleven months following the above-mentioned scans, when MARS became available, to compare to the data already collected.

3.2.4. Curve fitting for $T_1$ calculation
Quantitative $T_1$ maps were obtained using in-house developed code (MATLAB, Mathworks, MA, USA, function lsqcurvefit) to fit the magnitude signal intensities versus inversion times and repetition times respectively for each pixel of the image series. The in vivo images were manually registered and cartilage was segmented by one experienced observer. Since the phantom was not moved between any of the images there was no need to register these images.
Equation 3.1 is the fit equation for the IR series, and Equation 3.2 is the fit equation for the SR series. SI is signal intensity in the image, $S_0$ is the signal intensity at equilibrium conditions, TI is inversion time, TR is repetition time and $f_{IR}$ and $f_{SR}$ are fit factors that account for imperfect flip angles and slice excitation ($f_{IR} = 2$ for perfect inversion, $f_{SR} = 1$ for perfect excitation). SI, TI, and TR are known values, and $S_0$, $T_1$ and $f$ are calculated.

Twenty-five random initial values sets, centered around initial guesses (IR: $T_{1,initial} = TI(S_{Imin}/\ln2)$, $S_{0,initial} = SI(TI_{max})$, $f_{IR,initial} = 2$; SR: $T_{1,initial} = 500$ ms, $S_{0,initial} = SI(TR_{max})$, $f_{SR,initial} = 1$) were used for each pixel and the result with the lowest residual was selected as the best result. Bounds for IR were: $T_1 = 0$ to 3500 ms, $S_0 = 0$ to 300, $f_{IR} = 0$ to 2. Bounds for SR were: $T_1 = 0$ to 3500 ms, $S_0 = 0$ to 300, $f_{SR} = 0$ to 1. Initial work showed large differences in calculated $T_1$ in IR artifact areas when bounds for $f_{IR}$ were limited versus using wide lower bounds.

The calculated $T_1$ maps from both phantom and in vivo images contained pixel values that were obviously outliers, especially in the presence of metal or increased noise in the signal. Since the physiological range of mean post-contrast $T_1$ (both normal and OA) has been found to be 400-900 ms\textsuperscript{255} we chose to conservatively remove pixels above 1200 ms and below 100 ms from all data sets.

For the phantom, four regions of interest (ROI) of 900 pixels each (about the same number as in the cartilage area) were defined: one was located in the approximate region where one would expect to find cartilage with respect to the superior screw in vivo, as determined from relative position on in vivo images (ROI_{cartilage}), two were located at the superior and inferior edges of the image (ROI_{away1} and ROI_{away2}), and one was chosen to cross the large artifact visible in IR maps and lower TI images.
Calculated $T_1$ values were separated into 10 ms bins and histograms of these bins were created and compared.

### 3.2.5. Effect of noise on curve fitting

To investigate the effect of noise level on the resulting calculated $T_1$ value, a simulation of both IR and SR was performed using MATLAB (Mathworks, MA, USA). Base data sets for both IR and SR were created using equations 1 and 2 respectively, with values of $T_1$, $S_0$ and $f$ chosen to match the IR and SR ‘no metal, no MARS’ phantom values (IR: $T_{1,initial} = 570$, $S_{0,initial} = 41$, $f_{IR,initial} = 1.870$; SR: $T_{1,initial} = 537$, $S_{0,initial} = 41$, $f_{SR,initial} = 0.987$) and the same TIs and TRs used in the IR and SR imaging respectively (Table 3.1).

Random normally distributed noise vectors of a given standard deviation (or signal to noise ratio (SNR)) were added to the base data sets (SR(real), SR(imaginary), IR(real) and IR(imaginary)) to create noisy data sets. The magnitude of the complex noisy data was calculated from real and imaginary values to obtain IR(magnitude) and SR(magnitude), which is equivalent to data output by the scanner (i.e. Rician noise). Both noisy data sets, SR(magnitude) and IR(magnitude), were then fit using the appropriate equation and a least squares fit (MATLAB function lsqcurvefit). Twenty-five random initial values sets, centered around the nominal values, were used for each noisy data set and the result with the lowest residual was selected as the best result. The noise addition and fit were repeated 900 times at each noise level for each measurement type, and the resulting $T_1$ values were averaged.

SNR was estimated from phantom and in vivo $T_1$ maps as the ratio between calculated signal intensity at equilibrium ($S_0$) and the mean residual (absolute value), for each pixel in the map. Pixel SNR values were then averaged over the ROI.

### 3.2.6. Statistical analysis

Summary statistics were performed for the phantom overall, each ROI, and the noise simulation. We tested the null hypothesis that mean $T_1$ values were the same between sequences in a particular phantom ROI or tissue using the Student’s t-test with Bonferroni correction (MATLAB, Mathworks, MA, USA).
3.3. Results

3.3.1. Initial in vivo testing
Our initial in vivo images showed that it is not possible to obtain accurate dGEMRIC scores in tibial cartilage after implantation of either stainless steel or titanium osteotomy plates using our conventional IR sequence. 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 (Figure 3.2, left). Images from the subject with a titanium plate implanted in the proximal tibia exhibited much less distortion (Figure 3.2, center). The cartilage area, in particular, appeared unaffected. However, many of the signal intensity versus T$_1$ time curves for single pixels in the cartilage areas did not show the typical null point in a standard IR-curve and were often nearly flat (Figure 3.2, below). Consequently calculated T$_1$-values from these regions were unreliable. When mapped, the calculated T$_1$ values showed large variations across the cartilage plate, and there was a clear demarcation in the medial tibiofemoral cartilage (Figure 3.2, right, white arrow).

3.3.1. Phantom studies
Compared with the IR images, we observed much less distortion of T$_1$ when using the SR series on the same phantom with a titanium plate in the same location (Figure 3.3). However, the SR series resulted in a noisier image than the IR series because of a lower intrinsic signal-to-noise ratio in the basis images and the absence of the characteristic null-point to aid in curve fitting. MARS subtly reduced the extent of the artifact in the IR-MARS map (see lower right edge of map, for example), and in the SR-MARS map (improvement may be seen at the lower screw, for example) (Figure 3.3).
Figure 3.2: Initial *in vivo* dGEMRIC results with metal.
IR images (left, center) of subjects with high tibial osteotomy implants, and $T_1$ map (right) from images with titanium (arrow indicates demarcation which indicates the presence of an artifact not apparent in the image). Below, single pixel curves from outside and within the artifact (location of pixels denoted by crosshairs).
The effect of metal on ROI artifact was dramatic: because so many of the IR and IR-MARS values were excluded as outliers, data for ROI artifact both with and without outliers is presented (Table 3.2). Adding metal resulted in an increased $T_1$ in IR and IR-MARS (14% and 0.5% respectively); including the outliers, the increases were much larger (151% IR and 135% IR-MARS). The mean $f_{IR}$ values in ROI artifact with metal were 0.45 (IR) and 0.41 (IR-MARS), compared to a nominal value of $f_{IR} = 2$. For SR, adding metal increased mean $T_1$ values (+13% SR, +7% SR-MARS), with no substantial difference when outliers were included (Table 3.2). The values of $f_{SR}$ were 0.95 (SR) and 0.96 (SR-MARS) in ROI artifact, compared to a nominal value of $f_{SR} = 1$. The sequence that best recovered ROI artifact ‘no metal’ values was SR-MARS (+6.8%) when outliers are considered. [See Appendix A for complete phantom maps, including $M_0$ and f maps].

For the cartilage region of interest in the phantom (ROI cartilage), adding metal had a slightly larger effect on the mean $T_1$ for the SR sequence than for IR (+11% IR, +18% SR). Adding metal had a slightly larger effect on the standard deviation of $T_1$ for the IR sequence than for SR (+34 ms IR, +30 ms SR). Both IR-MARS and SR-MARS obtained similarly recovered ROI cartilage values without metal (+10.1% and +10.5% from original), partly due to the reduction in extent of artifact such that it intruded less into ROI cartilage (Figure 3.3, Table 3.2).

In the small ROIs, there were no outliers in ROI cartilage, ROI away1 or ROI away2 for any condition. For ROI artifact, outliers in the metal condition for IR (39% of pixels) and IR-MARS (41% of pixels) were primarily $T_1$ values above 1200 ms (99.7% and 86.1% of outliers respectively), while for SR outliers were above 1200 ms (0.4% of pixels).

The overall mean $T_1$ value for the SR sequence (without metal or MARS) was 31 ms (5%) lower ($p < 0.00067, \text{alpha}_{\text{Bonferroni}} = 0.00067$) than the IR result (Table 2). Adding MARS (without metal) changed the overall mean $T_1$ by -0.2% (IR, $p < 0.00067$) and +2.2% (SR, $p < 0.00067$) and increased the standard deviation minimally (average of 3 ms) (Table 3.2, Figure 3.4).
Figure 3.3: $T_1$ maps phantom study.

$T_1$ maps of IR and SR phantom studies with metal, with and without MARS. The white rectangles outline the small ROIs defined in Figure 3.1.
Table 3.2: Results from ROI analyses of phantom and in vivo T₁ maps.
ROI_{artifact} contained many outliers (pixels outside 100-1200 ms range) in the IR scans, so ROI_{artifact} T₁ results with outliers included (all 900 pixels) are also presented.

<table>
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<tr>
<th>Phantom results</th>
<th>No. of pixels (outliers) in image</th>
<th>Mean (SD) all pixels [ms]</th>
<th>Mean (SD) ROI_{cartilage} [ms]</th>
<th>Mean (SD) ROI_{away1} [ms]</th>
<th>Mean (SD) ROI_{away2} [ms]</th>
<th>No. of pixels (outliers) in ROI_{artifact}</th>
<th>Mean (SD) ROI_{artifact} [ms]</th>
<th>Incl. outliers</th>
</tr>
</thead>
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<td>IR, no metal</td>
<td>65430 (106)</td>
<td>569.7 (25.1)</td>
<td>541.0 (9.4)</td>
<td>600.1 (11.5)</td>
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<td>900 (0)</td>
<td>594.7 (10.8)</td>
<td>594.7 (10.8)</td>
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<td>SR, no metal</td>
<td>65430 (106)</td>
<td>538.6 (26.7)</td>
<td>520.7 (18.4)</td>
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<td>900 (0)</td>
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<tr>
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<td>65430 (106)</td>
<td>568.4 (26.7)</td>
<td>540.7 (12.3)</td>
<td>597.1 (15.3)</td>
<td>537.7 (12.7)</td>
<td>900 (0)</td>
<td>594.5 (13.3)</td>
<td>594.5 (13.3)</td>
</tr>
<tr>
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<td>65430 (106)</td>
<td>550.3 (31.3)</td>
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<td>514.8 (24.1)</td>
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<td>IR, metal</td>
<td>57343 (8193)</td>
<td>606.9 (97.7)</td>
<td>601.7 (43.9)</td>
<td>561.0 (10.8)</td>
<td>594.8 (10.8)</td>
<td>552 (348)</td>
<td>675.8 (206.8)</td>
<td>1491.2 (1180.6)</td>
</tr>
<tr>
<td>SR, metal</td>
<td>59185 (6351)</td>
<td>616.8 (104.8)</td>
<td>616.2 (48.3)</td>
<td>565.5 (25.9)</td>
<td>596.9 (26.5)</td>
<td>896 (4)</td>
<td>635.6 (58.6)</td>
<td>638.9 (77.1)</td>
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<td>IR-MARS, metal</td>
<td>55871 (9665)</td>
<td>606.7 (90.5)</td>
<td>595.4 (24.7)</td>
<td>563.7 (14.6)</td>
<td>595.8 (13.7)</td>
<td>527 (373)</td>
<td>597.7 (234.5)</td>
<td>1396.0 (1266.0)</td>
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<td>SR-MARS, metal</td>
<td>58540 (6996)</td>
<td>613.1 (112.8)</td>
<td>589.7 (52.1)</td>
<td>539.1 (31.4)</td>
<td>559.9 (30.1)</td>
<td>900 (0)</td>
<td>606.5 (43.6)</td>
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</tr>
</tbody>
</table>

In vivo results

<table>
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<tr>
<th>No. of pixels (outliers) in ROI</th>
<th>Mean (SD) all pixels [ms]</th>
<th>Mean (SD) incl. outliers [ms]</th>
<th>Imaging timeline</th>
</tr>
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<tbody>
<tr>
<td>PF IR</td>
<td>854 (2)</td>
<td>547 (133)</td>
<td>549 (139)</td>
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<tr>
<td>PF SR</td>
<td>896 (7)</td>
<td>596 (177)</td>
<td>604 (212)</td>
</tr>
<tr>
<td>TF IR</td>
<td>891 (7)</td>
<td>436 (116)</td>
<td>448 (187)</td>
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<tr>
<td>TF SR</td>
<td>830 (112)</td>
<td>486 (212)</td>
<td>730 (769)</td>
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<td>TF SR</td>
<td>811 (24)</td>
<td>546 (164)</td>
<td>585 (313)</td>
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<tr>
<td>TF SR-MARS</td>
<td>839 (77)</td>
<td>589 (205)</td>
<td>720 (543)</td>
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</table>
Figure 3.4: Histograms of phantom studies.
Results with and without metal, and with and without MARS (including outliers). Dotted lines indicate the position of largest bin for IR and SR respectively in the ‘no metal, no MARS’ condition.

No statistical differences were found between the standard and MARS sequences for: the overall image: IR with metal (outliers excluded, p = 0.46); ROI\textsubscript{cartilage}: IR without metal (p = 0.55); ROI\textsubscript{away2}: IR with metal (p = 0.10); and ROI\textsubscript{artifact}: IR without metal (p = 0.76), SR without metal (p = 0.00074), IR with metal (outliers included, p = 0.10). There was no statistical difference between IR and SR for: ROI\textsubscript{away2} with metal (p = 0.03); or between IR-MARS and SR-MARS for: ROI\textsubscript{cartilage} with metal (p = 0.003), ROI\textsubscript{artifact} with metal (outliers excluded, p = 0.27). For ROI\textsubscript{artifact}, no difference was found between IR without metal and IR-MARS with metal (outliers excluded, p = 0.70); or in
IR-MARS between metal and no metal conditions (outliers excluded, $p = 0.69$). All other comparisons between sequences within ROIs were significantly different ($p < 0.00067$).

IR and SR phantom histogram results show similar ranges without MARS or metal (Figure 3.4). Adding MARS without metal resulted in similar $T_1$ values for both IR and SR. Adding metal resulted in a greater spread of values (including a number of low outliers for IR and high outliers (not plotted) for IR and SR) and a shift of the peak to higher $T_1$ values for both IR and SR. When MARS was added, the IR-MARS histogram stayed about the same but the SR-MARS histogram spread further and the peak shifted toward the ‘no metal’ mean (Figure 3.4).

A large area of artifact was evident in the IR images with metal where TI was 700 ms or less (Figure 3.5). For a line of adjacent pixels crossing into the artifact, the null point of the measured inversion curve shifted left, implying a shorter and shorter $T_1$ within the homogeneous phantom (Figure 3.5, right). About six pixels (approximately 2.3 mm) into the artifact 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 preliminary in vivo subject with titanium. The effect on the $T_1$ map was an area of altered and consequently inaccurate $T_1$ values (Figure 3.3). In these areas, $f_{IR}$ was often quite low, at or below 1.

**3.3.1. In vivo studies**

In the patellofemoral (PF) joint images (axial), the mean value of $T_1$ for SR was 9% higher than for IR ($p < 0.00067$) (Table 3.2, Figure 3.6). The SR series had a 33% higher standard deviation. In the IR and SR PF scans, outliers excluded by the 100-1200 ms range were on average 0.5% of all pixels. There was no visible artifact in the PF images. Since there was no artifact detectable in the PF images (Figure 3.6), the testing of the MARS sequence was limited to the tibiofemoral (TF) images (coronal).
Figure 3.5: IR images and data curves in artifact area.
IR images at TI = 1800 ms (left) and TI = 50 ms (centre) of phantom with metal plate and screws. The dark lines around the artifact edges indicate lines of constant $B_1$ which gave rise to a null point at that TI time. Right, eight single pixel curves (spaced every four pixels) showing the change in values within the dark-line artifact (arrows indicate direction from outside artifact across dark line). Each curve represents the data from one pixel (location indicated by colour on the centre image) over the eight images with different inversion times (each data point in the curve is obtained from a different inversion time image).
In the tibiofemoral (TF) maps, the mean value of $T_1$ for SR was 12% higher than for IR (significantly different, $p < 0.00067$) (Figure 3.6). Mean SR-MARS $T_1$ was 7% lower than mean SR $T_1$ ($p < 0.00067$) at the same timepoint. Due to the nearly complete loss of cartilage in the subject’s medial tibiofemoral compartment associated with varus malalignment, only the lateral compartment was considered. Outliers excluded by the 100-1200 ms range in the tibiofemoral joint were an average of 6% of pixels in ROIs over all TF maps.

There were clear artifacts in the TF images below the cartilage region, however it was not clear how far the artifact extended. The TF IR single pixel curves and f-factor map show that the artifact extended into the cartilage of the tibial plateau (shift of null point below 50 ms and f-factor values below 1) (Figure 3.6).

### 3.3.1. Effect of noise on curve fitting

The averaged $T_1$ values calculated from the simulated base data sets without noise were 570 ms (IR) and 537 ms (SR), as expected (Table 3.3). As noise was added the calculated $T_1$ values obtained from the IR simulation decreased slightly (to $T_1 = 561$ ms at SNR = 20) and then increased (605 ms at SNR = 5), while the $T_1$ values from the SR simulation increased from 537 ms as noise increased ($T_1 = 570$ ms at SNR = 20, $T_1 = 714$ ms at SNR = 5).

Estimates of average SNR for phantom ROIs (no metal, no MARS) were 212 (SD 81) for IR, and 118 (SD 42) for SR. For in vivo PF images, estimates of average SNR in the cartilage were 38 (SD 22) for IR, and 30 (SD 14) for SR.
Figure 3.6: $T_1$ maps (PF and TF) from in vivo dGEMRIC scanning with metal.
$T_1$ maps of the same patellofemoral joint (axial) using IR and SR (top left and right). Images were taken two days apart. $T_1$ maps of the same tibiofemoral joint (lateral compartment, coronal) using IR, SR and SR-MARS (middle left, center and right). The SR-MARS image was taken eleven months later, however it was statistically compared to an SR image taken at the same time. A single pixel result from the TF IR map (location bottom left) shows the same shifted null point (bottom centre), and a disruption in the $f_{IR}$ map (bottom right) with values far below the nominal $f_{IR} = 2$. 
Table 3.3: Results from noise level simulation.
900 noisy data sets fitted and averaged for each noise level and T₁ measurement type. Nominal values of T₁, M₀ and f were taken from curve fit results for the separate IR and SR ‘no metal, no MARS’ phantom data. For these results, a random set of 25 initial values of T₁ and SI were used for each noisy data set, and the solution with the lowest norm of residual was selected as the best result for that set.

<table>
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<tr>
<th>Signal to noise ratio (SNR)</th>
<th>Average calc. T₁ IR [ms]</th>
<th>SD T₁ IR [ms]</th>
<th>Average calc. T₁ SR [ms]</th>
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3.4. Discussion

We assessed methods for reducing metal artifact in the dGEMRIC procedure because there are many applications for dGEMRIC in joints with implanted surgical hardware. We found that artifact in the T₁ map may be present with titanium hardware, even if the high TI images do not appear distorted, and that using SR instead of IR can significantly reduce artifacts in the T₁ map. We found that dGEMRIC imaging near stainless steel implants is not possible, and that the addition of MARS can reduce T₁ map artifact somewhat. This paper is focused on one particular surgery and surgical implant, however the methods and strategies presented would be similar for the evaluation of any joint and implant.

Our results show that artifacts from metal can disrupt T₁ measurements in a clinically relevant situation, particularly when using IR sequences. The pattern of the IR artifact varied greatly with phantom material (Figure 3.1), and IR artifact was also
apparent in the cartilage in vivo (Figure 3.2, Figure 3.6: TF IR). The effect of the IR artifact in the phantom was typically to increase the calculated T1 value when the f-factor was allowed to vary widely (when the f-factor was narrowly bounded in IR artifact areas, fits were poor and T1 values varied). In the IR artifact areas, both in vivo and in the phantom, the null point of the curve shifted below our lowest TI value, indicating that the IR pulse was close to 90 degrees. Because the artifact depends on multiple factors, the extent of artifact is particular to a type of surgery and type of implant, and even orientation in the main magnetic field. To determine if the artifact will extend into cartilage, each type of surgery and imaging set-up must be considered individually.

It is not surprising that MARS does not completely eliminate metal artifacts. MARS corrects mis-mapping due to B0 inhomogeneity in the imaging plane, but does not affect other metal artifacts, while the SR sequence is more robust in the presence of B1 inhomogeneity. Metal affects both the B0 and B1 fields and generally causes degradation in MR images due to a variety of artifacts. Off-resonance artifacts are caused by alterations in the local magnetic field that cause spins to be mapped to the wrong spatial location due to B0 radiofrequency field inhomogeneity, while B1 field inhomogeneities lead to imperfect 180 degree pulses near the metal which changes the nature of the experiment such that the standard curve fitting equation is invalid. The location and severity of these artifacts depends on the pulse sequence and imaging parameters123,256, as well as other factors that one has less control over such as the type of metal115,118,257, orientation of implant in the main magnetic field118,257 and field strength118,257,258. Our finding that images with stainless steel implants were much more distorted than those with titanium implants is consistent with results in the literature115.

MARS produced a small improvement to the extent of artifact in the phantom, however even a small reduction in extent of artifact may increase the possibility of obtaining dGEMRIC results in an important area of cartilage. For example, in the phantom maps with metal, MARS reduced the artifact extent such that it extended less within ROI_{cartilage} for both IR and SR. Similarly, in the in vivo comparison SR-MARS reduced the area of artifact in the overall TF images compared to SR, although it was more difficult to evaluate the extent of artifact in the TF cartilage area.
Differences in $T_1$ values with sequence where no metal was present (5% ‘no metal’ phantom, 9% PF in vivo) are not adequately explained by SNR factors. As our simulations demonstrated, the curve fitting for SR is less robust in the presence of noise, and increased noise leads to increased $T_1$ values while the IR curve fitting is more stable in the presence of noise. As was seen in the estimates of SNR from images, SR is noisier than IR in practical usage and in vivo images are noisier than phantom images (due to differences in tuning, flow artifacts, and subject movement), and therefore the effect may be compounded when using SR in vivo, where we observed that IR values tend to be smaller than SR values without metal artifact. However, the phantom condition results without metal exhibit the opposite pattern, where IR $T_1$ values are larger than SR results. It is not clear what other factors may be involved in the differences between experimental values of $T_1$ measured with IR and SR without metal. Since the value of $T_1$ depends only on tissue and field strength, the observed differences in $T_1$ between IR and SR measurements are likely functions of the curve fits and/or the sequences themselves rather than real differences in $T_1$. Overall the values of dGEMRIC index in vivo in this study fall within the range of 400–900 ms found in previous work\textsuperscript{255}.

Patterns of artifact in the phantom $T_1$ maps with metal present varied with phantom material and sequence (IR, SR, IR-MARS, SR-MARS). The pattern of IR artifact was different with the agarose-based phantom than with previous work done with a saline-based phantom (Figure 3.1). While neither material adequately represents cartilage tissue, it seems clear that many factors affect the location of artifact, and each imaging set-up should be evaluated individually. Area of artifact was larger with the IR sequence than the SR sequence, and reduced somewhat when MARS was added to either sequence. In the phantom $T_1$ maps, the artifact area tended to include values above the actual $T_1$ of the agarose, with some especially high values in the IR map (Figure 3.3).

Differences in $T_1$ value between small ROIs within a phantom and within ROIs between phantoms may be partly explained by having two separate phantoms that were made with gel rather than liquid. The phantoms were made from the same batch of doped agarose, but because they were necessarily different phantoms, and because we
expect the gadolinium to be less mobile in the gel, differences in $T_1$ between the phantoms and areas of a phantom may be expected. It is not clear how large an effect this might have on $T_1$, or what other factors may be involved. Differences in the away ROIs were less than 6% within phantoms, and less than 19% between phantoms.

Our results suggest that a number of factors must be considered when choosing between SR and IR sequences for dGEMRIC and when comparing dGEMRIC results using these sequences. It is clear from the smaller extent of artifacts that SR is more robust than IR in the presence of $B_1$ inhomogeneity. However SR suffers from lower SNR.

The changes of 10% or less in ROI\textsubscript{away1} and ROI\textsubscript{away2} in the IR series with metal (MARS and no MARS) are around or below the level of typical clinical significance (examples from literature show differences between groups in the range of 7% to 20%\textsuperscript{3,148,249}). The differences may be partly due to using two different phantoms, with potential spatial variations in gadolinium concentration. We expect that outside of the artifact area, the values will be stable for IR. Determining the extent and direction of artifact will be critical for the application of this technique.

The strengths of this work include the application of several metal artifact reduction strategies both in a phantom and \textit{in vivo} and the use of a relevant surgical implant. One limitation of this work is that few subjects with titanium osteotomy plates have been available for imaging \textit{in vivo}, which has limited our subject numbers, although imaging more than one joint compartment in each subject mitigates this somewhat because we are able to consider cartilage in various loading environments and with varying levels of artifact. A second limitation is that MARS corrects for mis-mapping in the imaging plane, but does not affect mis-mapping of signal into adjacent slices. New protocols for metal artifact correction are now available, and may improve the use of dGEMRIC with surgical hardware\textsuperscript{110,259}. We have also used a titanium implant, where stainless steel is the clinical standard. With this type of surgery and hardware, we were unable to obtain any cartilage information near a stainless steel implant. This limits the applicability of this work in this particular population to patients receiving titanium implants.
dGEMRIC in the presence of surgical hardware at 3 Tesla may be possible with some appropriately applied strategies. Titanium hardware rather than stainless steel is essential to imaging near metal. Implanted surgical hardware may produce artifacts in T1 maps used for dGEMRIC that are not obvious on the images used to generate these maps. Depending on the proximity of the cartilage to the hardware and other factors, the artifact may or may not extend into the cartilage. For implanted hardware where the artifact does not extend through the cartilage, the IR series with MARS provides results consistent with the original (no metal) values within 10%. For experimental situations where the IR artifact extends into the cartilage (shifted null point curves and low f values are obtained), the SR series with MARS has a much smaller area of artifact, though its larger variability may preclude finding smaller clinically significant changes. Using these modified dGEMRIC approaches may allow investigators to study the effects of some surgical procedures on cartilage longitudinally. Caution is advised, however, as the specifics of each implant and imaging experiment set-up influence the extent of artifact and the interference in obtaining reliable dGEMRIC values, and should be evaluated individually.
Chapter 4. Effect of high tibial osteotomy on cartilage health using dGEMRIC

4.1. Introduction

Opening-wedge high tibial osteotomy is a procedure used to treat medial tibiofemoral (TF) osteoarthritis (OA) in knees with varus malalignment. This procedure is performed to change the alignment of the lower limb in an effort to shift load from the diseased medial compartment of the tibiofemoral joint to the lateral compartment. The procedure is often performed in young, active individuals who are not good candidates for total or unicompartmental knee arthroplasty.

The clinical results of this surgery have been moderately good, with ten year survival rates of between 45% and 80%, where survival is defined by conversion to TKA or an unacceptable clinical metric, such as a pain or function score. However, for patients who are too young for knee arthroplasty (due to the limited number of revisions possible), high tibial osteotomy is the only effective surgical treatment option. Evidence of medial compartment cartilage repair has been found following the mechanical change caused by high tibial osteotomy; evidence of degradation of lateral compartment and patellar cartilage has also been found in some subjects. It is not clear why cartilage is protected or restored in some cases while in others it is not.

A limitation to understanding the links between HTO and cartilage health is that most techniques for assessing cartilage health require direct access to the cartilage through arthroscopic surgery, which is invasive. Delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), a validated method for estimating glycosaminoglycan content of cartilage in vivo using T1 mapping, presents a less invasive approach. Low glycosaminoglycan (GAG) content assessed with dGEMRIC is associated with early osteoarthritis (OA). A version of this chapter (which comprises the unedited, pre-publication draft) is in press as: Agnes G. d’Entremont, Robert G. McCormack, Kenard Agbanlog, Simon G.D. Horlick, Trevor B. Stone, Mojieb M. Manzary, David R. Wilson. “Cartilage health in high tibial osteotomy using dGEMRIC: Relationships with joint kinematics”. The Knee. DOI: 10.1016/j.knee.2015.02.005
The limitation of the MR approach is that MR scans are prone to artifact from metal surgical hardware, such as the plates used during high tibial osteotomy.

The objective of this study was to determine how opening-wedge high tibial osteotomy affected cartilage GAG content in the tibiofemoral and patellofemoral compartments.

4.2. Methods

Fourteen (14) male subjects (mean age 48.3, SD 7.2) undergoing opening-wedge high tibial osteotomy for medial compartment osteoarthritis participated in this study (Table 4.1). All subjects gave informed consent and institutional research ethics board approval was granted. Each subject was scanned at three time points: within a month before surgery, 6 months after surgery, and 12 months after surgery using a 3T Philips Achieva scanner. Several subjects were unable to complete one or more of the follow-up scans: one subject had stainless steel hardware implanted at surgery, one subject had a non-union and an additional operation after the 6 month follow-up, two subjects missed the 6 month follow-up due to scheduling conflicts, and two subjects were lost to follow-up after baseline. One subject’s baseline scans were unusable due to data corruption. Our final subject numbers were 13 at baseline, 9 at 6 months, and 10 at 12 months.

The primary participant inclusion criterion was that they were a patient undergoing opening-wedge high tibial osteotomy for treatment of medial tibiofemoral osteoarthritis. Exclusion criteria included previous surgery beyond arthroscopic lavage or debridement, and injury or disorder beyond varus deformity and medial tibiofemoral osteoarthritis (such as cruciate ligament rupture or excessive joint laxity). This sample represents consecutive consenting participants available for recruitment in the authors’ practices.
Table 4.1: Description of HTO subjects.
* Indicates same subject.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age</th>
<th>HTO knee</th>
<th>Dominant knee</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>BMI</th>
<th>Baseline (days)</th>
<th>6MOS (months)</th>
<th>12MOS (months)</th>
<th>Baseline</th>
<th>6MOS</th>
<th>12MOS</th>
<th>Surgeon</th>
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<td>1</td>
<td>35.8</td>
<td>R</td>
<td>R</td>
<td>193</td>
<td>112</td>
<td>30.0</td>
<td>4</td>
<td>7.4</td>
<td>12.8</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SH</td>
</tr>
<tr>
<td>2</td>
<td>41.8</td>
<td>L</td>
<td>R</td>
<td>174</td>
<td>83</td>
<td>27.4</td>
<td>1</td>
<td>6.3</td>
<td>12.0</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SH</td>
</tr>
<tr>
<td>3</td>
<td>54.0</td>
<td>L</td>
<td>R</td>
<td>176</td>
<td>84</td>
<td>27.1</td>
<td>7</td>
<td>6.2</td>
<td>12.0</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>SH</td>
</tr>
<tr>
<td>4</td>
<td>38.8</td>
<td>L</td>
<td>L</td>
<td>172</td>
<td>77</td>
<td>26.1</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>SH</td>
</tr>
<tr>
<td>5</td>
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<td>L</td>
<td>R</td>
<td>173</td>
<td>66</td>
<td>22.0</td>
<td>49</td>
<td>6.1</td>
<td>15.4</td>
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<td>No</td>
<td>MARS</td>
<td>RGM</td>
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<tr>
<td>6</td>
<td>59.8</td>
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<td>L</td>
<td>160</td>
<td>88</td>
<td>34.6</td>
<td>13</td>
<td>5.8</td>
<td>12.5</td>
<td>No</td>
<td>No</td>
<td>MARS</td>
<td>TS</td>
</tr>
<tr>
<td>7</td>
<td>51.3</td>
<td>R</td>
<td>R</td>
<td>185</td>
<td>107</td>
<td>31.1</td>
<td>4</td>
<td>7.6</td>
<td>13.8</td>
<td>No</td>
<td>No</td>
<td>MARS</td>
<td>TS</td>
</tr>
<tr>
<td>8</td>
<td>50.4</td>
<td>L</td>
<td>R</td>
<td>177</td>
<td>100</td>
<td>31.9</td>
<td>5</td>
<td>7.8</td>
<td>12.0</td>
<td>No</td>
<td>No</td>
<td>MARS</td>
<td>RGM</td>
</tr>
<tr>
<td>9</td>
<td>50.2</td>
<td>L</td>
<td>R</td>
<td>177</td>
<td>80</td>
<td>25.6</td>
<td>9</td>
<td>-</td>
<td>-</td>
<td>No</td>
<td>-</td>
<td>-</td>
<td>TS</td>
</tr>
<tr>
<td>10</td>
<td>57.4</td>
<td>R</td>
<td>R</td>
<td>173</td>
<td>86</td>
<td>28.6</td>
<td>15</td>
<td>6.6</td>
<td>15.8</td>
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<td>No</td>
<td>MARS</td>
<td>TS</td>
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<td>11</td>
<td>53.4</td>
<td>L</td>
<td>R</td>
<td>162</td>
<td>65</td>
<td>24.7</td>
<td>25</td>
<td>-</td>
<td>-</td>
<td>MARS</td>
<td>-</td>
<td>-</td>
<td>TS</td>
</tr>
<tr>
<td>12</td>
<td>55.1</td>
<td>R</td>
<td>R</td>
<td>175</td>
<td>83</td>
<td>27.1</td>
<td>53</td>
<td>-</td>
<td>12.3</td>
<td>MARS</td>
<td>-</td>
<td>MARS</td>
<td>RGM</td>
</tr>
<tr>
<td>13*</td>
<td>40.8</td>
<td>R</td>
<td>R</td>
<td>180</td>
<td>107</td>
<td>32.9</td>
<td>18</td>
<td>-</td>
<td>12.5</td>
<td>No</td>
<td>-</td>
<td>MARS</td>
<td>RGM</td>
</tr>
<tr>
<td>14*</td>
<td>42.3</td>
<td>L</td>
<td>R</td>
<td>180</td>
<td>109</td>
<td>33.6</td>
<td>11</td>
<td>6.0</td>
<td>-</td>
<td>No</td>
<td>MARS</td>
<td>-</td>
<td>RGM</td>
</tr>
</tbody>
</table>
4.2.1. Surgical procedure
Preoperative radiological work-up included weight bearing anteroposterior films of the knee as well as notch view, modified Rosenberg view (PA in 30 degrees of flexion), and bilateral weight-bearing full-length AP hip-to-ankle films. Preoperative planning was templated to change the weightbearing axis to pass through a position of 62.5% across the tibial plateau (lateral to or at the downslope of the lateral tibial spine). The percentage width of the tibial plateau is based on the most medial edge of the tibial plateau being 0% and the most lateral point being 100%.

A medial approach was used to the proximal tibia, the sartorial fascia was elevated and the osteotomy was placed superior to the tibial tubercle. Intraoperatively, a baseline true lateral image was taken by making sure that the femoral condyles are strictly superimposed on each other. This allowed intraoperative assessment of tibial slope.

The osteotomy plane was marked by two k-wires which were placed parallel to the slope of the tibia, in the midcoronal plane. An oblique osteotomy was performed with a combination of osteotomes and sagittal saw, leaving the lateral cortex intact as a hinge. Using fluoroscopy the tibial slope is checked and the position of the weightbearing axis is confirmed using a 3-foot alignment rod.

Titanium surgical hardware was used to minimize image artifacts in follow-up MRI scans (Puddu plate, Arthrex, Ti6Al4V, approximately 5 cm x 1.5 cm). The design of Puddu plate used was trapezoidal with a 3-degree anterior angle (the anterior part being narrower than posterior part) and was placed posterior to the midline to avoid any increase in the tibial slope. The plate was fixed proximally with two partially threaded cancellous screws of 6.5 mm diameter and distally with two 4.5 mm cortical screws. The osteotomy opening was filled with tricocorticocancellous autograft from the iliac crest, or calcium triphosphate wedges. Standardized antibiotic and antithrombotic prophylaxis was followed.

Post-operatively patients were kept non-weightbearing for 6-8 weeks (depending on the amount of correction), followed by partial weightbearing for a further 2-4 weeks.
4.2.2. MR imaging

We performed dGEMRIC scans on the tibiofemoral and patellofemoral joints of the operated knee of each subject to quantify cartilage GAG concentration. Each subject was first injected with an intravenous double dose (0.2 mmol/kg) of gadopentatate dimeglumine (Gd-DTPA$^2$, Magnevist, Berlex Laboratories, USA). Subjects then performed ten minutes of brisk walking following the injection and scanning began 90 minutes post-injection.

For each subject, we first obtained a dGEMRIC scan series of the tibiofemoral joint of the operated knee (coronal plane). Because the metal osteotomy plate near the cartilage can cause artifact that disrupts the T$_1$ map in the tibiofemoral cartilage (Chapter 3), we used a sequence optimized to reduce metal artifact$^{260}$ for scans of the tibiofemoral joint. This sequence used two strategies to reduce metal artifact in the tibiofemoral joint: using saturation recovery (SR) instead of inversion recovery (IR) and applying the Metal Artifact Reduction Sequence (MARS) to the SR series. MARS is based on view-angle tilting (VAT)$^{128}$ with an increased read bandwidth (from +/- 26.9 kHz to +/- 46.0 kHz) to combat the blurring associated with VAT$^{105}$. We obtained a series of single-slice coronal plane saturation recovery turbo spin-echo (TSE) scans (Table 4.2) with two surface coils (SENSE Flex-M, Philips, Best, Netherlands) positioned one on either side of the joint.

For each subject, we then obtained a dGEMRIC scan of the patellofemoral joint of the operated knee. This scan was started about two hours post-injection. The scan series consisted of a series of single-slice inversion recovery (IR) turbo spin-echo (TSE) scans in the axial plane (Table 4.2). We used the inversion recovery sequence at the patellofemoral joint because the metal implant was sufficiently distant and the inversion recovery sequence has a higher signal-to-noise ratio than the saturation recovery sequence. The inversion preparation was achieved with a commercially available hyperbolic secant adiabatic pulse (amplitude and frequency modulated) which was designed to produce accurate inversion pulses even in presence of radiofrequency field (B$_1$) inhomogeneities$^{254}$. 


Table 4.2: MR sequence parameters for dGEMRIC.
*Used for 11 subject-timepoints.

<table>
<thead>
<tr>
<th></th>
<th>IR</th>
<th>SR</th>
<th>SR-MARS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time (TR)</td>
<td>2200 ms</td>
<td>2200, 1800, 1200, 700, 400, 300, 200, 150, 100 ms</td>
<td>2200, 1800, 1200, 700, 400, 300, 200, 150, 100 ms</td>
</tr>
<tr>
<td>Inversion time (TI)</td>
<td>1800, 1200, 700, 400, 200, 150, 100, 50 ms</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Echo time (TE)</td>
<td>15 ms</td>
<td>15 ms</td>
<td>15 ms</td>
</tr>
<tr>
<td>TSE factor</td>
<td>9</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Field of view (FOV)</td>
<td>100 mm</td>
<td>100 mm</td>
<td>100 mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>3 mm</td>
<td>3 mm</td>
<td>3 mm</td>
</tr>
<tr>
<td>Matrix size (scanned)</td>
<td>256 x 256</td>
<td>256 x 256</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Matrix size (reconstructed)</td>
<td>256 x 256</td>
<td>256 x 256</td>
<td>256 x 256</td>
</tr>
<tr>
<td>In-plane resolution</td>
<td>0.39 x 0.39 mm</td>
<td>0.39 x 0.39 mm</td>
<td>0.39 x 0.39 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Scan time (total)</td>
<td>16:25</td>
<td>12:53</td>
<td>12:53</td>
</tr>
<tr>
<td>VAT</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Bandwidth</td>
<td>+/- 26.9 kHz</td>
<td>+/- 26.9 kHz</td>
<td>+/- 46.0 kHz</td>
</tr>
</tbody>
</table>

4.2.3. Data analysis
For each set of eight scans, each image was manually aligned to the image with the highest inversion time (for the IR sequence) or the highest repetition time (for the SR sequence). The cartilage area of interest (tibiofemoral or patellofemoral) was segmented manually (MATLAB, MathWorks, MA). Quantitative T₁ maps were obtained using in-house developed code (MATLAB, Mathworks, MA, USA, function lsqcurvefit) to fit the magnitude signal intensities versus inversion times (IR series - Equation 4.1) or saturation recovery times (SR series - Equation 4.2) by minimizing the sum of the squared residuals of signal intensity for each pixel of the image set.

\[
SI = \left| S_0 \left( 1 - f_{IR} e^{-\frac{TI}{T_1}} \right) \right|
\]

Equation 4.1

\[
SI = S_0 \left( 1 - f_{SR} e^{-\frac{TR}{T_1}} \right)
\]

Equation 4.2
Equation 4.1 is the fit equation for the IR series, and Equation 4.2 is the fit equation for the SR series. SI is signal intensity in the image, S₀ is the signal intensity at equilibrium conditions, TI is inversion time, TR is repetition time and f_IR and f_SR are fit factors that account for imperfect inversion and excitation pulses. SI, TI, and TR are known values, and S₀, T₁, and f are calculated. The nominal f-factor values are f_IR = 2 for perfect inversion, and f_SR = 1 for perfect excitation; these values were allowed to vary to accommodate imperfect inversion or excitation.

Twenty-five random initial values sets, centered around initial guesses (IR: T₁,initial = TΙ(SI_min)/ln2, SI_initial = SI(TΙ_max), f_initial = 1.9; SR: T₁,initial = 600 ms, SI_initial = SI(TR_max), f_initial = 1) were used for each pixel and the result with the lowest residual was selected as the best result.

The calculated T₁ maps contained pixel values that were obviously outliers, especially in the presence of metal or increased noise in the signal. Since the physiological range of mean post-contrast T₁ (both normal and OA) has been found to be 400-900 ms[^255] we chose to conservatively remove pixels with T1 values calculated to be above 1200 ms and below 100 ms from all data sets.

### 4.2.4. Statistical analysis

For each cartilage region of interest, we tested the null hypothesis that there was no difference in mean T₁ between the preoperative condition, 6 months after surgery, and 12 months after surgery using a linear mixed-effects model. The general statistical model used for dGEMRIC analyses was:

\[
y_{ij} = \beta_{0j} + \beta_1 * \text{timepoint}_i
\]

where y is any one of the dGEMRIC region scores, j = 1 to 10 (individuals) and i = 1, 2, 3 (timepoints). \( \beta_{0j} \) is the model mean dGEMRIC score (T₁) at the pre-operative time point for an individual. Timepoint 1 was pre-operative (coefficient \( \beta_0 \)), timepoint 2 was 6 months follow-up (add \( \beta_1 \) for timepoint 2), and timepoint 3 was 12 months follow-up (add \( \beta_1 \) for timepoint 3). Individuals (j) were allowed to vary in intercept from the model mean:
\[ \beta_{0j} = \gamma_0 + u_{0j} \]

Equation 4.4

where Equation 4.4 represents model mean dGEMRIC score for an individual subject at the pre-operative timepoint; \( \gamma \) is the model mean dGEMRIC value for all subjects, and \( u \) is the difference from the model mean dGEMRIC value for an individual subject. All statistical analysis was performed using Stata 10.1 (StataCorp, Texas).

Initial sample size calculations based on a paired t-test (the effect size estimated at 26 ms (1.5T) from differences between intact and damaged tibiofemoral compartments\(^{143} \) and the underlying standard deviation in the tibiofemoral compartments estimated at 30 ms (1.5T) for a range of activity levels\(^{3} \)) suggested a sample size of 13 to have adequate power (0.80) to detect clinically significant differences.

4.3. Results

Outliers excluded from tibiofemoral dGEMRIC maps averaged 12.8% of pixels per map (over all timepoints (means: baseline 11.6% of pixels; 6 months 15.8% of pixels; 12 months 14.9% of pixels)), with higher percentage outliers in the lateral compartment (16.3% versus 8.9%). Outliers excluded from patellar dGEMRIC maps averaged 0.4% of pixels per map over all timepoints (means: baseline 0.5% of pixels; 6 months 0.3% of pixels; 12 months 0.4% of pixels), and consisted of pixels with values above 1200 ms.

Visible artifacts were present in post-operative tibiofemoral images despite the use of SR and MARS (Figure 4.1), though they did not appear to extend into cartilage. None of the patellofemoral images had visible artifacts.

No statistically significant changes were found in overall tibiofemoral dGEMRIC score between the baseline (598 ms) scan and the 6 month post-op (578 ms) scan (\( p = 0.37 \)), between the baseline scan and the 12 month post-op (607 ms) scan (\( p = 0.67 \)) or between 6 months and 12 months post-op (\( p = 0.21 \)) (Table 4.3, Figure 4.2). We did, however, see a broad range of patterns of change in dGEMRIC across the individual subjects. [See Appendix B for data by subject]
Table 4.3: Mixed linear model results for patellofemoral (PF) and tibiofemoral (TF) dGEMRIC scores.
BASE = pre-operative baseline, 6MOS = 6 months follow-up, 12MOS = 12 months follow-up. ** indicates p < 0.001.

<table>
<thead>
<tr>
<th></th>
<th>TF T&lt;sub&gt;1&lt;/sub&gt; mean (SE) [ms]</th>
<th>PF T&lt;sub&gt;1&lt;/sub&gt; mean (SE) [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>β&lt;sub&gt;0&lt;/sub&gt; (intercept)</td>
<td>598.0 (16.1) **</td>
<td>664.4 (23.7) **</td>
</tr>
<tr>
<td>β&lt;sub&gt;1&lt;/sub&gt; (difference in intercept)</td>
<td>BASE to 6MOS -20.1 (22.3)</td>
<td>-13.9 (21.1)</td>
</tr>
<tr>
<td></td>
<td>BASE to 12MOS 9.2 (21.5)</td>
<td>9.3 (21.1)</td>
</tr>
<tr>
<td></td>
<td>6MOS to 12MOS 29.3 (23.3)</td>
<td>23.2 (22.3)</td>
</tr>
</tbody>
</table>

In the tibiofemoral compartments, mean medial dGEMRIC scores were lower than mean lateral dGEMRIC scores at each timepoint (Figure 4.3). [See Appendix B for data by subject]

No statistically significant changes were found in patellar dGEMRIC score between the baseline (664 ms) scan and the 6 month post-op (650 ms) scan (p = 0.51), between the baseline scan and the 12 month post-op (674 ms) scan (p = 0.66) or between 6 months and 12 months post-op (p =0.30) (Table 4.3, Figure 4.4). [See Appendix B for data by subject]

To consider the effect of varied used of MARS on TF outcomes, the mean 12 month T<sub>1</sub> with and without MARS (612 ms versus 583 ms) has a difference of 30 ms or 4.8%. Over all post-operative subject-timepoints, the difference of mean dGEMRIC score with and without MARS (622 versus 567 ms) was 55 ms or 8.8%. [See Appendix B for data by subject]
Figure 4.1: Patellar and tibiofemoral dGEMRIC maps for all timepoints for sample subject (subject 8). Colourmap represents T₁ values in ms.
Figure 4.2: Overall TF mean dGEMRIC scores for all ROIs. The mean linear mixed model results are shown in bold, and individual results are shown in grey. Mean model results and standard errors in Table 4.3, summary statistics and individual data in Appendix B.

Figure 4.3: Mean dGEMRIC scores from linear mixed-model for each region of the tibiofemoral joint over all timepoints.
* indicates statistically significant difference (* p < 0.05, ** p < 0.001). Mean model results, standard errors, summary statistics and individual data in Appendix B.
4.4. Discussion

We used dGEMRIC to determine how opening-wedge high tibial osteotomy affected cartilage GAG content in the tibiofemoral and patellofemoral compartments. Despite known kinematic changes in both the patellofemoral and tibiofemoral joints with opening-wedge high tibial osteotomy, we found no significant difference in patellar or tibiofemoral dGEMRIC score between baseline and 6 or 12 months post-surgery. The dGEMRIC scores were within the range of 400-900 ms mean dGEMRIC $T_1$ value found in another study at 3T\textsuperscript{255}; the largest mean changes in patellar dGEMRIC score (23 ms) and tibiofemoral dGEMRIC score (29 ms) were 4.6% and 5.8% of this range, respectively. These changes are small relative to the 71 ms lower dGEMRIC score value in the tibiofemoral joint at baseline associated with development of radiographic OA by 6 years\textsuperscript{144} (at 1.5T, therefore smaller range of $T_1$ values expected\textsuperscript{255}). However, we saw changes in individual participants (both increases and decreases in $T_1$) larger than that magnitude.

The finding of apparent recovery of cartilage GAG content, which we saw in some individual participants, has been seen previously. In a case study of PCL rupture, overall tibiofemoral dGEMRIC score compared to pre-injury values decreased by 15% at 1 month post-injury, 19%
at 3 months post-injury, but then recovered to only 3% less than pre-injury values at 6 months post-injury. The large changes we observed in some participants at 6 months in dGEMRIC scores, such as -129 ms (-23%, TF) in subject 6, might reflect an adjustment to a change in mechanics in the joint, and are larger than clinically important differences previously reported. Our finding that the medial tibiofemoral compartment had lower T₁ values than the lateral compartment at all timepoints is consistent with the indication for the operation, which is degeneration of the medial TF compartment cartilage due to varus malalignment.

Our findings for tibiofemoral cartilage are generally consistent with those of a recent study, also performed at 3T. Like our study, these authors found no statistically significant differences in tibiofemoral cartilage dGEMRIC score between the pre-op, 6 months and 1 year post-op states. Our mean values for the baseline medial compartment (563 ms) and lateral compartment (622 ms) in the current study are consistent with the baseline values from Parker et al. (medial at 562 ms, lateral at 628 ms; n = 10). At 6 months follow-up, our tibiofemoral results show a decrease in both compartments (medial 554 ms, lateral 590 ms) similar to the Parker study (medial about 510 ms, lateral about 590 ms), though neither study shows significant differences. At 12 months follow-up, our results show an increase to above baseline values (medial 568 ms, lateral 634 ms), which is different from the much smaller medial increase (little change in lateral) seen by Parker and colleagues (medial about 520 ms, lateral about 590 ms), again not statistically significant. One key difference between these two studies is that Parker et al. did not remove the metal implant or employ metal artifact reduction strategies. It is possible that metal artifact affected the post-operative results in their study.

Our results for the tibiofemoral joint are also generally consistent with those from a study of opening-wedge HTO performed at 1.5 T, in which the implants were removed prior to post-operative imaging to avoid metal artifact. Like in our study, these authors found no significant differences between pre- and post-operative dGEMRIC (range of time post-surgery varied), although there was a slight but non-significant decrease in T₁ values. The T₁ values from this study (overall mean: baseline 533 ms, post-operative about 12 months 466 ms; n = 10) are not directly comparable to our study because the scanning was performed at 1.5 T and T₁ is a function of magnetic field strength. Cartilage without contrast agent has been shown to have a 14.5% higher T₁ at 3 T than at 1.5 T, and dGEMRIC results comparing post-
contrast $T_1$ in the same subjects has seen an increase on the order of 25% at 3 T$^{255}$. Scaling these numbers to 3T, we expect the Rutgers results to be around 610 - 666 ms at baseline, and 534 - 583 ms at 12 months, which compare to our overall mean tibiofemoral results of 594 ms at baseline and 603 ms at 12 months post-op. It is also important to note that both of these previous studies of HTO used inversion recovery scans, which may produce slightly different values of $T_1$ (within 9%) than the saturation recovery scans we have used for the tibiofemoral joint (Chapter 3).

Our findings for patellofemoral dGEMRIC are somewhat higher than what has been reported in the literature. One study at 3 T of patellae in TKA found a preoperative mean $T_1$ of 321 ms ($n = 12$) over all regions, which is substantially lower than our preoperative mean of 664 ms$^{149}$. However, it is reasonable to presume that these participants had more advanced patellofemoral degeneration, on average, than the relatively young and active patients in the current study. Another study at 1.5 T in ten normal volunteers found a mean patellar $T_1$ of 469 ms, which, if we scale to approximately 537 - 586 ms at 3 T, is closer to our preoperative finding$^{261}$.

A strength of this study is that we used metal artifact reduction techniques, including saturation recovery and MARS, at the tibiofemoral joint. This is important because we have shown that $T_1$ measurements can be disrupted substantially by metal artifacts that are not visible on higher TI value scans (Chapter 3). Another strength is that we assessed patellofemoral cartilage in addition to tibiofemoral cartilage. This is important because the patella is often involved in knee OA$^{262}$.

Limitations of this study include having only one 2D slice of cartilage to evaluate dGEMRIC scores in each joint. Three-dimensional sequences would allow more complete coverage of the joint. Another limitation is that matching slices between timepoints was challenging, both due to typical difficulties in obtaining the same slice and to geometric changes in the joint as a result of surgery and healing. The number of outlier pixels from the dGEMRIC scans is another limitation. While the increase in outliers (by a mean of 15 pixels) in the post-operative TF scans may be due to some metal artifact causing erroneous $T_1$ values, it is unclear what caused the higher numbers of outliers in the TF cartilage than in the PF cartilage at pre-operative baseline. We previously demonstrated that patellar cartilage dGEMRIC outliers were similarly small in vivo with IR and SR (0.2% and 0.8%; Chapter 3). A
A further limitation is that application of MARS to only some of the tibiofemoral results is confounding. Over the length of this study, MARS was unavailable at certain times (at the start due to a need to program the patch, and in the middle due to a MR system software upgrade; see Table 4.1). We expect the effect of MARS on non-artifact areas to be small, but the changes in areas of artifact may be larger. In phantom work without metal present, we have seen a small increase (2.2% SR) in $T_1$ values with MARS (Chapter 3). In a direct *in vivo* comparison in one subject (subject 6, at 17 months post-surgery), $T_1$ at the tibiofemoral joint increased by 43 ms (7%) when MARS was applied (see Chapter 3, Table 4.1). While it is not a controlled comparison, especially as many of the MARS results were at the 12 month timepoint, we saw higher values of $T_1$ in post-operative subject-timepoints in this study that employed MARS (55 ms or 9.7%). It is not clear if these differences reflect a correction of $T_1$ in the presence of metal.

Opening-wedge high tibial osteotomy does not appear to be associated with an overall change in cartilage GAG concentration in the tibiofemoral compartments in the first year post-surgery, but there are substantial differences in GAG change patterns from patient to patient. Opening-wedge high tibial osteotomy does not appear to be associated with an overall change cartilage GAG concentration at the patella in the first year post-surgery. These results indicate that cartilage may not be degenerating in the short term, however there may be focal changes or changes associated with differences in treatment (or other subject parameters) that are not apparent due to the aggregation of whole compartment $T_1$ data and the lack of differentiation of subjects by as yet unrecognized factors that may affect outcomes.
Chapter 5. Effect of opening-wedge high tibial osteotomy on three-dimensional knee kinematics

5.1. Introduction

Medial opening-wedge high tibial osteotomy is a treatment for medial tibiofemoral osteoarthritis associated with varus malalignment in young, active patients. Varus malalignment shifts the line of action of the ground reaction force medially, which increases joint contact force in the medial tibiofemoral compartment. Varus malalignment is associated with progression of preexisting medial tibiofemoral osteoarthritis, although its association with the incidence of medial tibiofemoral osteoarthritis is controversial. A valgus high tibial osteotomy restores the line of action to a neutral or slightly lateral position, with the objective of redistributing load between the tibiofemoral compartments. The clinical results of this surgery are moderately good, with ten year survival rates of between 45% and 80%. There appears to be a consensus that the angular correction (measured from a standing frontal radiograph) should result in 8° to 10° of anatomical valgus. However statistical links between the angular alignment correction and clinical outcome are not consistent, with some studies showing correlation, and others not. One of the factors that may account for the moderate clinical outcomes of high tibial osteotomy and the imperfect relationship between optimal alignment and optimal outcome is that knee mechanics may not be restored to normal following surgery when correction in the coronal plane is the only measure of correction.

Restoring the alignment to a value within an optimal range may be insufficient for clinical success, in part because of limitations of measuring alignment. While direct measures of joint mechanics would provide evidence of successful medial compartment unloading, they are not typically available in vivo. However, the mechanics of a joint may be inferred from measurements of the three-dimensional kinematics of the joint over a range of motion. Standing radiographs, the current standard assessment of tibiofemoral alignment, describe the joint at a single flexion angle and in only one plane. In addition to changing varus

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4 A version of this chapter (which comprises the unedited, pre-publication draft) has been published. Reproduced with permission and copyright © of the British Editorial Society of Bone and Joint Surgery, d’Entremont AG, McCormack RG, Horlick SGD, et al. Effect of opening-wedge high tibial osteotomy on the three-dimensional kinematics of the knee. Bone Joint J 2014;96-B:1214-1221.
angulation, closing-wedge high tibial osteotomy has been shown to change aspects of three-dimensional tibiofemoral kinematics in vivo using Roentgen stereophotogrammetric analysis (medial translation of tibia (1.3 mm) in one patient; increased range of tibial internal/external rotation (3.7 degrees) in seven patients). However, it is not clear how opening wedge high tibial osteotomy affects the three-dimensional kinematics of the joint in loaded flexion.

In this study, our research question was: How does opening-wedge high tibial osteotomy change three-dimensional tibiofemoral and patellofemoral kinematics in loaded flexion in patients with varus deformity?

5.2. Methods

Three-dimensional tibiofemoral and patellofemoral kinematics and WOMAC scores were assessed before and after opening-wedge high tibial osteotomy in 14 knees of 13 male subjects (age 48.3 +/- 7.2 years) before surgery and at 6 and 12 months’ follow-up. Ethics board approval was granted by our institutions and informed consent was obtained from all participants.

5.2.1. Participants

Our primary inclusion criterion was that patients were scheduled to undergo opening-wedge high tibial osteotomy for treatment of medial tibiofemoral osteoarthritis. Exclusion criteria included previous surgery beyond arthroscopic debridement and additional injury or disorder (such as cruciate ligament rupture or excessive joint laxity). This sample represents consecutive consenting participants available for recruitment in the authors’ practices.

5.2.2. Surgical technique

Preoperative radiological work up included weight bearing anteroposterior films of the knee as well as well as notch view, modified Rosenberg view (PA in 30 degrees of flexion), and bilateral weight-bearing full-length AP hip-to-ankle films. Preoperative planning was templated to change the weightbearing axis to pass through a position of 62.5% across the tibial plateau (lateral to or at the downslope of the lateral tibial spine). The percentage width of the tibial plateau is based on the most medial edge of the tibial plateau being 0% and the most lateral point being 100%.
A medial approach was used to the proximal tibia, the sartorial fascia was elevated, and the osteotomy was placed superior to the tibial tubercle. Intraoperatively, a baseline true lateral image was taken by making sure that the femoral condyles are strictly superimposed on each other. This allowed intraoperative assessment of tibial slope.

The osteotomy plane was marked by two k-wires which were placed parallel to the slope of the tibia, in the midcoronal plane. An oblique osteotomy was performed with a combination of osteotomes and sagittal saw, leaving the lateral cortex intact as a hinge. Using fluoroscopy the tibial slope is checked and the position of the weightbearing axis is confirmed using a 3-foot alignment rod.

Titanium surgical hardware was used to minimize image artifacts in follow-up MRI scans (Puddu plate, Arthrex). The design of Puddu plate used was trapezoidal with a 3-degree anterior angle (the anterior part being narrower than posterior part) and was placed posterior to the midline to avoid any increase in the tibial slope. The plate was fixed proximally with two partially threaded cancellous screws of 6.5 mm diameter and distally with two 4.5 mm cortical screws. The osteotomy opening was filled with tricocorticocancellous autograft from the iliac crest, or calcium triphosphate wedges. Standardized antibiotic and antithrombotic prophylaxis was followed.

Post-operatively patients were kept non-weightbearing for 6-8 weeks (depending on the amount of correction), followed by partial weightbearing for a further 2-4 weeks.

5.2.3. Kinematics
Three-dimensional tibiofemoral and patellofemoral kinematics during loaded flexion were measured before surgery, at six months and 12 months post operatively using a validated MRI-based method\textsuperscript{265,266}. For each assessment, the participant first lay supine in a Philips 3T Achieva MR scanner (Philips Healthcare, Best, NL). A high-resolution T\textsubscript{1}-weighted multislice scan was performed in a relaxed position. Rapid scans (with lower resolution) were then obtained at six flexion angles (10°-60°) while the participant loaded his knee using a specially designed MR-compatible rig with an approximately 80 N load\textsuperscript{267} (Table 5.1).
5.2.4. Data analysis
Rotations and translations defining the pose of the tibia and patella relative to the femur at each imaged flexion angle were determined. First, bone was segmented from the relaxed MR images (Analyze, AnalyzeDirect, Overland Park, KS) and high-resolution three-dimensional models of the tibia, femur and patella were generated. Anatomical axes were assigned to each bone using anatomical landmarks. Each bone model was then registered to its corresponding positions defined by the segmented loaded rapid scan data using an iterative closest points algorithm (MATLAB, Mathworks, Natick, MA) (Figure 5.1). Rotations and translations of the tibia and the patella with respect to the femur were calculated using a joint coordinate system approach. Calculated kinematic parameters were patellar flexion, patellar spin, patellar tilt, patellar proximal translation, patellar lateral translation, patellar anterior translation, tibial adduction, tibial internal rotation, tibial proximal translation, tibial lateral translation, and tibial anterior translation. The mean accuracy of this method for each parameter is 1.0°/0.9 mm or less (patellar kinematics), the mean repeatability for each parameter is 1.4°/0.8 mm or less and the mean repeatability of patellar spin, tilt and lateral translation over 12 months in a population of healthy young males are 1.2°, 1.0°, and 0.8 mm respectively.

Table 5.1: MR scan parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Relaxed high-resolution scan</th>
<th>Loaded rapid scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetition time (TR)</td>
<td>700 ms</td>
<td>700 ms</td>
</tr>
<tr>
<td>Echo time (TE)</td>
<td>10 ms</td>
<td>10 ms</td>
</tr>
<tr>
<td>TSE factor</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Field of view (FOV)</td>
<td>320 x 320 mm</td>
<td>320 x 320 mm</td>
</tr>
<tr>
<td>Slice thickness</td>
<td>2 mm</td>
<td>2 mm</td>
</tr>
<tr>
<td>Slice gap</td>
<td>0 mm</td>
<td>5 mm</td>
</tr>
<tr>
<td>Matrix size (scanned)</td>
<td>512 x 512</td>
<td>128 x 128</td>
</tr>
<tr>
<td>Matrix size (reconstructed)</td>
<td>512 x 512</td>
<td>256 x 256</td>
</tr>
<tr>
<td>Final in-plane resolution</td>
<td>0.625 x 0.625 mm</td>
<td>1.25 x 1.25 mm</td>
</tr>
<tr>
<td>Number of slices</td>
<td>46-52 (knee size)</td>
<td>16</td>
</tr>
<tr>
<td>Scan time (total)</td>
<td>16:18 (46 slices)</td>
<td>6 x 0:28</td>
</tr>
</tbody>
</table>

5.2.5. Statistical analysis
We tested the null hypothesis that there was no difference in kinematics between the knees before surgery, six months after HTO and twelve months after HTO for each kinematic parameter using a linear mixed-effects model. This statistical test is the most appropriate and accurate for repeated-measures or nested data, particularly with fixed effects (knee
angles) that are unequal between participants. The general principle of the method is to apply individual regression models to each subject and condition, then compare between conditions (within person comparison). We used a similar test for WOMAC scores.

The general model used for kinematic analyses was:

\[ y_{ij} = \beta_{0j} + \beta_{1j} \times \text{kneeangle} + \beta_{2} \times \text{kneeangle}^2 + \beta_{3} \times \text{timepoint}_i + \beta_{4} \times \text{kneeangle} \times \text{timepoint}_i + \beta_{5} \times \text{kneeangle}^2 \times \text{timepoint}_i \]

Equation 5.1

where \( y \) is any one of the 11 kinematic parameters, \( j = 1 \) to 10 (individuals) and \( i = 1, 2, 3 \) (timepoints). Knee angles were obtained from 3D models. Timepoint 1 was pre-operative baseline (coefficients \( \beta_0, \beta_1, \beta_2 \)), timepoint 2 was 6 months follow-up (add \( \beta_3, \beta_4, \beta_5 \) for timepoint 2), and timepoint 3 was 12 months follow-up (add \( \beta_3, \beta_4, \beta_5 \) for timepoint 3). Individuals (\( j \)) were allowed to vary in both intercept and slope from the model mean:

\[ \beta_{0j} = \gamma_0 + u_{0j} \]

Equation 5.2

and

\[ \beta_{1j} = \gamma_1 + u_{1j} \]

Equation 5.3

where Equation 5.2 represents model mean kinematic parameter intercept for an individual for the pre-operative timepoint, and Equation 5.3 represents model mean kinematic parameter slope for an individual for the pre-operative timepoint; \( \gamma \) is the model mean value for all participants, and \( u \) is the difference from the model mean value for an individual participant.

The quadratic terms (\( \beta_2, \beta_5 \)), \( u_{1j} \) (part of \( \beta_1 \)) and \( \text{knee_angle} \times \text{timepoint} \) (\( \beta_4 \)) were included when they improved the model (as compared to the linear model) as determined by lowering the Bayesian information criterion (BIC), which indicates quality of fit but penalizes for extra terms in the model.
Figure 5.1: The image processing procedure for obtaining kinematic data. Example showing six static flexion angles for one subject. Modified from d’Entremon et al., “Do dynamic-based MR knee kinematics methods produce the same results as static methods?”, Magn Reson Med. 2013, 69(6):1634-44, used with permission from John Wiley and Sons272
The general model used for WOMAC analyses was:

\[ y_{ij} = \beta_0 + \beta_1 \times \text{timepoint}_i \]

Equation 5.4

where \( y \) is any one of the 3 WOMAC sub-scores or the overall WOMAC score, \( j = 1 \) to 10 (individuals) and \( i = 1, 2, 3 \) (timepoints). \( \beta_0 \) is the model mean WOMAC score (or sub-score) at the pre-operative time point for an individual. Timepoint 1 was baseline (coefficient \( \beta_0 \)), timepoint 2 was 6 months follow-up (add \( \beta_1 \) for timepoint 2), and timepoint 3 was 12 months follow-up (add \( \beta_1 \) for timepoint 3). Individuals (\( j \)) were allowed to vary in intercept from the model mean:

\[ \beta_{0j} = \gamma_0 + u_{0j} \]

Equation 5.5

where Equation 5.5 represents model mean WOMAC score (or sub-score) for an individual subject at the pre-operative timepoint; \( \gamma \) is the model mean WOMAC value for all participants, and \( u \) is the difference from the model mean WOMAC value for an individual participant.

Statistical analyses were performed using Stata 10.1 (StataCorp, Texas).

5.3. Results

Some participants missed follow-up scans for various reasons. One participant had stainless steel hardware implanted at surgery, one participant had non-union and a repeat operation after the 6 month follow-up, two participants missed the 6 month follow-up due to scheduling conflicts, and two participants were lost to follow-up. The total participant numbers were, at baseline, \( n = 14 \); at 6 months, \( n = 9 \); and at 12 months, \( n = 10 \).

Opening-wedge high tibial osteotomy shifted the tibia anteriorly through the range of flexion by a mean of 2.6 mm (\( p < 0.001 \)) and this was maintained at both post-op timepoints (Figure 5.2, Table 1.2). In all participants the tibia translated posteriorly with flexion before surgery, and in all participants but one (who went on to revision after the six month follow-up) this pattern remained after surgery, but with the tibia in a more anterior position over the range of motion.

Opening-wedge high tibial osteotomy also shifted the patella distally (Figure 5.3) and this was maintained at both post-op timepoints (mean 2.2 mm, \( p < 0.001 \)). In all participants the patella translated distally with flexion before surgery. After HTO no participants exhibited
proximal shift of the patella with high tibial osteotomy but four participants showed similar patellar translation patterns between pre and post-operative scans.

Statistically significant differences in intercept between baseline and both follow-ups also showed that opening wedge high tibial osteotomy decreased patellar spin (mean -1.4 degrees, \( p < 0.05 \)), increased patellar tilt (mean 2.2 deg, \( p < 0.05 \)), shifted the patella laterally (mean 0.9 mm, \( p < 0.001 \)) (Figure 5.4), shifted the tibia distally (mean 0.5 mm, \( p < 0.05 \)), and shifted the tibia laterally (mean 0.9 mm, \( p < 0.001 \)) (Figure 5.5). Significant differences were seen in intercept between all three timepoints for tibial adduction (mean between baseline and 6 months, -7.8 deg, \( p < 0.001 \)), and differences were seen in intercept between 6 months and other timepoints for tibial internal rotation (mean -2.2 deg, \( p < 0.01 \)). For the number of participants studied, no significant differences were observed for patellar flexion.

The mean total WOMAC score preoperatively was 49.6 (SD 16.4), and was significantly decreased (indicating an improvement in clinical outcome) at 6 months (28.2 (SD 16.6), \( p < 0.001 \)) and 12 months (22.5 (SD 14.4), \( p < 0.001 \)). There was no significant difference between the 6 and 12 month results (\( p = 0.34 \)). The same pattern was observed for all sub-scores (\( p < 0.01 \) between baseline and either follow-up, no significant difference (\( p = 0.28 \) to 0.55) between 6 and 12 months; Table 5.2).

Table 5.2: WOMAC results for all time points.
Mean model (SE), including sub scores. * indicates statistical difference compared to pre-op values with \( p \leq 0.01 \). No statistical difference between 6 month and 12 month follow-ups (\( p = 0.28 \) to 0.55).

<table>
<thead>
<tr>
<th>Time</th>
<th>Pain</th>
<th>Stiffness</th>
<th>Daily Activities</th>
<th>Total WOMAC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-op</td>
<td>9.3 (0.8)</td>
<td>4.6 (0.5)</td>
<td>35.8 (3.2)</td>
<td>49.6 (4.2)</td>
</tr>
<tr>
<td>6 months</td>
<td>5.9 (1.2) *</td>
<td>2.8 (0.6) *</td>
<td>21.6 (3.8) *</td>
<td>28.2 (5.1) *</td>
</tr>
<tr>
<td>12 months</td>
<td>4.5 (1.2) *</td>
<td>3.2 (0.5) *</td>
<td>17.2 (3.7) *</td>
<td>22.5 (5.0) *</td>
</tr>
</tbody>
</table>
### Table 5.3: Mixed linear model results.

β₀ is the constant term, β₁ is the linear term, and β₂ is the quadratic term (if included in model) for the pre-operative results. β₃ is the difference in the constant term between two timepoints (PREOP = pre-operative, 6MOS = 6 month follow-up, 12MOS = 12 month follow-up). β₄ is the difference in the linear term between two timepoints (if timepoint by linear term was included in model), and β₅ is the difference in the quadratic term between two timepoints (if timepoint by quadratic term was included in model). The term u₁j (individual slope) was included in the model for all parameters except patellar flexion and patellar spin. Mean and standard error of model values; units of mm or deg depending on parameter; * p =< 0.05, ** p =< 0.01, *** p =< 0.001.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>β₀ (intercept)</th>
<th>β₁ (knee_angle)</th>
<th>β₂ (knee_angle²)</th>
<th>β₃ (difference in intercept)</th>
<th>β₄ (difference in knee_angle)</th>
<th>β₅ (difference in knee_angle²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patellar flexion [deg]</td>
<td>-10.81 (2.21)***</td>
<td>0.75 (0.01)***</td>
<td>not included</td>
<td>0.55 (0.54)</td>
<td>-10.8 (0.01)***</td>
<td>not included</td>
</tr>
<tr>
<td>Patellar spin [deg]</td>
<td>4.78 (1.31)***</td>
<td>0.02 (0.01)</td>
<td>not included</td>
<td>-1.70 (0.51)***</td>
<td>-1.64 (0.02)</td>
<td>-1.04 (0.57)</td>
</tr>
<tr>
<td>Patellar tilt [deg]</td>
<td>8.53 (1.75)***</td>
<td>0.16 (0.05)***</td>
<td>-0.002 (0.001)***</td>
<td>1.08 (0.02)***</td>
<td>0.66 (0.02)</td>
<td>0.92 (0.63)</td>
</tr>
<tr>
<td>Patellar proximal translation [mm]</td>
<td>30.47 (2.02)***</td>
<td>-0.74 (0.03)***</td>
<td>0.003 (0.000)***</td>
<td>-6.28 (0.54)***</td>
<td>-1.08 (0.02)</td>
<td>-1.10 (0.57)</td>
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<tr>
<td>Patellar anterior translation [mm]</td>
<td>15.74 (1.44)</td>
<td>-0.02 (0.02)</td>
<td>not included</td>
<td>0.70 (0.20)***</td>
<td>0.66 (0.02)</td>
<td>0.92 (0.63)</td>
</tr>
<tr>
<td>Tibial adduction [deg]</td>
<td>13.25 (2.09)***</td>
<td>0.18 (0.06)***</td>
<td>-0.004 (0.001)***</td>
<td>-7.85 (1.08)***</td>
<td>-3.08 (0.02)</td>
<td>-4.78 (1.16)***</td>
</tr>
<tr>
<td>Tibial internal rotation [deg]</td>
<td>2.39 (1.67)</td>
<td>0.05 (0.03)</td>
<td>not included</td>
<td>-5.22 (0.63)***</td>
<td>-0.72 (0.02)</td>
<td>-1.80 (0.65)**</td>
</tr>
<tr>
<td>Tibial proximal translation [mm]</td>
<td>-4.32 (1.20)***</td>
<td>0.12 (0.01)***</td>
<td>not included</td>
<td>-5.05 (0.21)***</td>
<td>-0.46 (0.20)</td>
<td>-0.04 (0.21)</td>
</tr>
<tr>
<td>Tibial lateral translation [mm]</td>
<td>-3.18 (1.15)**</td>
<td>-0.05 (0.01)***</td>
<td>not included</td>
<td>0.94 (0.18)***</td>
<td>0.85 (0.17)</td>
<td>0.09 (0.19)</td>
</tr>
<tr>
<td>Tibial anterior translation [mm]</td>
<td>-15.93 (0.93)***</td>
<td>-0.26 (0.03)***</td>
<td>not included</td>
<td>2.51 (0.40)***</td>
<td>2.54 (0.38)</td>
<td>0.001 (0.001)*</td>
</tr>
</tbody>
</table>

<table>
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<tr>
<th>Parameter</th>
<th>β₀ (intercept)</th>
<th>β₁ (knee_angle)</th>
<th>β₂ (knee_angle²)</th>
<th>β₃ (difference in intercept)</th>
<th>β₄ (difference in knee_angle)</th>
<th>β₅ (difference in knee_angle²)</th>
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<tr>
<td>Patellar flexion [deg]</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Patellar spin [deg]</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Patellar tilt [deg]</td>
<td>-0.01 (0.02)</td>
<td>-0.02 (0.02)</td>
<td>0.01 (0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patellar proximal translation [mm]</td>
<td>0.03 (0.02)*</td>
<td>0.01 (0.01)</td>
<td>0.02 (0.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patellar anterior translation [mm]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial adduction [deg]</td>
<td>-0.18 (0.04)***</td>
<td>-0.08 (0.04)*</td>
<td>-0.09 (0.05)*</td>
<td>0.002 (0.001)***</td>
<td>0.001 (0.001)</td>
<td>0.001 (0.001)*</td>
</tr>
<tr>
<td>Tibial internal rotation [deg]</td>
<td>0.02 (0.03)</td>
<td>-0.02 (0.03)</td>
<td>0.04 (0.03)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial proximal translation [mm]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial lateral translation [mm]</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tibial anterior translation [mm]</td>
<td></td>
<td></td>
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</tbody>
</table>
Figure 5.2: Effect of opening-wedge high tibial osteotomy on tibial anterior translation with knee flexion.
Data points for all participants at all three time points, and mean models. Mean difference at extension of 2.6 mm (p < 0.001).

Figure 5.3: Effect of opening-wedge high tibial osteotomy on patellar proximal translation with knee flexion.
Data points for all participants at all three time points, and mean models. Mean difference at extension of -2.2 mm (p < 0.001).
Figure 5.4: Effect of opening-wedge high tibial osteotomy on patellar lateral translation with knee flexion. Data points for all participants at all three time points, and mean models. Mean difference at extension of 0.9 mm ($p < 0.001$).

Figure 5.5: Effect of opening-wedge high tibial osteotomy on tibial lateral translation with knee flexion. Data points for all participants at all three time points, and mean models. Mean difference at extension of 0.9 mm ($p < 0.001$). For plots of other kinematic parameters, see Appendix C.1.
5.4. Discussion

We sought to determine how an opening-wedge high tibial osteotomy changes three-dimensional tibiofemoral and patellofemoral kinematics in loaded flexion in patients with varus deformity, to better understand how the procedure changes joint mechanics. High tibial osteotomy shifted the tibia anteriorly, distally, and laterally, and abducted it. High tibial osteotomy shifted the patella distally and laterally, and rotated it in lateral spin and medial tilt. We observed changes caused by high tibial osteotomy that cannot be assessed from standing frontal radiographs.

Our finding of a reduction in WOMAC score from 49.6 to 22.5 after 1 year is consistent with a previous finding of a decrease in WOMAC score from 51.9 to 20.0 after opening-wedge high tibial osteotomy patients at one year post-op.

Our finding that high tibial osteotomy abducted the knee is consistent with the objective of the surgery because our measure of tibial adduction is related to (but may not be identical to) the anatomical varus angle as measured on standing-film radiographs, due to the use of the different anatomical landmarks and the non-orthogonal joint coordinate system. We saw an abduction of 7.9 degrees at 6 months, which is consistent with the surgical goal of approximately 8° to 10° correction. The loss of correction (varus change) of 4.8 degrees between 6 and 12 months is somewhat surprising, although previous work in opening-wedge high tibial osteotomy has shown that in patients with an initial mean valgus correction of 10.5 degrees (at 10 days post-op), a loss of correction (varus) of 1.5 degrees was observed at 12 months post-op, and an additional loss of correction (varus) of 2 degrees was observed at 10 to 13 years follow-up.

Our finding that high tibial osteotomy shifted the tibia anteriorly may be clinically important. This anterior tibial shift may be undesirable because the associated shift in contact centers on the tibia may cause high forces on regions of the joint surface that are not adapted to these levels. Anterior tibial shift after HTO is thought to be related to an increase in tibial slope. Increased posterior slope may also lead to increased tension or strain in the anterior cruciate ligament (ACL), but may be advantageous as a compensation for missing posterior cruciate ligaments.
In our participants, the measured anterior translation is not due to a substantial change in tibial slope: strict protocols were employed to control tibial slope and intraoperative fluoroscopy confirmed that high tibial osteotomy changed tibial slope by less than 3 degrees. We hypothesize that the anterior translation of the tibia that we observed in this study is related to an increase in the distance between the tibial tuberosity and the tibial plateau combined with limited length change in the extensor mechanism. It is unclear whether the anterior translation seen in our study is also associated with changes in contact centers and loads in the cruciate ligaments in the absence of a change in tibial slope.

Our finding that opening-wedge high tibial osteotomy shifted the patella distally is consistent with a static radiographic study, which found an average 14% distal patellar translation at 30 degrees of flexion that is virtually identical to our measure of distal patellar translation at 30 degrees. Patella infera secondary to shortening of the patellar tendon has caused problems when converting to total knee replacement in closing-wedge osteotomy patients. In an opening wedge osteotomy, with internal fixation the cause of distal patellar movement is likely a geometrical change (shift of the tibial tuberosity relative to the tibial plateau) rather than a change in the length or stiffness of the tendon. It is not clear what effect this will have on conversion to total knee arthroplasty but successful total knee arthroplasty has been described following an opening wedge HTO.

Our findings of decreased proximal translation (-2.7 mm at 6 months), increased medial tilt (+2.6° at 6 months) and decreased medial spin (-1.7° at 6 months) at the patella are consistent with findings of -1.5 mm proximal translation, +1.7° medial tilt, and -1.6° medial spin with 7° anatomical valgus osteotomy observed in an ex vivo study. It is unclear what clinical effect these kinematic changes may have on the patellofemoral joint, although the changes produced by high tibial osteotomy are of a similar magnitude (2.25 mm) to the difference in patellar lateral translation that was associated with a clinical difference between patellofemoral pain and control groups.

One advantage of our study is that assessments were made through a substantial range of loaded knee flexion, therefore the results are more likely to reflect physiological activity than images taken at a single pose of the knee. A second advantage is that
all components of tibiofemoral and patellofemoral motion were measured, which has allowed us to find changes in knee kinematics that would not be measured with standard radiographic views. A final advantage is that the accuracy and repeatability of the measurement is well characterized. Accuracies for this method in the tibiofemoral joint have not been published, however unpublished work has shown mean errors in tibiofemoral kinematic parameters of 0.85°/0.76 mm or less compared to Roentgen stereophotogrammetric analysis.\textsuperscript{279} Except for tibial proximal translation and the first follow-up of patellar lateral translation, changes due to high tibial osteotomy are larger than expected accuracies for this method\textsuperscript{266,279}.

Limitations of this study include the static nature of the individual rapid scans and the sub-weightbearing loads applied, however as the pre- and post-operative data were collected the same way, the comparison is consistent and the changes observed can be directly related to high tibial osteotomy. While the statistical models generally show that changes in joint angle and position remain consistent through the tested range of flexion, patterns were different in some subjects, and particular kinematic parameters showed more or less variability in pattern between subjects. All of our participants were male, which was not a part of the study design, but reflects the higher proportion of male patients undergoing high tibial osteotomy\textsuperscript{280}.

Opening-wedge high tibial osteotomy changes both tibiofemoral and patellofemoral kinematics in ways that cannot be assessed using conventional radiology. These changes may be related to clinical success of the procedure, and identifying these relationships may lead to improved success of high tibial osteotomy in the future.
Chapter 6. Do dynamic-based MR knee kinematics methods produce the same results as static methods?

6.1. Introduction

In vivo measurement of knee joint kinematics or tracking can be useful in studying disorders at both the patellofemoral and tibiofemoral joints, such as osteoarthritis\textsuperscript{267,281}, patellofemoral pain\textsuperscript{278,282}, or ACL injury\textsuperscript{283}. The primary functions of the knee are to allow movement and transmit load, and a primary aim of surgery is to restore movement and load transmission to normal when these have been disrupted by injury or disease. Load has not been measured directly in vivo in natural joints, but joint movement has. Assessing how joint movement is affected by injury or disease, and how effectively it has been corrected, is of substantial interest for improving joint health.

Knee kinematics have been measured in vivo using MR\textsuperscript{266,284,285}, CT\textsuperscript{286}, fluoroscopy, RSA and combinations of these\textsuperscript{287,288}, optical tracking of markers fixed to bone pins\textsuperscript{289} and molded patellar clamps\textsuperscript{290}. Methods using ionizing radiation and invasive bone pins or fiducial markers have greater potential risks and discomfort for research participants than MR-based methods.

Since the knee’s primary functions are to move in three dimensions and transmit substantial loads, it makes sense that kinematics should be assessed in three dimensions while the joint is loaded physiologically and moving at a physiological rate, as is done in clinical tests of joint function. However, in most studies of knee kinematics compromises have been made. 2D dynamic MR methods\textsuperscript{291-293} obtain kinematic information from one slice at a particular flexion angle, which can be problematic because the relationship between 2D measures and 3D kinematics will depend on slice position and orientation, and patient position\textsuperscript{294}. Differences between static and dynamic 2D measures have been documented for MR and other

\footnote{A version of this chapter has been published as: Agnes G. d'Entremont, Jurek A. Nordmeyer-Massner, Clemens Bos, David R. Wilson, Klaas P. Pruessmann. “Do dynamic-based MR knee kinematics methods produce the same results as static methods?” Magnetic Resonance in Medicine. 2013, 69(6): 1634-44, used with permission from John Wiley and Sons.}
modalities\textsuperscript{286,291,293}, but comparisons between 3D static and dynamic MR measures have not been made. 3D dynamic MR knee kinematics methods based on cine-phase contrast (cine-PC) or fast-PC imaging have been developed\textsuperscript{295,298}. These methods rely on one sagittal image with velocity encoding in three directions, integrated to obtain positions. Subjects are required to repeat the motion as accurately as possible over one or more minutes assisted by an audible beat. While physiological rates of motion (35 cycles per minute) can be captured with an accuracy that is sufficient to detect clinically relevant changes using these methods, the requirement for careful repetition and large number of cycles required may limit both the loading possibilities and the application in populations with pain or injury. A critical limitation in the context of our research question is that cine-PC methods rely on velocity data for positional information, and velocity is zero in static images. Therefore cine-PC methods are unable provide direct comparisons between static and dynamic results. Many three-dimensional \textit{in vivo} assessments of MR kinematics utilize sequential static images acquired over the range of motion\textsuperscript{266,284,285}, however it is unclear how well sequential static postures represent continuous motion of the knee.

The objective of this study was to compare the 3D kinematic results approximated from a series of sequential static poses of the knee with the 3D kinematic results obtained from continuous dynamic movement of the knee. In order to accomplish this objective, we compared kinematic data from a validated static MR method to a fast static MR method, and compared kinematic data from both static methods to a newly developed dynamic MR method.

6.2. Methods and materials

We compared 3D knee kinematics measured using a new MR dynamic method to two versions of a sequential static MR method in ten normal volunteers (7 right and dominant knees, 3 left and non-dominant knees, 8 males, ages 28-40 (mean 31), height 179.8 cm (+/- 9.3 cm)). Volunteers were excluded if they had any MR contraindications, and dominant knees were always scanned unless they had a history of knee injury involving ambulatory aids or knee surgery, in which case the healthy non-dominant knee was imaged. All volunteers gave written informed consent, and the study was conducted according to institutional ethics guidelines.
6.2.1. Imaging

All imaging was done on a Philips Achieva 3T scanner. All knees were imaged using a novel stretchable 8-channel knee coil array which permits knee flexion while maximizing the signal-to-noise ratio (SNR) independently of the knee size and shape (Figure 6.1 (a)). The high-resolution scan of each knee was performed to obtain detailed subject-specific anatomical information (Table 6.1). To produce loaded flexion, a MR-compatible loading rig was created that allowed free leg motion with a force of 8% body weight applied in the ankle-hip direction (Figure 6.1 (b) and (c)). Foam wedges supported the thigh during scanning. A fast imaging protocol based on a commercially available ultrafast gradient echo sequence with water suppression for increased contrast (Table 6.1) was developed to image the knee in continuous motion (dynamic). To test whether this sequence produced different kinematic results, it was used to obtain images of static poses (static fast) and compared to the standard sequence (static standard). Three sets of images were taken in loaded flexion: static standard (16 slices, 2D TSE, 23 seconds), static fast (8 slices, ultrafast gradient echo, 1.9 seconds) and dynamic (30 sets, 8 slices each, ultrafast gradient echo, 56 seconds) (Table 6.1). The two types of static scans were performed together at each of six flexion angles, for a loaded time at each angle of about 40 seconds (including a short system delay between scans), after which the weight was removed and the subject was repositioned. Total time taken for all static scans, including positioning, reference scans, and scan planning, was about 30 minutes. The dynamic scan was performed following six pairs of static scans. Angles for the static scans were chosen to cover the same flexion range as the dynamic scan. The subject was asked to move very slowly during the dynamic scan, but no specific rate of motion was required. Thirty temporal sets of dynamic scans were acquired, each taking 1.9 seconds, with no interpolation.
Figure 6.1: Stretchable knee coil and loading rig.
(a) Stretchable eight-channel knee coil array. (b) Schematic of loading rig with free floating pedal attached to foot with two straps, and attached with rope on either side of the ankle joint through pulleys to hanging weight. A range of foam wedges were used to support the thigh during static imaging, with the largest of these wedges supporting the thigh as the lower leg was flexed and extended dynamically. (c) Photo of loading rig on scanner bed.
### Table 6.1: MRI sequence parameters.

<table>
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<th>High Resolution</th>
<th>Static Standard</th>
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<td>TSE</td>
<td>TFE</td>
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<td>256 x 256</td>
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<td>320 x 320</td>
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<tr>
<td><strong>Slices</strong></td>
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<td>8 x 30 sets</td>
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<td>1.00 x 1.00 x 5</td>
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<td>320 x 320</td>
<td>320 x 320</td>
<td>320 x 320</td>
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<td><strong>TR (ms)</strong></td>
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<td>650</td>
<td>2.4</td>
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<tr>
<td><strong>TE (ms)</strong></td>
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<td>1.20</td>
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</tr>
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<td>90</td>
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<td>15</td>
</tr>
<tr>
<td><strong>Slice gap (mm)</strong></td>
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<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td><strong>Total coverage (mm)</strong></td>
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<td><strong>Scan time</strong></td>
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<td><strong>TSE/TFE factor</strong></td>
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<td>86</td>
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<td>1</td>
<td>1</td>
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</tbody>
</table>

#### 6.2.2. Image Processing

Bone models were generated and coordinate systems were defined in them, and they were then registered to the loaded flexion positions from which kinematics were calculated (Figure 6.2). All three knee bones were segmented manually from the high-resolution image using Analyze (Mayo Clinic, MN) by one experienced operator to create bone models. Anatomical axes for each bone were defined in the high-resolution models following our established protocol\textsuperscript{265,266}. Positive patellar rotations were defined as follows: patellar flexion entailed the superior patellar edge rotating anteriorly; patellar tilt entailed the medial patellar edge rotating posteriorly; and patellar spin entailed the superior patellar edge rotating medially. Due to the somewhat reduced useable field of view along the leg (a function of the extent of the knee coil), the definition of the long axes of the tibia and femur were altered from the original method (origin to the most superior centroid of the femur shaft or to the most inferior centroid of the tibia shaft) to a direction along the centroids at 25% and 5% from the visible superior end of the femur shaft or the visible inferior end of the tibia shaft. The bone models were then registered to each low-resolution set (static standard, static fast, dynamic) using an iterative closest points algorithm\textsuperscript{268}. Finally, translations and rotations for the tibia and patella were calculated with respect to the femur\textsuperscript{300}. 
6.2.3. Data analysis

We assessed whether the new fast sequence, used for static postures, changed the measured kinematics relative to the standard sequence used for static postures using the Bland-Altman method for multiple observations per subject. The Bland-Altman, or Limits of Agreement, method is used to compare the results of two different measurement methods to determine if they are sufficiently similar to be able to use one method in place of the other. The method used accounted for within-person correlation due to multiple measures at different knee angles per subject. Linear correlations on the limits of agreement plots were performed with standard error estimates allowing for clustering by subject (using a Huber-White sandwich estimator). Assessing the correlation helps to identify if differences between methods change systematically over the range of the value measured.

We assessed whether there was a difference between static standard, static fast and dynamic images. We tested the null hypothesis that there was no difference between the three conditions using a linear mixed-effects model. This statistical test is the most appropriate and accurate for repeated-measures or nested data, particularly with fixed effects (knee angles) that are unequal between subjects. The general principle of the method is to apply individual regression models to each subject and condition, then compare between conditions (within person comparison). The general model was:
\[ y_{ij} = \beta_j + \beta_j \ast \text{knee\_angle} + \beta \ast \text{knee\_angle} + \beta \ast \text{condition}_i + \beta \ast \text{knee\_angle} \ast \text{condition}_i \]  

Equation 6.1

where \( y \) is any one of the 11 kinematic parameters, \( j = 1 \) to \( 10 \) (individuals) and \( i = 1, 2, 3 \) (conditions). Knee angles were obtained from 3D models. Condition 1 was dynamic (coefficients \( \beta_0, \beta_1, \beta_2 \)), condition 2 was static fast (add \( \beta_3, \beta_4, \beta_5 \) for condition 2), and condition 3 was static standard (add \( \beta_3, \beta_4, \beta_5 \) for condition 3).

Individuals (\( j \)) were allowed to vary in both intercept and slope from the mean:

\[ \beta_{0j} = \gamma_0 + u_{0j} \]  

Equation 6.2

\[ \beta_{1j} = \gamma_1 + u_{1j} \]  

Equation 6.3

where Equation 6.2 represents intercept, and Equation 6.3 represents slope; \( \gamma \) is the mean value for all subjects, and \( u \) is the value for individual subjects.

The quadratic terms (\( \beta_2, \beta_3 \), \( u_{1j} \) (part of \( \beta_1 \)) and \( \text{knee\_angle}\ast\text{condition} \) (\( \beta_4 \)) were included when they improved the model (as compared to the linear model) as determined by lowering the Bayesian information criterion (BIC), which indicates quality of fit but penalizes for extra terms in the model. Statistical analyses were performed using Stata 10.1 (StataCorp, Texas).

Observations were made from comparisons of the varying position of the slice stack and direction of motion, but since these were not the designed outcomes of the study, statistical analysis was not performed. We observed the effect of slice stack position within the knee on the kinematic results. Static fast images with 16 slices (87.3 mm coverage) were obtained in a relaxed position for four subjects (7 through 10). The images were segmented and then nine subsets of eight slices each were used to compare to the kinematic results from the full 16-slice set.

Repeated dynamic cycles with turnaround points removed were used to calculate intraclass correlation (ICC) results (from linear mixed-effects models) as an estimate of repeatability.
6.3. Results

Subjects performed between two and four dynamic flexion-extension cycles (mean 2.75 (SD 0.7) cycles) in the 56 second scan time, for an average rate of motion of 0.9 (SD 0.2) degrees/sec (range 0.6 to 1 degrees/sec). Tibial flexion for all subjects ranged between a mean lowest flexion angle of 8.1 (SD 2.5) and mean highest flexion angle of 29.1 (SD 3.5) degrees (overall range 4.2 to 36.4 degrees). Sample images are presented in Figure 6.3.

Bland-Altman analysis, evaluating the agreement between the static fast and static standard sequences, resulted in overall mean differences of 0.15 degrees and 0.36 mm (Table 6.2), and average ranges of limits of agreement of +/- 2.07 degrees or +/- 1.09 mm. Through-plane translations showed the largest ranges of limits of agreement for translations (patellar lateral translation at +/- 1.4 mm, and tibial lateral translation at +/- 1.7 mm). Rotations out of the plane (patellar spin, patellar tilt, tibial adduction and tibial internal rotation) had the largest ranges of limits of agreement and three out of four had the lowest p values in the linear regression. Significant correlations (trends) between differences in each kinematic measure and mean measure were found for patellar tilt and tibial adduction (Figure 6.4). Linear regression on the Bland-Altman plots showed a change in difference between the two static methods of 1.3 degrees for every 10 degrees of adduction and 0.25 degrees for every 10 degrees of patellar tilt over the range measured. The limits of agreement obtained using correct standard error estimates for multiple comparisons were a mean 1.9% (SD 0.7%) larger in range than those obtained by assuming independent observations.

Our findings indicate that 3D dynamic kinematic results are different from static results. We found significant kinematic differences between dynamic imaging and both types of static imaging (static fast and static standard) for eight out of 11 kinematic parameters: patellar flexion, patellar tilt, patellar proximal translation, patellar lateral translation, patellar anterior translation, tibial adduction, tibial internal rotation, tibial anterior translation (Table 6.3, Figure 6.5). All of the included slope and quadratic terms show differences between dynamic and both static results, and no differences between the static results. Tibial proximal translation and tibial lateral translation showed differences in intercept between static fast and static
For tibial proximal translation, there was no statistical difference between dynamic and static fast in intercept, but there were differences for slope.

![Sample images from the stretchable knee coil for one subject.](image)

**Figure 6.3:** Sample images from the stretchable knee coil for one subject. High-resolution, and the three types of low-resolution scans (static standard; static fast; and the first 12 of 30 dynamic scans, representing a full motion cycle). The bone edges are discernable on even the low-resolution dynamic images.

At full extension, mean absolute differences between the dynamic and static models with statistically different intercepts were 2.0 mm and 2.9 degrees, and near the
other end of the range (35 degrees) the mean absolute differences between these same models were 1.9 mm and 3.6 degrees. Difference values for patellar flexion, patellar proximal translation, patellar anterior translation, tibial internal rotation and tibial anterior translation were outside of the limits of agreement (upper LOA minus lower LOA, Table 6.2), indicating that they are not likely due to differences between the standard and fast sequences. Difference values for tibial adduction and patellar tilt were not outside the limits of agreement, likely due to the trends leading to larger limits of agreement. Together with the Bland-Altman results, these findings indicate that 3D dynamic kinematic results are different from static results.

**Table 6.2: Bland-Altman results.**

Limits of agreement (LOA) show the upper and lower limits of agreement and the mean difference (bias) in mm or degrees, depending on the parameter. Linear regression shows trend results, with coefficient and standard error in mm or degrees, depending on the parameter, and p-value.

<table>
<thead>
<tr>
<th>Kinematic parameter</th>
<th>Upper LOA</th>
<th>Mean diff.</th>
<th>Lower LOA</th>
<th>Coefficient</th>
<th>SE</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patellar flexion [deg]</td>
<td>1.96</td>
<td>0.44</td>
<td>-1.08</td>
<td>0.01</td>
<td>0.01</td>
<td>0.592</td>
</tr>
<tr>
<td>Patellar spin [deg]</td>
<td>3.65</td>
<td>0.11</td>
<td>-3.43</td>
<td>-0.06</td>
<td>0.09</td>
<td>0.519</td>
</tr>
<tr>
<td>Patellar tilt [deg]</td>
<td>2.45</td>
<td>-0.08</td>
<td>-2.60</td>
<td><strong>-0.03</strong></td>
<td><strong>0.01</strong></td>
<td><strong>0.017</strong></td>
</tr>
<tr>
<td>Patellar proximal translation [mm]</td>
<td>0.65</td>
<td>-0.50</td>
<td>-1.65</td>
<td>-0.01</td>
<td>0.02</td>
<td>0.538</td>
</tr>
<tr>
<td>Patellar lateral translation [mm]</td>
<td>1.54</td>
<td>0.17</td>
<td>-1.21</td>
<td>0.05</td>
<td>0.05</td>
<td>0.346</td>
</tr>
<tr>
<td>Patellar anterior translation [mm]</td>
<td>0.74</td>
<td>0.18</td>
<td>-0.39</td>
<td>-0.02</td>
<td>0.02</td>
<td>0.412</td>
</tr>
<tr>
<td>Tibial flexion [deg]</td>
<td>1.01</td>
<td>0.18</td>
<td>-0.64</td>
<td>0.01</td>
<td>0.01</td>
<td>0.379</td>
</tr>
<tr>
<td>Tibial adduction [deg]</td>
<td>2.05</td>
<td>0.01</td>
<td>-2.02</td>
<td><strong>-0.13</strong></td>
<td><strong>0.04</strong></td>
<td><strong>0.017</strong></td>
</tr>
<tr>
<td>Tibial internal rotation [deg]</td>
<td>2.04</td>
<td>0.06</td>
<td>-1.92</td>
<td>0.05</td>
<td>0.03</td>
<td>0.098</td>
</tr>
<tr>
<td>Tibial proximal translation [mm]</td>
<td>0.42</td>
<td>-0.45</td>
<td>-1.32</td>
<td>0.01</td>
<td>0.05</td>
<td>0.797</td>
</tr>
<tr>
<td>Tibial lateral translation [mm]</td>
<td>1.11</td>
<td>-0.61</td>
<td>-2.33</td>
<td>0.07</td>
<td>0.07</td>
<td>0.339</td>
</tr>
<tr>
<td>Tibial anterior translation [mm]</td>
<td>0.58</td>
<td>-0.28</td>
<td>-1.13</td>
<td>0.00</td>
<td>0.03</td>
<td>0.865</td>
</tr>
</tbody>
</table>

Kinematic parameter values were affected by the position of the stack and the number of slices capturing a particular bone (Figure 6.6). Typically, stacks that were positioned centrally had values close to the full stack, and those with more slices containing a bone also had values closer to the full stack values. For the low-resolution scans, the number of slices containing a particular bone varied between subjects (due to subject size), and within subjects (due to subject position and orientation, and slice stack position).

ICC values for repeated dynamic cycles ranged from 0.840 (95% CI: 0.711, 0.969) for patellar spin, to 0.991 (95% CI: 0.984, 0.999) for patellar anterior translation.
Figure 6.4: Bland-Altman plots of (a) patellar tilt and (b) tibial adduction.
For each subject and flexion angle, the difference between static fast and static standard results has been plotted against the mean of static fast and static standard results. Individual points labeled with subject number (1 to 10); six points per subject. Limits of agreement (LOA) show the upper and lower limits of agreement (95% of points lie within) and the mean difference (bias) in degrees. Trend lines plotted for each parameter. These two parameters were the only ones to have statistically significant trends in difference versus mean. For the plots of the rest of the kinematic parameters, please see Appendix D.1.
Figure 6.5: Selected kinematics results, with data points for ten subjects and mixed-effects models chosen based on lowest BIC for three type of low resolution scans. (a) Patellar flexion, (b) patellar proximal translation, (c) tibial anterior translation, (d) tibial internal rotation, all plotted version tibial flexion (knee flexion angle). (DYN = dynamic, SF = static fast, SS = static standard). For plots of the rest of the kinematic parameters, please see Appendix D.2.
Table 6.3: Mixed linear model results.

\( \beta_0 \) is the constant term, \( \beta_1 \) is the linear term, and \( \beta_2 \) is the quadratic term (if included in model) for the dynamic results. \( \beta_3 \) is the difference in the constant term between two conditions (DYN = dynamic, SS = static standard, SF = static fast). \( \beta_4 \) is the difference in the linear term between two conditions (if condition by linear term was included in model), and \( \beta_5 \) is the difference in the quadratic term between two conditions (if condition by quadratic term was included in model). The term \( u_{ij} \) (individual slope, Equation 6.3) was included in the model for all parameters except patellar spin and tibial internal rotation. Mean and standard error of model values; units of mm or deg depending on parameter; * \( p <= 0.05 \), ** \( p <= 0.01 \), *** \( p <= 0.001 \).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>( \beta_0 ) (intercept)</th>
<th>( \beta_1 ) (knee_angle)</th>
<th>( \beta_2 ) (knee_angle(^2))</th>
<th>( \beta_3 ) (difference in intercept)</th>
<th>( \beta_4 ) (difference in knee_angle)</th>
<th>( \beta_5 ) (difference in knee_angle(^2))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patellar flexion [deg]</td>
<td>-7.63 (1.07) ***</td>
<td>0.51 (0.02) ***</td>
<td>not included</td>
<td>-1.64 (0.50) ***</td>
<td>-1.95 (0.50) ***</td>
<td>0.31 (0.61)</td>
</tr>
<tr>
<td>Patellar spin [deg]</td>
<td>-4.22 (1.22) ***</td>
<td>0.05 (0.02) **</td>
<td>not included</td>
<td>-0.11 (0.28)</td>
<td>-0.21 (0.28)</td>
<td>0.10 (0.36)</td>
</tr>
<tr>
<td>Patellar tilt [deg]</td>
<td>6.85 (3.37) *</td>
<td>0.42 (0.08) ***</td>
<td>-0.008 (0.002) ***</td>
<td>4.08 (0.59) ***</td>
<td>4.14 (0.59) ***</td>
<td>-0.06 (0.71)</td>
</tr>
<tr>
<td>Patellar proximal translation [mm]</td>
<td>39.82 (1.87) ***</td>
<td>-0.80 (0.06) ***</td>
<td>0.000 (0.002) ***</td>
<td>-2.79 (0.89) **</td>
<td>-2.25 (0.90) **</td>
<td>-0.53 (1.01)</td>
</tr>
<tr>
<td>Patellar lateral translation [mm]</td>
<td>-0.78 (1.14)</td>
<td>-0.07 (0.03) *</td>
<td>not included</td>
<td>-3.42 (0.41) ***</td>
<td>-3.72 (0.41) ***</td>
<td>0.30 (0.51)</td>
</tr>
<tr>
<td>Patellar anterior translation [mm]</td>
<td>26.47 (1.10) ***</td>
<td>0.27 (0.03) **</td>
<td>-0.007 (0.001) ***</td>
<td>-0.62 (0.32) *</td>
<td>-0.93 (0.32) **</td>
<td>0.31 (0.36)</td>
</tr>
<tr>
<td>Tibial adduction [deg]</td>
<td>-1.31 (1.33)</td>
<td>0.09 (0.01) **</td>
<td>not included</td>
<td>1.24 (0.12) ***</td>
<td>1.24 (0.12) ***</td>
<td>0.00 (0.15)</td>
</tr>
<tr>
<td>Tibial internal rotation [deg]</td>
<td>-1.98 (2.01)</td>
<td>0.56 (0.13) ***</td>
<td>-0.010 (0.003) **</td>
<td>4.31 (2.11) *</td>
<td>4.66 (2.14) *</td>
<td>-0.36 (2.54)</td>
</tr>
<tr>
<td>Tibial proximal translation [mm]</td>
<td>-7.27 (0.62) ***</td>
<td>0.01 (0.02) *</td>
<td>0.002 (0.000) ***</td>
<td>-0.22 (0.16)</td>
<td>0.40 (0.16) *</td>
<td>-0.62 (0.20)</td>
</tr>
<tr>
<td>Tibial lateral translation [mm]</td>
<td>-4.33 (0.36) ***</td>
<td>-0.09 (0.01) ***</td>
<td>not included</td>
<td>-1.17 (0.10) ***</td>
<td>-0.58 (0.10) ***</td>
<td>-0.60 (0.13)</td>
</tr>
<tr>
<td>Tibial anterior translation [mm]</td>
<td>-14.35 (0.72) ***</td>
<td>-0.39 (0.05) ***</td>
<td>0.004 (0.001) ***</td>
<td>-1.16 (0.37) **</td>
<td>-0.97 (0.37) **</td>
<td>-0.19 (0.46)</td>
</tr>
</tbody>
</table>

\( \beta_0 \) is the constant term, \( \beta_1 \) is the linear term, and \( \beta_2 \) is the quadratic term (if included in model) for the dynamic results. \( \beta_3 \) is the difference in the constant term between two conditions (DYN = dynamic, SS = static standard, SF = static fast). \( \beta_4 \) is the difference in the linear term between two conditions (if condition by linear term was included in model), and \( \beta_5 \) is the difference in the quadratic term between two conditions (if condition by quadratic term was included in model). The term \( u_{ij} \) (individual slope, Equation 6.3) was included in the model for all parameters except patellar spin and tibial internal rotation. Mean and standard error of model values; units of mm or deg depending on parameter; * \( p <= 0.05 \), ** \( p <= 0.01 \), *** \( p <= 0.001 \).
Figure 6.6: Typical result from slice stack analysis.
Patellar proximal translation, difference between subset and full 16-slice stack result (mean and standard deviation for four subjects), plotted (a) versus medial-lateral position (average and standard deviation of parameter difference) and (b) versus number of slices containing patella. Diagrams indicate generalized slice locations for various medial-lateral positions and bone slice numbers. For plots of the rest of the slice stack analysis results, please see Appendix D.3.

6.4. Discussion

In this paper we directly compared knee kinematic results from a dynamic 3D method in MR to kinematics obtained from a series of static poses. We found that the dynamic results are, in most cases, different from both static standard and static fast. In addition to the expected axial plane differences in patellar lateral translation and patellar tilt from the literature, differences between static and dynamic results were seen in kinematic parameters in all planes and both joints. The finding that there are differences between 3D kinematics for static and dynamic conditions is important because it suggests that static imaging does not provide a complete reflection of joint position and orientation during physiologic activity. Differences in pathological joints may be larger.
Range of motion is limited by scanner bore size and subject limb segment length (related to subject height). The range of motion obtained in this study is similar to that of Seisler et al. (35 degrees attained by 30% or more of subjects) and Barrance et al. (25 degrees), who had smaller mean subject heights (172.3 cm and 178 cm respectively, compared to 179.8 cm in this study)\textsuperscript{297,303}. The range of motion was not limited by the stretchable coil.

The Bland-Altman analysis indicates that differences between static and dynamic results are likely not due to the new fast sequence, but are instead due to differences in motion. Previous work indicates that the biases and limits of agreement found in our study show agreement between the static fast and static standard methods. Intrasubject variability (repeatability, grand mean error) using a static standard scan (as measured \textit{in vivo} for the patellofemoral joint) was found to be 0.30 to 1.75 degrees and 0.47 to 0.88 mm, depending on the parameter\textsuperscript{266}, which is larger than the mean biases seen here. Significant differences in patellar flexion (7.5 deg), patellar spin (6.4 deg), patellar proximal translation (8.8 mm), and patellar anterior translation (6.6 mm) using the static standard method have been seen between populations with varus and valgus malalignments and knee osteoarthritis\textsuperscript{267} - with the exception of patellar spin, the values are outside the limits of agreement in this study (upper LOA minus lower LOA). Differences in anterior translation between knees in ACL-injured non-copers has been found to be 2.6 to 3 mm depending on knee angle\textsuperscript{303}, which is outside the limits of agreement in this study. Together these results suggest that differences seen with actual motion are likely not related to the fast sequence, and that clinically relevant differences may be detected. Out of plane rotations may be most affected by the more limited coverage in the medial-lateral direction in the static fast scans, resulting in larger limits of agreement and trends (patellar tilt and tibial adduction). In normal subjects, tibial adduction for activities of daily living ranges within -2.2 to 10.0 degrees\textsuperscript{304}, and patellar tilt ranges from 12.5 to 19.2 degrees in supine extension from 40 degrees\textsuperscript{297}. Therefore with the trends observed, the largest differences between the two static methods over a range of motion in normal activities are 1.1 degrees for tibial adduction and 0.3 degrees for patellar tilt, which are still in the range of the grand mean error of the original method.
Our findings that 3D dynamic kinematic results are different from static results are consistent (pattern of change) with those seen in 2D measures of patellar lateral displacement and patellar tilt angle in both MR\textsuperscript{291,293} and CT\textsuperscript{286} (Figure 6.7). Actual values of 3D dynamic kinematic parameters (both patellar and tibial) are consistent in range and pattern with those measured in normals with a cine-PC/fast-PC method by Seisler and colleagues\textsuperscript{297} except for tibial proximal translation (pattern, range) and tibial anterior translation (range) (Table 4). These differences in tibial translations may be attributed to differences in the tibial origin location (tibial tubercule rather than the most superior point of the tibial spines in the current study). Barrance and colleagues, using another cine-PC method, show similar results to our dynamic results in control subjects for tibial anterior translation and tibial internal rotation, the only parameters reported\textsuperscript{303} (Table 4). Actual values of 3D static PF kinematic parameters are similar to those measured by Fellows and colleagues\textsuperscript{265}, and the normal subjects from MacIntyre and colleagues\textsuperscript{278} (with only patellar lateral translation having a different pattern) (Table 4). Patel and colleagues normalized for size in their 3D PF kinematic data; patellar spin was consistent, and patellar tilt (pattern and range) and patellar proximal translation (pattern) were slightly different\textsuperscript{305}. Patel et al. normalized for size, and shifted full extension values to 0 mm or degrees in their 3D TF kinematic data; patterns and ranges for parameters are consistent for tibial anterior translation, and tibial lateral translation, while the patterns of tibial internal rotation and tibial adduction were different\textsuperscript{284} (Table 6.4). It is known that the range of normal values in patellar kinematics is wide\textsuperscript{306}. The range of values of tibial kinematics is also wide in this study, for example tibial internal rotation has an average range of values of 25.6 degrees over the three types of low-resolution scans (23.2 - 29.3 degrees). This is consistent with Seisler and colleagues, where +/- 2 SD at a representative flexion angle containing data from all subjects gives a range of 25.6 degrees\textsuperscript{297}. Some of the differences noted may be related to the range of motion available in this study, and the consequent model shape fit to the data (e.g. linear model fits slightly quadratic data well over some ranges). There are also differences in types and magnitudes of loading between studies, which may affect results\textsuperscript{307}. Differences in results may also be attributed to differences in the definition of bone coordinate systems, as mentioned above, which are known to affect results\textsuperscript{308}. 


It is not surprising that, compared to the results from 16 slices of static fast, eight slice sub-sets of static fast images showed varying values of kinematic parameters depending on number of slices capturing bone (especially for patella) and position of slice stack in medial-lateral direction (e.g. centered or off centre). The ideal position of the slice stack has been shown to be centered medial-lateral on the knee, especially covering the patella completely. It is likely that the central position provides information from the tibial and femoral shafts, which more accurately orients those bones in space, and the patella, having fewer distinct landmarks, produces a better result when a maximum of information is provided.

While the estimate of repeatability (ICC) calculated using repeated dynamic cycles for each subject is not an overall measure of repeatability for the method, it does indicate that the procedure from imaging to data analysis has sufficient repeatability to address clinically relevant research questions. Patellar spin had the lowest ICC at 0.840, and is often found to be quite variable. All other ICCs were at or above 0.925 (see Table D.1).

Strengths of the method include allowing subjects to use a self-selected rate of motion, collecting all data in two to four cycles, and obtaining more data points in a shorter time than static methods which all may reduce subject burden. We could alternately have subjects move at a specific rate by providing audible or visual feedback. It is possible to apply the same methodology using cine images in place of ultrafast gradient echo images and obtain higher rates of motions (similar scan time, similar flexion angle number). We may be able to apply loads closer to those seen in activities of daily living, due to the short scan time. Studies comparing load magnitudes and types have found significant differences in several kinematic parameters with changes in loading. Strengths of this study include making a direct comparison to validated static method, studying a clinically important range of motion (for example, patellar subluxation is associated with lateral translation of the patella in the first 20 degrees of knee flexion), and loading the joint, which provides a mechanical environment closer to that of daily activities.
Figure 6.7: Comparison with 2D static and dynamic results. Comparison plot between 2D passive (static) and dynamic MR results from Brossmann and colleagues\textsuperscript{293}, and 3D static and dynamic results from the current study for (a) patellar tilt and (b) patellar lateral translation.
Table 6.4: Ranges of kinematic parameter values: comparison to published values.
Results from this and other 3D MR kinematics studies (static and dynamic). Selected 25 degree ranges of tibial flexion were compared based on range available in current study and range available in study from literature. All reported parameters included.  (DYN = dynamic, SS = static standard)

<table>
<thead>
<tr>
<th>Static</th>
<th>Static</th>
<th>Static</th>
<th>Static</th>
<th>Static</th>
<th>Static</th>
</tr>
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<tbody>
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<td>n = 20</td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 10</td>
<td>n = 1</td>
</tr>
<tr>
<td>Tibial flexion range</td>
<td>10° to 35°</td>
<td>10° to 35°</td>
<td>10° to 35°</td>
<td>10° to 35°</td>
<td>5° to 30°</td>
</tr>
<tr>
<td>Patellar flexion [deg]</td>
<td>17.8</td>
<td>14.9</td>
<td>17.8</td>
<td>15</td>
<td>12.8</td>
</tr>
<tr>
<td>Patellar spin [deg]</td>
<td>1.3</td>
<td>1.5</td>
<td>1.9</td>
<td>1.3</td>
<td>5</td>
</tr>
<tr>
<td>Patellar tilt [deg]</td>
<td>-3.8</td>
<td>2.5</td>
<td>0.8</td>
<td>-1.8</td>
<td>-3</td>
</tr>
<tr>
<td>Patellar proximal translation [mm]</td>
<td>-16.6</td>
<td>-16.9</td>
<td>-11.0</td>
<td>-18.9</td>
<td>-12</td>
</tr>
<tr>
<td>Patellar lateral translation [mm]</td>
<td>2.0</td>
<td>-1.6</td>
<td>2.0</td>
<td>2</td>
<td>-1.8</td>
</tr>
<tr>
<td>Patellar anterior translation [mm]</td>
<td>-3.0</td>
<td>-0.7</td>
<td>0.0</td>
<td>-4</td>
<td>0.6</td>
</tr>
<tr>
<td>Tibial adduction [deg]</td>
<td>2.3</td>
<td>-3.2</td>
<td>2.3</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Tibial internal rotation [deg]</td>
<td>2.9</td>
<td>2.7</td>
<td>5.3</td>
<td>4.4</td>
<td>5.0</td>
</tr>
<tr>
<td>Tibial proximal translation [mm]</td>
<td>3.3</td>
<td></td>
<td>2.0</td>
<td>-9.2</td>
<td></td>
</tr>
<tr>
<td>Tibial lateral translation [mm]</td>
<td>-2.3</td>
<td>-1.0</td>
<td>-2.3</td>
<td>-5.1</td>
<td></td>
</tr>
<tr>
<td>Tibial anterior translation [mm]</td>
<td>-7.0</td>
<td>-8.0</td>
<td>-6.3</td>
<td>-19.6</td>
<td>-5.0</td>
</tr>
</tbody>
</table>
A limitation of this study was that static positions differ from dynamic positions (different hip flexion at same knee flexion angles), due to the technical and practical requirements of static and dynamic scanning. There were several indications that the effect of this difference may be small. For one subject, there was little observable difference between the static and dynamic scans. For all subjects, the most flexed position in both static and dynamic is the same position; however these did not typically produce the same values. 2D studies have seen similar differences between static and dynamic kinematics. Together this indicates that the differences seen between static and dynamic results are likely due to movement. While we do not have a direct assessment of accuracy, larger or smaller standard error (noise) in the dynamic results is unlikely to influence the overall conclusions of the study, which is that dynamic and static kinematic results are different. While we were able to apply an axial load to the leg during imaging, the load magnitude was much smaller than that expected in activities of daily living. A limitation of this method was that we are currently restricted to slow motion (20 sec per cycle compared to 1.7 sec per cycle for cine-PC/fast-PC\textsuperscript{297}) however we saw similar differences between static and dynamic measures as those from Brossmann and colleagues with about 1.3 sec per cycle\textsuperscript{293}. It is likely that moving into a position under load requires different muscle activation than being placed in position and subsequently loaded, which results in different kinematics. Our subjects moved at self-selected rates of motion, which introduces potential variability. The similarity with Brossmann’s work at higher rate of motion seems to indicate that the differences between rates of motion would not affect the overall conclusions of the study.

A further limitation of the study is that the stretchable knee coil may alter patellar kinematics. Since it is not designed to medialize the patella (as in many knee sleeves and braces), and our subjects did not have any diagnosed PF disorders, the effect may be different from the changes reported in the literature, namely the patella being more medial, more posterior, and having more positive medial tilt with a brace\textsuperscript{310–315}. [For test results using two subjects repeated with a dual array surface coil, see Appendix D.5.]
While we have assessed the agreement of the new sequence with measurements from a validated method, rather than a direct assessment of accuracy, the size of the limits of agreement and the magnitudes of clinically important differences in the literature imply that the static fast/dynamic method may be able to detect relevant kinematic differences between populations. McWalter and colleagues found significant differences in patellar flexion, patellar proximal translation, and patellar anterior translation between populations with varus and valgus malalignments and knee osteoarthritis using the static standard method that are outside the limits of agreement in this study. Barrance and colleagues found significant side-to-side differences in tibial anterior position in ACL-injured non-copers with uninjured contralateral knees that are also outside the limits of agreement in this study.

While it has been shown that kinematic measures from a series of static positions can distinguish kinematic features between groups, dynamic scanning has the capability of eliciting distinct information about joint function. The short scan time and few knee cycles required may be beneficial for increasing the load applied to the joint to better represent the typical mechanical environment, reducing the burden on populations with pain or other movement difficulties, and reducing imaging cost.

Further work comparing static and dynamic imaging in joints with documented abnormalities, such as ACL-deficiency or patellofemoral dysmorphism, would be of interest, as the relative differences between the static and dynamic results may vary compared to the healthy normals in this study.

In this study, we have demonstrated the utility of a novel stretchable knee coil for fast imaging of a moving knee, providing images that are acceptable for use in kinematic analysis in a short time, and comfortably allowing flexion. We have shown that a new fast scan provides results that agree with the standard scans for our knee kinematics method, indicating that we can interchangeably use the fast scan for measuring kinematics. We found that 3D MR kinematics measured from dynamic knee motion are often different from those measured in a static knee at several positions, indicating that dynamic kinematics provides information that is not obtainable from static scans.
Chapter 7. Discussion and conclusions

Improving HTO outcomes requires an understanding about the changes, both intended and unintended, to kinematics and cartilage health resulting from the surgery. To obtain this knowledge, specialized methods need to be developed to correct the distortion caused by metal implants near the joint, and to measure knee mechanics in situations that more closely mimic activities of daily living. This thesis presents progress in developing these methods and some answers to some of the fundamental questions about the effect of surgical changes on joint mechanics and the measurement of the results of those changes.

7.1. Contributions and discussion

Metal can affect dGEMRIC results even in areas where many of the images do not appear to be distorted. The application of saturation recovery (SR) and the Metal Artifact Reduction Sequence (MARS), based on View Angle Tilting (VAT), can reduce the extent of the artifact in the T₁ maps, and may allow evaluation of cartilage health near metal that would not be possible with the standard inversion recovery (IR) method. The strengths of this work include the application of several metal artifact reduction strategies both in a phantom and in vivo and the use of a relevant surgical implant. However, we had limited subject numbers, corrected mis-mapping only in the imaging plane, and were only able to evaluate dGEMRIC near a titanium implant, where stainless steel is the clinical standard. This work represents the first exploration of the effect of metal and metal artifact reduction on dGEMRIC results. The methodology presented can be used to evaluate and minimize the effect of metal artifact on dGEMRIC results in a variety of clinical situations with titanium implants, leading to better understanding of the effect of surgical treatments on cartilage health.

HTO does not appear to negatively affect the patella or tibiofemoral cartilage health over one year of follow-up, as measured by dGEMRIC. This is a potentially positive result, as kinematic changes in the patellofemoral and tibiofemoral joints (and cartilage pressure changes) following HTO have been of concern in that they might lead to degeneration. Strengths of this study include using metal artifact reduction techniques and assessing both patellofemoral and tibiofemoral cartilage in a situation
where mechanics changed for both joints. Limitations of this study include having only one 2D slice of cartilage, and the challenges of matching slices between timepoints, limited subject numbers, and elevated outliers. This work is the first examination of patellar cartilage health using dGEMRIC in HTO. While this study showed no overall change in dGEMRIC scores, some individual subjects showed changes in a clinically significant range, particularly decreases in the TF joint at 6 months. These results suggest that the evaluation of a larger sample of HTO subjects by dGEMRIC pattern (in relation to kinematic or clinical measures) may provide a clearer picture of mechanical factors influencing cartilage health.

HTO changes 3D knee kinematics at both the patellofemoral and tibiofemoral joints. Changes were found in 7 of 11 kinematic parameters over a range of motion, indicating that current clinical assessment of frontal radiographs in one position do not capture the multiplicity of alterations in joint mechanics. These changes may be related to the moderate clinical outcomes of HTO. Advantages of our study include assessments made through a substantial range of loaded knee flexion with a validated measure, and measurement of all components of tibiofemoral and patellofemoral motion, compared with the few parameters from standard radiographs. Limitations of this study include the static nature of the scans and the sub-weightbearing loads applied. Patterns of change that did not follow the overall trend were seen in some subjects, and particular kinematic parameters showed more or less variability in pattern between subjects. This study is the first complete 3D characterization of kinematics in opening-wedge HTO. The multiple kinematic changes found in this study provide an avenue for investigation into the relationship between mechanical changes and clinical outcomes in HTO, and pattern differences between subjects in 3D kinematics over a range of motion may provide a new basis for comparing clinical outcomes between groups of patients beyond simple coronal plane alignment in one joint position.

In normal subjects, 3D MR kinematics results are different if obtained from a dynamic scan of a moving knee rather than from a series of static poses. Strengths of using a dynamic scan include allowing subjects to use a self-selected rate of motion, collecting all data in two to four cycles, and obtaining more data points in a shorter time, reducing subject burden. We also made a direct comparison to a validated static
method, studied a clinically important range of motion, and loaded the joint. Limitations of this study were static positions that differed in hip flexion from dynamic positions, no direct assessment of accuracy, sub-weightbearing loads, the unclear effect of the stretchable knee coil on patellar kinematics, and slow motion. This is the first direct comparison of 3D MR kinematics between dynamic movement and a range of static positions. While differences in kinematics longitudinally and/or between groups are captured using static scanning, dynamic scanning may lead to results that are closer to the kinematics of the knee in activities of daily living and may elicit further information about clinically important differences with injury or treatment. The method developed here can be applied to a variety of clinical situations, leading to a better understanding of the effect of disease, injury, and surgery on changes in joint mechanics.

7.2. Future work

Dynamic MR kinematics to further understand changes in HTO. Static scans have been shown to produce different measures of kinematics than dynamic scans. We expect there will be differences between dynamic and static MR kinematic measurement in a HTO population, but it is unclear if the same types of differences will occur. Dynamic measurement may highlight or confirm which kinematic changes caused by HTO are more important in activities of daily living, and lead to focused study in future evaluations of relationships between kinematic change and clinical outcome.

Weightbearing MR kinematics of HTO. The relatively small axial load applied during scanning is limited by the requirement for subjects to be supine in the scanner, and the associated difficulty in applying high loads. Upright open MR scanners, such as the new MROpen (Paramed, Italy) here at UBC can be used to obtain scans while subjects are weightbearing. This imaging configuration may also result in different kinematics than even a supine scan that was highly loaded, due to the position of the body centre of gravity over the feet. We expect that the kinematics results would be different from those obtained with supine scanning\textsuperscript{282}, and that they would more closely represent kinematics of the joint in activities of everyday living.
Connection of mechanical changes to outcomes. We found that many unintended mechanical changes are associated with opening-wedge HTO. It is unclear if these changes are connected to medium- and long-term clinical outcomes. Further clinical work is required to evaluate kinematics and clinical outcomes at longer follow-ups, along with increasing the number of patients enrolled in the study.

Further application of metal artifact reduction to dGEMRIC imaging. SEMAC and MAVRIC have been shown to produce images with much less artifact than VAT or MARS, which correct only within the imaging plane. It is not clear what effect they may have on T1 mapping. Currently, these methods are time intensive for each image, and dGEMRIC overall is time intensive (because a series of images is required). Acceleration techniques currently being developed may allow their application with dGEMRIC measures.

3D dGEMRIC measures in HTO. 3D dGEMRIC methods have been described and utilized in human studies. The application of 3D dGEMRIC would allow a better understanding of changes throughout the whole joint, rather than within a 2D slice. They may also reduce errors associated with slice matching between timepoints. However, 3D methods can rely on gradient recalled echo (GRE) sequences, which are more prone to metal artifact. Therefore testing would be required to determine whether metal artifact reduction could be combined with 3D imaging for dGEMRIC mapping.

7.3. Conclusions
We are able to assess the effect of HTO on cartilage with dGEMRIC, but need to be aware that metal artifact may not be apparent in IR images, and that IR scans produce much larger areas of artifact; SR sequences and MARS should be used at the TF joint in HTO. The overall dGEMRIC results suggest little cartilage change within one year of HTO, however the results of individual subjects may indicate differing responses to mechanical change; more subjects would be necessary to explore connections between dGEMRIC and kinematic changes. HTO changes 3D knee kinematics in a number of ways that are not captured by clinical assessments and these changes may impact clinical outcomes. HTO kinematic changes as assessed dynamically are likely to be different from those assessed by a series of static scans, but the nature of those differences are unclear; for example, differences in normal subjects between static
and dynamic results for tibial anterior translation and patellar proximal translation are larger than differences in those parameters between pre- and post-op results from HTO. Based on the work in this thesis, a longer term study with more subjects may help to identify which kinematic changes may be related to long-term clinical outcomes, and if patterns of change in dGEMRIC can be identified in subject subgroups based on kinematics or clinical outcome.

The studies presented in this thesis have shown evidence of numerous changes in knee joint kinematics with HTO and no apparent changes in cartilage health within one year following HTO. The methods developed here may be applied to answer important questions about kinematic and cartilage health differences in other orthopaedic disorders.
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APPENDICIES

Appendix A. Chapter 3 additional plots

A.1. Additional curve fit maps for phantoms

Figure A.1: $T_1$ maps for ‘no metal’ phantom, all sequences.
Figure A.2: $M_0$ maps for ‘no metal’ phantom, all sequences.
Figure A.3: $M_0$ maps for phantom with metal, all sequences.
Figure A.4: f maps for ‘no metal’ phantom, all sequences.
Figure A.5: f maps for phantom with metal, all sequences.
### Appendix B. Chapter 4 additional plots and tables

#### B.1. Patellofemoral dGEMRIC

Table B.1: Patellar dGEMRIC $T_1$ results for each subject.

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<th>Pixels (outliers)</th>
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### B.2. Tibiofemoral dGEMRIC

Table B.2: Mean overall TF dGEMRIC $T_1$ for all timepoints.

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<th>Pixels (outliers)</th>
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Table B.3: Medial tibial dGEMRIC results for all subjects.

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Table B.4: Lateral tibial dGEMRIC results for all subjects.

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<td>-</td>
<td>776 (199)</td>
<td>519 (140)</td>
</tr>
<tr>
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<td>744 (222)</td>
<td>464 (321)</td>
<td>758 (213)</td>
<td>519 (445)</td>
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</tr>
</tbody>
</table>
Table B.5: Medial femoral dGEMRIC results for all subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline T₁ (mean (SD)) [ms]</th>
<th>Baseline Pixels (outliers)</th>
<th>6 months T₁ (mean (SD)) [ms]</th>
<th>6 months Pixels (outliers)</th>
<th>12 months T₁ (mean (SD)) [ms]</th>
<th>12 months Pixels (outliers)</th>
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</thead>
<tbody>
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<td>497 (178)</td>
<td>336 (6)</td>
<td>512 (179)</td>
<td>296 (8)</td>
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<td>529 (130)</td>
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<td>474 (143)</td>
<td>212 (2)</td>
<td>467 (150)</td>
<td>362 (17)</td>
</tr>
<tr>
<td>3</td>
<td>574 (150)</td>
<td>399 (4)</td>
<td>526 (148)</td>
<td>234 (3)</td>
<td>651 (208)</td>
<td>296 (41)</td>
</tr>
<tr>
<td>4</td>
<td>663 (151)</td>
<td>292 (12)</td>
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<td>-</td>
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<tr>
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<td>583 (177)</td>
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<td>434 (63)</td>
<td>550 (187)</td>
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<tr>
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<td>-</td>
<td>-</td>
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</tr>
<tr>
<td>12</td>
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<td>-</td>
<td>612 (176)</td>
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</tr>
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<td>561 (183)</td>
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Table B.6: Lateral femoral dGEMRIC results for all subjects.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Baseline T₁ (mean (SD)) [ms]</th>
<th>Baseline Pixels (outliers)</th>
<th>6 months T₁ (mean (SD)) [ms]</th>
<th>6 months Pixels (outliers)</th>
<th>12 months T₁ (mean (SD)) [ms]</th>
<th>12 months Pixels (outliers)</th>
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<td>626 (214)</td>
<td>349 (49)</td>
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<td>176 (26)</td>
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<td>584 (187)</td>
<td>163 (8)</td>
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<tr>
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<td>-</td>
<td>-</td>
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<td>462 (213)</td>
<td>281 (10)</td>
<td>553 (205)</td>
<td>364 (13)</td>
</tr>
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<td>490 (147)</td>
<td>416 (7)</td>
<td>576 (146)</td>
<td>395 (5)</td>
<td>734 (222)</td>
<td>463 (144)</td>
</tr>
<tr>
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<td>678 (195)</td>
<td>426 (50)</td>
<td>657 (216)</td>
<td>425 (55)</td>
<td>659 (211)</td>
<td>503 (127)</td>
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<tr>
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<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
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<td>421 (113)</td>
<td>255 (1)</td>
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<td>390 (13)</td>
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<td>683 (196)</td>
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<td>-</td>
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<td>455 (115)</td>
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<tr>
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<td>756 (194)</td>
<td>463 (147)</td>
<td>765 (208)</td>
<td>381 (177)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Table B.7: Summary statistics for dGEMRIC subject means at each timepoint.
Note that these means are different from model means, as the model uses weighting to determine estimates of population mean.

<table>
<thead>
<tr>
<th>TF T1 (mean (SD)) [ms]</th>
<th>PF T1 (mean (SD)) [ms]</th>
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</thead>
<tbody>
<tr>
<td><strong>All</strong></td>
<td><strong>Medial tibia</strong></td>
</tr>
<tr>
<td>Baseline</td>
<td>597 (49)</td>
</tr>
<tr>
<td>6 months</td>
<td>576 (80)</td>
</tr>
<tr>
<td>12 months</td>
<td>603 (55)</td>
</tr>
</tbody>
</table>

Table B.8: Mean dGEMRIC results for TF at all timepoints, compared between cartilage regions.
The intercept value in this case indicates the mean model for the medial tibial cartilage at each timepoint. * indicates p < 0.05, ** indicates p < 0.001. Bold indicates statistically significant difference between regions.

<table>
<thead>
<tr>
<th>β0 (intercept)</th>
<th>T1 mean (SE) [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>567 (19.9) **</td>
</tr>
<tr>
<td>6 months</td>
<td>50.1 (27.4)</td>
</tr>
<tr>
<td>12 months</td>
<td>56.5 (27.9) *</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>β1 (difference in intercept)</th>
<th>T1 mean (SE) [ms]</th>
</tr>
</thead>
<tbody>
<tr>
<td>M tibia to L tibia</td>
<td>36.2 (21.1)</td>
</tr>
<tr>
<td>M tibia to M femur</td>
<td>-10.5 (21.4)</td>
</tr>
<tr>
<td>M tibia to L femur</td>
<td>74.2 (21.1) **</td>
</tr>
<tr>
<td>L tibia to M femur</td>
<td>-46.7 (21.1) *</td>
</tr>
<tr>
<td>L tibia to L femur</td>
<td>38.1 (20.5)</td>
</tr>
<tr>
<td>M femur to L femur</td>
<td>84.7 (21.1) **</td>
</tr>
</tbody>
</table>

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Figure B.1: Medial tibia dGEMRIC scores.
The mean linear mixed model results are shown in bold, and individual results are shown in grey.

Figure B.2: Lateral tibia dGEMRIC scores.
The mean linear mixed model results are shown in bold, and individual results are shown in grey.
Figure B.3: Medial femur dGEMRIC scores.
The mean linear mixed model results are shown in bold, and individual results are shown in grey.

Figure B.4: Lateral femur dGEMRIC scores.
The mean linear mixed model results are shown in bold, and individual results are shown in grey.
Appendix C. Chapter 5 additional plots

C.1. Kinematic results

Figure C.1: Kinematic results for patellar flexion at three timepoints following HTO.

Figure C.2: Kinematic results for patellar spin at three timepoints following HTO.
Figure C.3: Kinematic results for patellar tilt at three timepoints following HTO.

Figure C.4: Kinematic results for patellar anterior translation at three timepoints following HTO.
Figure C.5: Kinematic results for tibial adduction at three timepoints following HTO.

Figure C.6: Kinematic results for tibial internal rotation at three timepoints following HTO.
Figure C.7: Kinematic results for tibial proximal translation at three timepoints following HTO.
C.2. WOMAC results

Figure C.8: WOMAC total score for HTO subjects at three timepoints. Bold line indicates the mean model, grey lines indicate individual subjects. Line at top of plot indicates the extent of the range of the metric.

Figure C.9: WOMAC pain subscore for HTO subjects at three timepoints. Bold line indicates the mean model, grey lines indicate individual subjects. Line at top of plot indicates the extent of the range of the metric.
Figure C.10: WOMAC stiffness subscore for HTO subjects at three timepoints. Bold line indicates the mean model, grey lines indicate individual subjects. Line at top of plot indicates the extent of the range of the metric.

Figure C.11: WOMAC difficulty in performing daily activities subscore for HTO subjects at three timepoints. Bold line indicates the mean model, grey lines indicate individual subjects. Line at top of plot indicates the extent of the range of the metric.
Appendix D.  Chapter 6 additional plots and table

D.1.  Bland-Altman plots

Figure D.1: Bland-Altman plot between static standard and static fast for patellar flexion.

Figure D.2: Bland-Altman plot between static standard and static fast for patellar spin.
Figure D.3: Bland-Altman plot between static standard and static fast for patellar proximal translation.

Figure D.4: Bland-Altman plot between static standard and static fast for patellar lateral translation.
Figure D.5: Bland-Altman plot between static standard and static fast for patellar anterior translation.

Figure D.6: Bland-Altman plot between static standard and static fast for tibial flexion.
Figure D.7: Bland-Altman plot between static standard and static fast for tibial internal rotation.

Figure D.8: Bland-Altman plot between static standard and static fast for tibial proximal translation.
Figure D.9: Bland-Altman plot between static standard and static fast for tibial lateral translation.

Figure D.10: Bland-Altman plot between static standard and static fast for tibial anterior translation.
D.2. Kinematic results

Figure D.11: Kinematic results for patellar spin with dynamic and two static methods.

Figure D.12: Kinematic results for patellar tilt with dynamic and two static methods.
Figure D.13: Kinematic results for patellar lateral translation with dynamic and two static methods.

Figure D.14: Kinematic results for patellar anterior translation with dynamic and two static methods.
Figure D.15: Kinematic results for tibial adduction with dynamic and two static methods.

Figure D.16: Kinematic results for tibial proximal translation with dynamic and two static methods.
Figure D.17: Kinematic results for tibial lateral translation with dynamic and two static methods.
D.3. Effect of slice stack position on kinematics

Figure D.18: Difference in patellar flexion from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing patella.

Figure D.19: Difference in patellar spin from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing patella.
Figure D.20: Difference in patellar tilt from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing patella.

Figure D.21: Difference in patellar proximal translation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing patella.
Figure D.22: Difference in patellar lateral translation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing patella.

Figure D.23: Difference in patellar anterior translation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing patella.
Figure D.24: Difference in tibial adduction from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing tibia.

Figure D.25: Difference in tibial internal rotation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing tibia.
Figure D.26: Difference in tibial proximal translation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing tibia.

Figure D.27: Difference in tibial lateral translation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing tibia.
Figure D.28: Difference in tibial anterior translation from 16 slice stack to 8 slice stack based on (a) medial-lateral position of stack, and (b) number of slices containing tibia.

D.4. Intraclass correlation results

Table D.1: Intraclass correlation results between cycles of dynamic movement.

<table>
<thead>
<tr>
<th>Measure</th>
<th>ICC</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patellar flexion [deg]</td>
<td>0.947</td>
<td>(0.900, 0.993)</td>
</tr>
<tr>
<td>Patellar spin [deg]</td>
<td>0.840</td>
<td>(0.711, 0.969)</td>
</tr>
<tr>
<td>Patellar tilt [deg]</td>
<td>0.976</td>
<td>(0.955, 0.997)</td>
</tr>
<tr>
<td>Patellar proximal translation [mm]</td>
<td>0.988</td>
<td>(0.978, 0.999)</td>
</tr>
<tr>
<td>Patellar lateral translation [mm]</td>
<td>0.930</td>
<td>(0.870, 0.991)</td>
</tr>
<tr>
<td>Patellar anterior translation [mm]</td>
<td>0.991</td>
<td>(0.984, 0.999)</td>
</tr>
<tr>
<td>Tibial adduction [deg]</td>
<td>0.985</td>
<td>(0.972, 0.998)</td>
</tr>
<tr>
<td>Tibial internal rotation [deg]</td>
<td>0.937</td>
<td>(0.880, 0.994)</td>
</tr>
<tr>
<td>Tibial proximal translation [mm]</td>
<td>0.977</td>
<td>(0.956, 0.997)</td>
</tr>
<tr>
<td>Tibial lateral translation [mm]</td>
<td>0.925</td>
<td>(0.861, 0.988)</td>
</tr>
<tr>
<td>Tibial anterior translation [mm]</td>
<td>0.927</td>
<td>(0.861, 0.993)</td>
</tr>
</tbody>
</table>
D.5. Effect of stretchable coil pressure on kinematics

Figure D.29: Kinematic results for patellar flexion with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.

Figure D.30: Kinematic results for patellar spin with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.
Figure D.31: Kinematic results for patellar tilt with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.

Figure D.32: Kinematic results for patellar proximal translation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.
Figure D.33: Kinematic results for patellar lateral translation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.

Figure D.34: Kinematic results for patellar anterior translation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.
Figure D.35: Kinematic results for tibial adduction with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.

Figure D.36: Kinematic results for tibial internal rotation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.
Figure D.37: Kinematic results for tibial proximal translation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.

Figure D.38: Kinematic results for tibial lateral translation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.
Figure D.39: Kinematic results for tibial anterior translation with dynamic and two static methods, comparing stretch and dual-array coils for two subjects.