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Three-dimensional Ultrasound Imaging For Quantifying Knee Cartilage Volume

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Abstract

Arthritis is the most common chronic health condition in Canada, with the most common form being osteoarthritis (OA). There is a great clinical need for an objective imaging-based point-of-care tool to assess OA status, progression, and response to treatment. This thesis aims to validate a handheld mechanical three-dimensional (3D) ultrasound (US) device against the current clinical standard of magnetic resonance imaging (MRI) for quantifying femoral articular cartilage (FAC) volume. Knee images of 25 healthy volunteers were acquired using 3D US and 3.0 Tesla MRI scans. Two raters manually segmented the trochlear FAC during separate sessions to assess intra- and inter-rater reliabilities. The results demonstrated that 3D US has excellent reliability and strong concurrent validity with MRI for measuring healthy FAC volume. 3D US is a promising, inexpensive, and widely accessible imaging modality that will enable clinicians and researchers to obtain additional information without added complexity or discomfort to patients.

Keywords

Three-dimensional ultrasound, knee arthritis, cartilage, osteoarthritis, MRI, validation, reliability, segmentation, image processing

Summary for Lay Audience

Arthritis is the most common disease in Canada, affecting around 21% of the population. There are over 100 different types of arthritis, with the most common type being osteoarthritis (OA). Medical imaging systems such as x-ray imaging and magnetic resonance imaging (MRI) are utilized to diagnose and monitor OA by taking pictures of joints such as the knee. Structures within the knee joint are observed to assess disease progression and response to treatment. While x-ray imaging is excellent at visualizing bone, it cannot visualize soft tissues such as cartilage, ligaments, and fat. It is challenging to use x-ray imaging to assess cartilage abnormalities caused by OA. MRI is excellent at visualizing soft tissues, but MRI systems are expensive to operate and have long waitlists and imaging times. Furthermore, neither x-ray imaging nor MRI can be used to acquire images at the patient's bedside. There is a tremendous clinical need for an imaging system that can assess knee cartilage at the patient's bedside without the limitations of x-ray and MRI. This work aimed to use 3D ultrasound (US) imaging to meet this clinical need and compare it against MRI for measuring knee cartilage volume.

Knee images of 25 healthy volunteers were acquired using MRI and 3D US. Two raters traced the cartilage from MRI and 3D US images to measure the cartilage volume. The cartilage was traced multiple times to assess the reliability of each rater. The cartilage volumes were compared between MRI and 3D US to evaluate the performance of 3D US against the current clinical standard of MRI. The results demonstrated that clinicians and researchers could use 3D US to measure knee cartilage volume at the patient's bedside with excellent reliability and strong agreement with MRI. 3D US is a promising, inexpensive, and widely accessible imaging modality that will enable clinicians and researchers to measure knee cartilage volume without the limitations of x-ray and MRI.

Co-Authorship Statement

This thesis contains one manuscript that has been published as an original research article. As the first author of this manuscript, I contributed significantly to all aspects of the study, including study design, data analysis and interpretation, drafting, and revising the manuscript. The manuscript was co-authored by Sam Papernick, Robert Dima, Derek J. Gillies, Tom Appleton, and Aaron Fenster. My specific contributions to the study included manual segmentations of the femoral articular cartilage (FAC) from magnetic resonance imaging (MRI) and three-dimensional (3D) ultrasound (US) images, semi-automatic segmentation registration and trimming, experimental design, phantom fabrication and testing, device validation, data analysis and interpretation, and manuscript preparation. Robert Dima was responsible for image acquisition, manual segmentation, and image analysis. Derek J. Gillies contributed to developing the image processing, segmentation, and analysis workflow. Tom Appleton and Aaron Fenster were the co-Principal Investigators and provided supervision on experimental design, image analysis, data interpretation, and manuscript writing. All authors contributed editorial feedback during the manuscript review.

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List of Abbreviations

2D	Two-dimensional
3D	Three-dimensional
BLOKS	Boston-Leeds Osteoarthritis Knee Score
BMI	Body Mass Index
CI	Confidence Interval
CT	Computed Tomography
DSC	Dice Similarity Coefficient
ECM	Extracellular Matrix
FAC	Femoral Articular Cartilage
FOV	Field-of-view
HD	Hausdorff Distance
ICC	Intraclass Correlation Coefficient
JSN	Joint Space Narrowing
KL	Kellgren-Lawrence
KOA	Knee Osteoarthritis
KOSS	Knee Osteoarthritis Scoring System
MERGE	Multiple Echo Recombined Gradient Echo
MOAKS	MRI Osteoarthritis Knee Score
MRI	Magnetic Resonance Imaging
MSD	Mean Surface Distance
NSAID	Nonsteroidal Anti-inflammatory Drugs
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
OMERACT	Outcome Measures in Rheumatoid Arthritis Clinical Trials
PET	Positron Emission Tomography
PF	Patellofemoral
POC	Point-of-care
ROI	Region-of-interest
SD	Standard Deviation

TE	Echo Time
TF	Tibiofemoral
tFAC	Trochlear Femoral Articular Cartilage
TKA	Total Knee Arthroplasty
TR	Repetition Time
US	Ultrasound
WORMS	Whole-organ MRI Score

Chapter 1

1 Introduction

Medical imaging has advanced drastically since the discovery of x-rays in 1895 by Wilhelm Röntgen. Currently, radiologists are capable of observing the human body with magnificent detail through the use of x-ray radiography, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), ultrasound (US), and various other modalities.[1] Medical imaging has had significant positive impacts on diagnosing, monitoring, and treating various diseases. As technologies continue to improve, new imaging modalities are being developed to overcome challenges in visualizing the human body and treating various diseases. However, with the growth of medical imaging, concerns over radiation risks, high manufacturing and operating costs, and accessibility to many patients have intensified.[2] It is vital to keep these concerns in mind when developing new modalities to increase their accessibility and effectiveness for disease diagnosis and monitoring.

Diagnosing and monitoring musculoskeletal diseases can be accomplished with medical imaging using x-ray radiography, MRI, and US. However, these methods are associated with limitations in sensitivity and accuracy when assessing musculoskeletal diseases such as arthritis.[3] Therefore, there is an unmet clinical need for a new imaging tool to directly visualize musculoskeletal disease pathology for assisting in diagnosis and monitoring response to therapy. Three-dimensional (3D) US imaging is a relatively new modality that can meet this clinical need and overcome the limitations of x-ray radiography, MRI, and conventional US. This thesis will explore the application of handheld 3D US imaging as a lower-cost imaging modality to provide clinicians and researchers with the ability to monitor arthritis progression and response to treatment. This thesis will specifically investigate the application of 3D US imaging to monitor knee arthritis progression, but 3D US techniques have been applied to other areas such as neonatal, gynecological, and vascular applications, among others.[4,5,6] 3D US imaging has the potential to alter the workflow of orthopedic, sports medicine, primary care, and arthritis clinics by enabling bedside disease monitoring. The remainder of this chapter provides a background on knee

arthritis and current methods of diagnosis, treatment, and monitoring. It also outlines the underlying principles of 3D US imaging and medical image processing techniques and describes the unmet needs, hypothesis, and specific objectives of this thesis.

1.1 Knee osteoarthritis

Arthritis is the most common chronic health condition in Canada, affecting approximately 21% of the population.[7] There are over 100 different forms of arthritis, including rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, and other inflammatory forms.[8] The most common form of arthritis is osteoarthritis (OA) which was previously thought to be caused by the "wear and tear" of joint tissues such as cartilage and the underlying bone. However, OA is a whole-joint disease and is described as an abnormal remodelling of joint tissues caused by a host of inflammatory agents. OA can affect any joint in the body, with the most common sites being the knee and hip.[9] Patients with OA suffer from debilitating pain, disability, and a decreased quality of life.[10] Furthermore, OA has high comorbidity with other chronic health conditions such as cardiovascular diseases, diabetes mellitus, and depression.[11,12,13,14] The presence of comorbidities causes higher mortality, increased hospitalization, poor physical and mental health, and worse disease outcomes.[15]

Knee OA (KOA) is of particular importance to study because of its high prevalence rate compared to other types of OA and its appearance earlier in life, specifically in young obese women.[16] The prevalence of KOA is higher for women than men and is higher in older age groups.[17] Females over 55 years tend to experience more severe OA in the knee joint but not in other sites.[18] Furthermore, the prevalence of KOA is increasing with rising obesity rates and population ageing.[19] The impact KOA has on an individual's quality of life, and its high prevalence, stresses the need for further research.

1.1.1 Risk factors

A *risk factor* is a variable associated with an increase in the risk of a particular disease. Variables that affect the risk of KOA include age, biological sex, congenital joint abnormalities, history of injury, body mass index (BMI), occupational factors, physical activity, comorbidities, and more. The prevalence of KOA increases with every decade of

life, with the highest incidence between 55 and 64 years of age.[20] Many studies have demonstrated consistent evidence that females are at higher risk for KOA than males, according to biological sex.[21] Large areas of cartilage loss can lead to joint malalignment, which is the most significant risk factor for knee structural degradation due to unequal focal loading.[22] Joint malalignment can also be congenital, increasing the risk of KOA incidence. Anterior cruciate ligament and meniscal injuries are substantial risk factors for KOA at ten or more years following injury.[23] Studies assessing BMI demonstrated that being overweight (BMI between 25 and 29.9) or obese (BMI of 30 and over) increases the risk for KOA.[24] OA environmental risk factors such as obesity, joint injury, and joint overload are primarily mechanical in nature. Studies have shown that muscle weakness, joint instability, and malalignment may be possible causes of KOA rather than results of KOA-induced joint damage.[25,26] There is some evidence that various occupation-related movements such as kneeling, squatting, climbing steps, excessive standing, and lifting increase KOA risk.[24] Physical activity is a recommended treatment option for KOA, but there is mixed evidence, with habitual and high-intensity physical exercise leading to an increased KOA risk.[21,24] In healthy and KOA joints, metabolism plays an essential role in remodelling various joint tissues.[27] Cartilage softening and catabolism have been observed in patients with diabetes, although there is little evidence to conclude that impaired glucose metabolism increases KOA risk independent of obesity and age.[28,29] Risk factors play an essential role in detecting and preventing KOA.

1.1.2 Knee anatomy

The knee is the largest synovial joint in humans and contains the distal femur, proximal tibia, patella, meniscus, hyaline cartilage, ligaments, and a synovial membrane.[30] KOA leads to articular cartilage loss of the femur, tibia, and patella. KOA also results in subchondral bone remodelling, synovial inflammation (synovitis), and periarticular muscle weakening (Fig. 1).[31] Localized cartilage loss increases the stress across the knee joint, which leads to further cartilage degradation and loss. The limited intrinsic healing capabilities of the articular cartilage highlight the importance of maintaining joint health.[32]

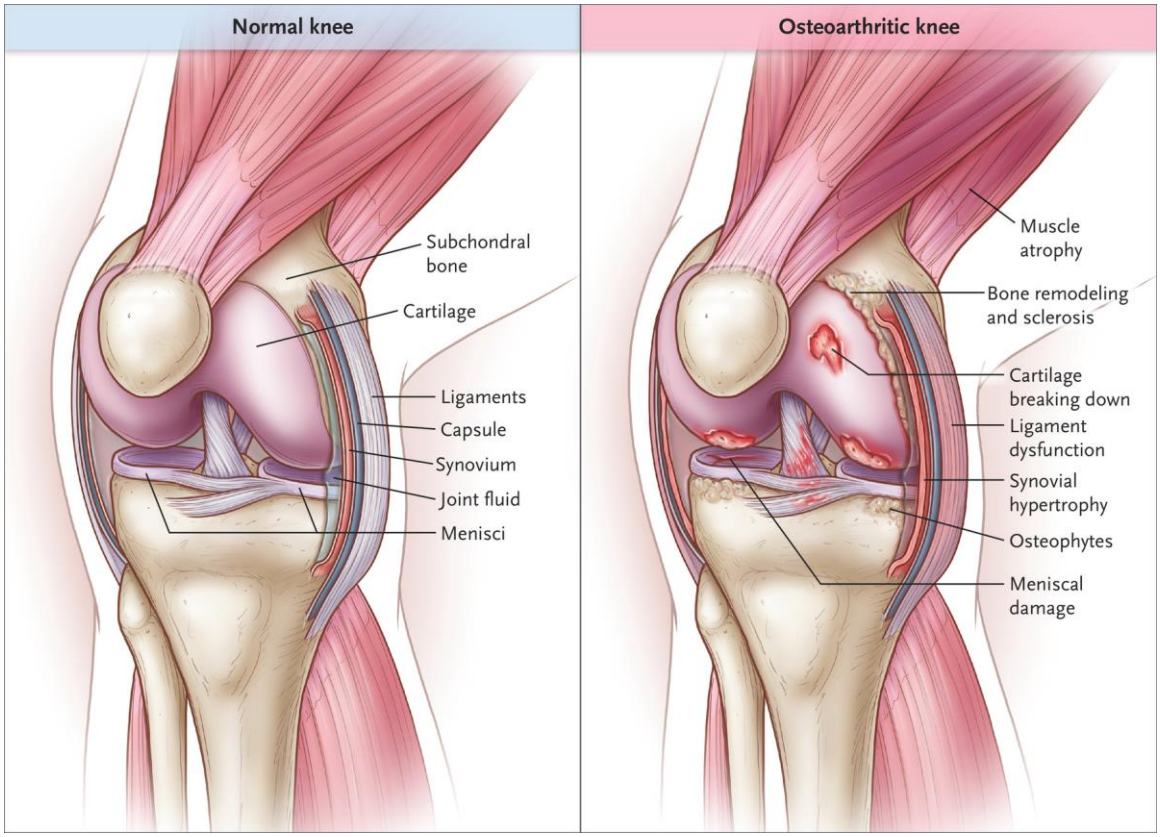

Figure 1.1 Anatomical diagrams depicting the difference between a normal knee and an osteoarthritic knee involving articular and periarticular tissues. Reproduced with permission from Sharma L. Osteoarthritis of the Knee. N Engl J Med. 2021;384:51-59. Doi:10.1056/NEJMcp1903768, Copyright Massachusetts Medical Society.

Articular cartilage is classified as hyaline cartilage and has an average thickness ranging between 2 to 4 mm. It does not contain blood vessels, lymphatics, or nerves and is composed of a dense extracellular matrix (ECM) and a sparse distribution of specialized cells called chondrocytes.[33] Chondrocytes are responsible for synthesizing articular cartilage during development, maintaining normal adult cartilage, and the degeneration of cartilage during KOA.[34] Proteoglycans, a type of protein, are embedded within the collagen matrix of the cartilage and draw water into the cartilage.[10] The high water content of the cartilage provides resistance to compressive forces within the joint. In addition to collagen fibre structure and ECM, chondrocytes contribute to the organization of four zones within articular cartilage: the superficial zone, the middle zone, the deep zone, and a calcified cartilage zone. The calcified cartilage is vital in securing the

articular cartilage to the bone by anchoring the deep zone's collagen fibrils to the subchondral bone.[33] A sharp boundary referred to as the tidemark separates the non-calcified and calcified cartilage zones.[35] In OA, the tidemark commonly becomes replicated, which is taken as an indicator of the underlying osteoarthritic process with the calcification front advancing into the non-calcified cartilage of the deep zone.[36,37]

1.1.3 Clinical presentation and symptoms

OA can only be clinically diagnosed if patients present with symptoms, and preventing or alleviating these symptoms is the goal of the intervention.[10] The most common OA symptom is joint pain, which tends to worsen with activity, especially following a rest period.[38] KOA patients frequently complain of joint instability leading to buckling, especially when descending stairs or steps.[39] Physician examinations of KOA patients are coupled with medical imaging to determine disease presence and severity.[10] Traditionally, weight-bearing radiography has been used to diagnose KOA through measuring tibiofemoral (TF) joint space narrowing (JSN), which serves as an indirect measure of femoral articular cartilage (FAC) loss. Medical imaging is rarely required to confirm the diagnosis of KOA; however, imaging is helpful to evaluate the severity of joint damage and to monitor disease progression longitudinally.[40] Semi-quantitative scoring systems, such as the Kellgren-Lawrence (KL) grading scale and the Osteoarthritis Research Society International (OARSI) atlas grading system, define the presence of KOA using TF JSN, where decreases in FAC quality and quantity are interpreted as increased KOA severity.[41,42] The KL grading scale defines OA severity in five grades (0-4, normal to severe) using a combination of osteophyte and JSN severity. The OARSI atlas uses separate scoring for osteophytes and JSN (grading 0-3). Using the KL system, a grade ≥ 2 is the typical threshold for OA, while the OARSI atlas threshold consists of three separate criteria: either JSN grade ≥ 2, osteophyte grade ≥ 2, or grade 1 JSN in combination with grade 1 osteophyte.[43,44]

1.1.4 Progression and treatment

In OA, the articular cartilage matrix undergoes proteolytic degradation, which is associated with increased synthesis of the same or slightly altered matrix components by

the chondrocytes.[45] This results in early morphological changes in the cartilage and later losses in cartilage volume. Osteophyte development and significant vascularity changes within bone might play an essential role in the pathogenesis of OA, but these events are less understood. Furthermore, signalling molecules released from the cartilage, synovium, and bone all have an impact on chondrocyte function. Although OA was previously thought of as non-inflammatory arthritis, improved detection methods demonstrate that inflammatory pathways are upregulated in OA.[46]

While there is no cure for OA, several treatment avenues and methods focus on alleviating symptoms with varying efficacies. The European League Against Rheumatism and OARSI have previously published evidence-based OA treatment guidelines.[47,48,49,50,51] The American College of Rheumatology has published the most recent guidelines for managing hand, hip, and knee OA.[52] One treatment option for KOA is regular physical exercise. Regular physical activity in KOA patients effectively reduces pain and improves function.[53] Improving knee joint stability is vital to prevent worsening KOA, particularly by increasing strength in the quadriceps and peripheral muscles around the joint.[54] Strength, flexibility, aquatic and aerobic exercises effectively relieve pain and improve function in patients with lower limb OA.[55] For obese patients, weight loss can reduce the risk of developing symptomatic lower limb OA and improves symptoms once disease evidence is found.[56,57] Studies have also demonstrated that weight loss leads to structural improvements of cartilage and positive changes in bone and cartilage biomarkers, especially in KOA.[58,59] However, weight reduction is not easy, and patients with lower limb OA have pain and physical limitations that limit their ability to participate in physical activity compared to the general population.[60,61]

Another KOA treatment option is the use of pharmaceutical therapies. Commonly prescribed medications include paracetamol (also referred to as acetaminophen), corticosteroids, and nonsteroidal anti-inflammatory drugs (NSAIDs).[62] Due to its cost and safety, paracetamol used to be regarded as the first-line treatment for mild to moderate OA pain.[63] However, systematic reviews and meta-analyses of paracetamol use in KOA patients suggest low efficacy for pain management.[64,65] NSAIDs are an alternative to paracetamol and are superior for treating widespread pain but can be associated with

upper gastrointestinal risks and are not recommended for patients with coexisting cardiovascular conditions.[52,63,66,67] Intra-articular treatment options such as glucocorticoid and hyaluronic acid injections may be recommended when other more conservative approaches to pain relief have failed. However, intra-articular injections elicit a strong placebo effect, and new intra-articular treatments may not be appropriate for every patient.[68,69] Ultimately, there is no pharmacological agent that regulatory agencies have approved as a disease-modifying OA drug.[70]

In addition to physical activity and pharmacological treatment options, surgical intervention may alleviate KOA symptoms. Arthroscopy is a minimally invasive surgical technique where two small incisions are made at the front of the knee to insert surgical instruments.[71] Arthroscopic lavage (irrigation of the joint using a sterile solution) and debridement (resecting damaged tissue within the knee joint) is focused on removing loose bodies or other defects in the knee.[72] However, the use of arthroscopic lavage and debridement to treat KOA is controversial as studies have shown no benefit compared to placebo groups that received only skin incisions.[73,74] Other KOA surgical interventions include high tibial osteotomy, unicompartmental knee replacement, and total knee arthroplasty (TKA), also referred to as total knee replacement, for end-stage KOA.[75] Approximately 80% of patients that undergo TKA procedures are satisfied with their procedure and experienced improvements in function and pain management, making TKA an effective treatment option for end-stage KOA.[76]

Another treatment option for KOA is the use of self-efficacy and self-management programs, which can be delivered remotely and include education, setting goals, behavioural interventions, and self-monitoring.[77] These programs have shown improved self-efficacy in patients with KOA in small to moderate effect sizes.[78] Furthermore, mental and social well-being improvements are also effective treatments for some patients due to the many components of pain, including sleeping problems, loneliness, and mood disorders.[79,80]

1.2 Knee osteoarthritis imaging

1.2.1 X-ray radiography

X-ray radiography is the current gold standard for assessing KOA in clinical and epidemiological settings. In 1957, Kellgren and Lawrence first described a grading system known as the KL grading scale, which was adopted as the standard method for assessing radiographic OA by the World Health Organization in 1961.[81] In 1995, an atlas from OARSI was published and updated in 2007 with better quality images and access to electronic images.[42,82] Radiography is widely available and is associated with lower costs than MRI. Radiography acquisition times are short, and there is little discomfort to patients undergoing imaging. The progression and severity of KOA can be monitored using radiography by assessing cartilage degradation through measurements of JSN and through observing the presence of osteophytes (Fig. 2).

There are several limitations associated with radiography and radiographic grading scales for monitoring the progression of KOA. Primarily, radiography lacks soft tissue contrast, and therefore it cannot be used to visualize the articular cartilage and various other tissues within the knee. Radiographic measures of JSN operate under the assumption that decreases in joint space over time represent decreased articular cartilage volume. This assumption is not entirely valid since the radiographic joint space comprises structures other than the articular cartilage, such as the meniscus.[83,84] Radiographic grading also has poor sensitivity to detect articular cartilage changes in the early stages of KOA.[85] With radiographic JSN, variations in knee positioning, alignment to the radiographic source, and joint angulation can decrease reliability and reproducibility.[86] Furthermore, sensitivity to change is limited when using ordinal scales with a small dynamic range such as 0-4 in the KL grading scale.

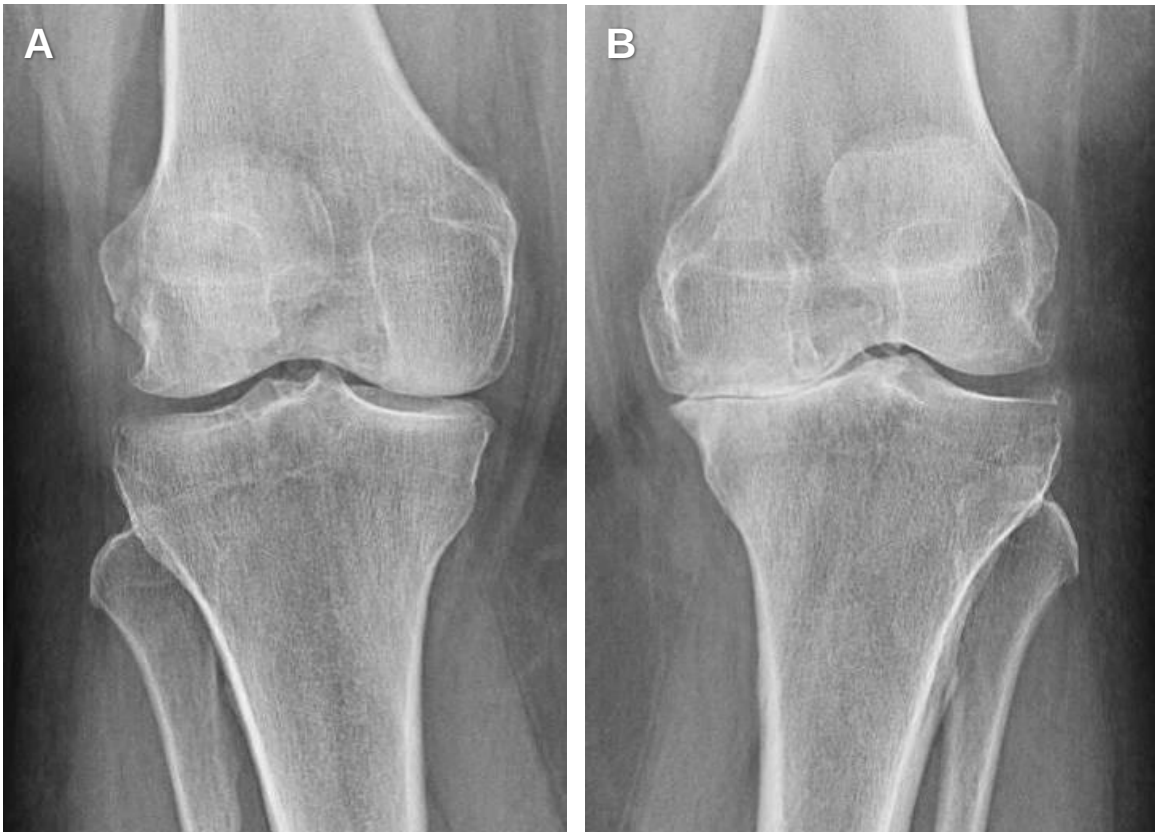

Figure 1.2 Radiographs of a normal (A) and an osteoarthritic (B) knee. The distance between the femur and tibia in the medial portion of the osteoarthritic knee is smaller than the healthy knee due to articular cartilage degradation.

1.2.2 Magnetic resonance imaging

The limitations of radiographic measures of articular cartilage degradation motivated MRI studies focused on imaging and monitoring KOA. While the risks associated with radiation exposure in radiography are low, MRI does not expose patients to radiation as images are created using magnetic fields. MRI has excellent soft-tissue contrast enabling direct assessments of the articular cartilage. The posterior condylar cartilage, trochlear cartilage, patellar cartilage, synovium, menisci, and other soft tissues affected by KOA are more straightforward to visualize using MRI than radiography (Fig. 3). MRI's high spatial resolution, excellent soft-tissue contrast, and ability to directly visualize vital musculoskeletal tissues make it the current clinical standard for KOA imaging. The use of MRI in clinical KOA studies involves using semi-quantitative scoring methods to evaluate morphological characteristics of the articular cartilage in combination with those

of the surrounding tissues to establish symptom risk factors and disease progression.[86] The 3D nature of MRI enables assessments of multiple quantitative articular cartilage measures, including cartilage volume, thickness, surface area, and percentage of bone not covered by cartilage. MRI-based quantitative measurements can also be used to assess the efficacy of pharmacologic therapies in KOA and cartilage biochemistry to monitor early-stage KOA. The MRI Osteoarthritis Knee Score (MOAKS), Boston-Leeds Osteoarthritis Knee Score (BLOKS), Knee Osteoarthritis Scoring System (KOSS), and Whole-Organ MRI score (WORMS) are all semi-quantitative scales that utilize MRI.[87,88,89,90]

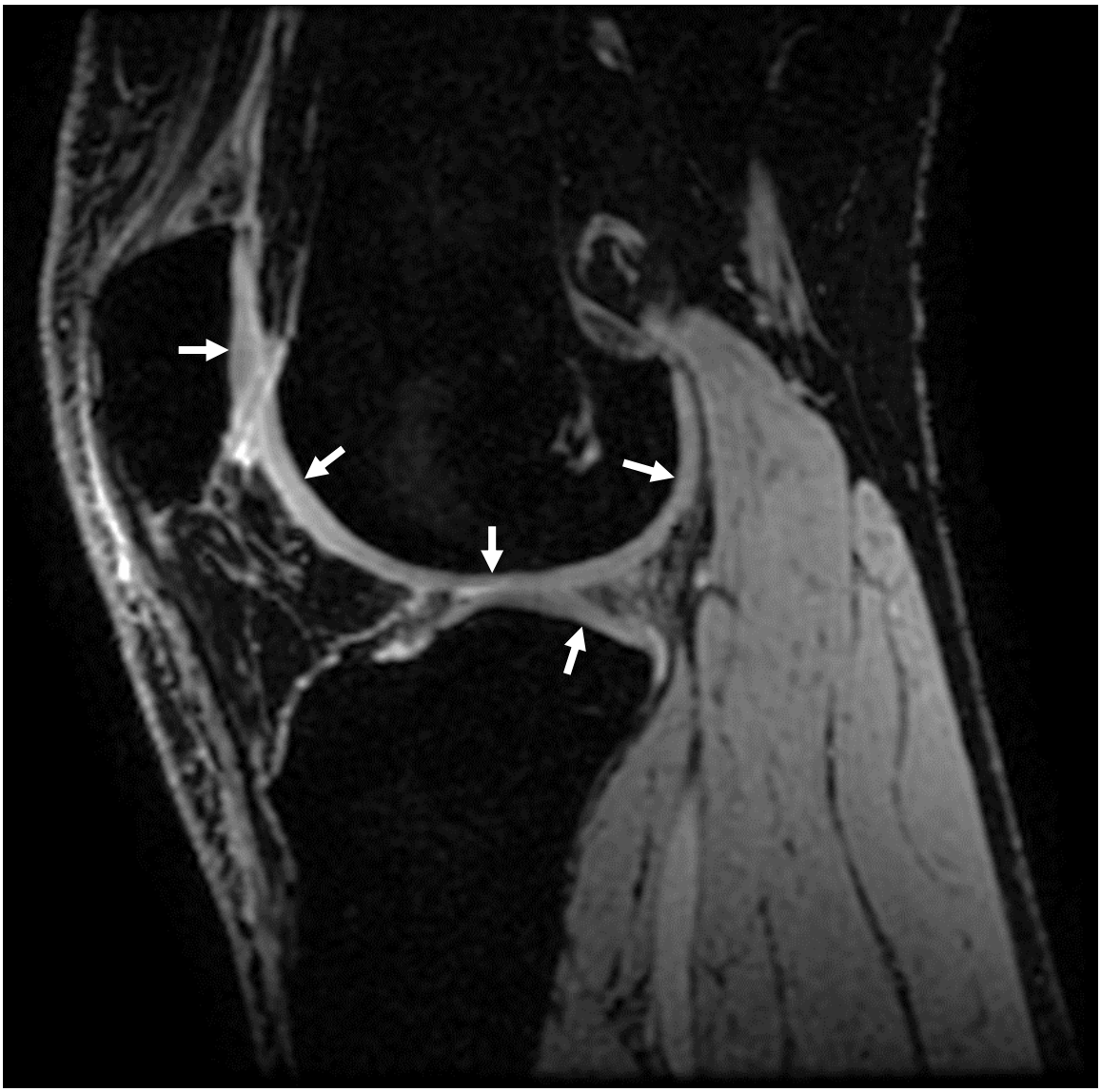

Figure 1.3 MRI scan of a healthy knee with arrows highlighting the articular cartilage.

Measurements of articular cartilage thickness using MRI have been investigated as a quantitative alternative to radiographic JSN measures to determine KOA severity and progression.[91] However, articular cartilage thickness measurements are associated with limitations for KOA assessments. The thickness of articular cartilage in the knee joint varies diurnally, while the cartilage volume does not, leading to variability in thickness measurements.[92] Additionally, longitudinal assessments of cartilage thickness changes are limited by reselecting the identical section of cartilage for measurements in future sessions.[93] An alternative to cartilage thickness measurements for assessing degradation is cartilage volume. Measurements of articular cartilage volume enable the entire cartilage structure to be assessed instead of a single anatomical slice with thickness measurements.

Although MRI has excellent soft-tissue contrast for monitoring the progression and severity of KOA, it is associated with several limitations. MRI is not feasible for point-of-care (POC) disease monitoring due to the limited mobility and physical size of MRI systems. Patients diagnosed with KOA may have substantial mobility limitations and severe pain when moving from one location to another. Another limitation of MRI is its high manufacturing and operating costs. Installing an MRI scanner requires constructing a specialized MRI scanning facility which increases costs and may not be possible in all locations where MRI would be needed. The limited number of MRI scanners available for clinical use in Canada results in patients being placed on long waitlists before receiving the imaging necessary for their care. Additionally, the time it takes to acquire an MRI scan can be long, requiring patients to remain motionless throughout the entire acquisition process. The long scan time is not ideal for patients that experience pain when remaining motionless in the positions required for MRI acquisitions. An ideal imaging modality for monitoring the progression and response to treatment of KOA would be capable of bedside image acquisition, be widely available, have low operating and manufacturing costs, and have relatively short acquisition times.

1.2.3 Conventional ultrasound

Conventional two-dimensional (2D) US imaging is a high-resolution, widely accessible, and relatively low-cost modality that creates images using acoustic waves transmitted and

received by a transducer. Conventional 2D US is capable of real-time imaging, meaning that 2D US images are continually acquired as the transducer is manipulated on the patient's skin. The real-time imaging capability enables the operator to rapidly interrogate an entire region-of-interest (ROI). Additionally, real-time imaging enables images of the patient to be acquired during flexion or extension of their joints to assess how joint tissues respond to the motion. The handheld nature of 2D US enables the operator to manipulate the transducer in any orientation to acquire images that would be difficult or impossible to acquire with radiography. The portability of US machines also enables images to be acquired directly at the patient's bedside, increasing accessibility to patients without increasing patient discomfort. 2D US imaging has been increasingly used to assess rheumatological and musculoskeletal diseases. Previous studies have demonstrated that US can be used to detect early inflammatory soft tissue and erosive bone lesions with correlations to MRI, one of the current clinical standards for monitoring arthritis.[94,95,96,97] The Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) US group has developed a semi-quantitative grading scale to implement 2D US into KOA research; however, this scale has not been formally validated.[98] Due to its high water content, FAC appears hypoechoic or darker and is easy to visualize using 2D US to monitor the progression of KOA (Fig. 4a). The suprapatellar synovial membrane is also visible using 2D US, enabling assessments of synovitis in KOA patients (Fig. 4b).

There are several limitations associated with conventional 2D US imaging. Since 2D US is a 2D imaging modality, it is difficult to interpret the 3D anatomy. Operators must cognitively integrate multiple 2D images to reconstruct the necessary 3D anatomy, which is inefficient and can lead to variability. 2D US techniques can estimate tissue volumes from measurements of height, width, and length in two orthogonal views by assuming idealized geometries. However, 2D US tissue volume measurements are associated with low accuracy, high variability, and high operator dependency during image acquisition. Additionally, human tissues are not always easily represented by idealized geometries, which is especially the case for the FAC and suprapatellar synovium in the knee, leading to incorrect volume estimations. With 2D US, it is impossible to acquire viewing planes perpendicular to the length of the transducer without rotating the transducer and changing the conventional viewing plane. This limitation is apparent during OA diagnosis and

monitoring, which may require an arbitrary selection of viewing planes for assessments and measurements.[99]

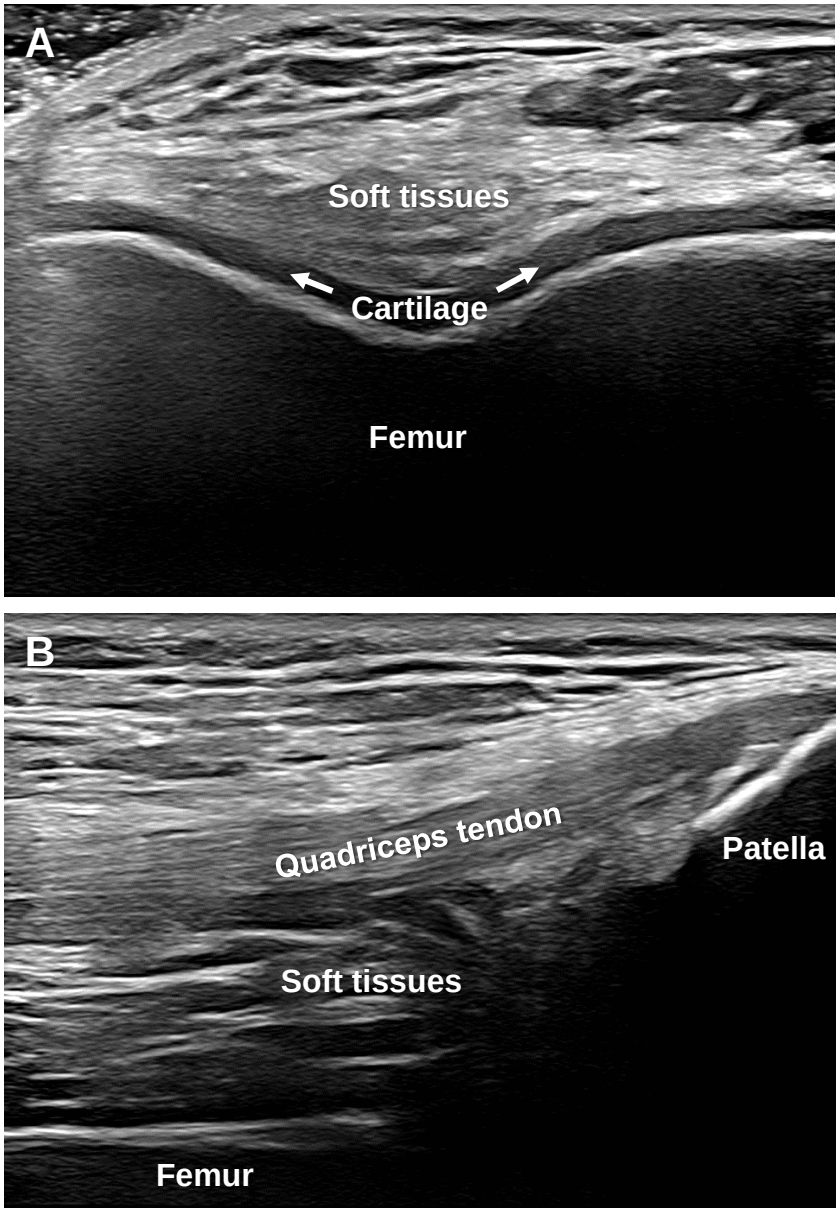

Figure 1.4 2D US images of the trochlear FAC (A) and suprapatellar synovial bursa (B) of a healthy knee. Images were acquired with an Aplio i800 US machine (Canon Medical Systems Corporation, Ōtawara, Tochigi, Japan) equipped with a 14L5 linear transducer (frequency range 3.8 MHz - 10.0 MHz).

Another limitation of conventional 2D US imaging is that the field-of-view (FOV) is small compared to radiography and MRI. The lateral dimension of a conventional 2D US

image acquired using a linear transducer is determined by the length of the transducer itself. The axial dimension of a conventional 2D US image is the depth at which the image is acquired. Higher frequency 2D US transducers result in increased spatial resolution but decreased penetration depth. In general, conventional 2D US cannot image deep tissues at high spatial resolutions. It is difficult to interrogate entire tissues of interest with a single 2D US image due to the limited FOV. Multiple images are often required, leading to difficulties with interpretation without the surrounding contextual anatomy. Furthermore, conventional US imaging is not well-suited to image bony or air-filled anatomy, making it challenging to acquire 2D US images of the knee joint due to the presence of the patella, femur, and tibia.

1.3 3D ultrasound imaging

The limitations of conventional 2D US imaging can be overcome using 3D US imaging. 3D US operates on the same physical principles as conventional 2D US imaging, where images are created by transmitting and receiving acoustic waves. 3D US imaging provides the operator with an interactive 3D representation of the anatomy eliminating the need for mentally reconstructing several 2D US images simultaneously. Three main factors must be optimized during the acquisition of 3D US images:

1. The scanning must be sufficiently rapid to avoid image artifacts due to involuntary operator and patient motion.
2. The location and orientation of the 2D images must be accurately known to avoid geometric distortions in the reconstruction of the 3D image.
3. The scanning device must be simple and easy to operate to avoid complicated scanning procedures.[99]

Several methods for acquiring 3D US images have been developed that satisfy these optimization factors. One approach uses a 2D array of transducer elements, also referred to as a matrix array, which enables acquisition in two simultaneous imaging planes. However, many elements and wiring requirements lead to high manufacturing costs.[100] Another method of acquiring 3D US images is for the operator to manipulate a 2D transducer manually. The trajectory of the transducer is then measured by tracking its

position and orientation during acquisition.[101,102] The position and orientation of the transducer can be tracked in real-time using an external optical tracking system that uses infrared cameras to track passive marker spheres that can be mounted to the transducer. A minimum of three spheres in a non-linear orientation is needed to track all degrees of freedom during transducer manipulation. An additional approach is to translate a conventional 2D US transducer along a path using a motorized drive mechanism with a known trajectory.[103] With this approach, 3D US images are formed by continually acquiring consecutive 2D US images as the transducer is translated along the subject to sweep out a 3D geometry. Consecutive 2D US images are then reconstructed to form a 3D volume using automated software.[99] This thesis focuses on applying mechanical 3D US imaging to monitoring KOA.

With mechanical 3D US image acquisition, there are different trajectories that the transducer can follow to produce unique 3D image geometries. Tilt scanning enables the transducer to be tilted around a contact point with the patient to sweep out a fan geometry. With tilt scanning, 2D US images are acquired at regular angular intervals with images radial to the rotation axis. However, the fan geometry of tilt scanning is associated with limitations. The varying distances between consecutive 2D US images as depth increases result in an anisotropic spatial resolution for the resulting 3D image. Additionally, US beam spreading in the elevational direction and within the 2D US acquisition plane leads to degradation of the spatial resolution with increasing depth.[104] Alternatively, a linear scanning device translates the transducer linearly along the patient's skin. With linear scanning, 2D US images are acquired at regular spatial intervals to sweep out a rectangular geometry. The rectangular geometry of linear scanning provides a broader FOV at shallow depths but a smaller FOV at increased depths than tilt scanning. Therefore, linear scanning would be better suited for monitoring KOA progression due to the superficial knee anatomy.

3D US images are comprised of multiple imaging planes. The imaging plane that is parallel to the direction of conventional 2D US is referred to as the acquisition plane, while the perpendicular plane is referred to as the reconstruction plane (Fig. 5). The acquisition plane possesses the exact spatial resolution as the 2D US transducer used to

acquire the images. In contrast, the reconstruction plane has a spatial resolution equal to the elevational resolution of the transducer. The different spatial resolutions of these two imaging planes result in an anisotropic spatial resolution for the overall 3D US image. The translation speed of the 2D US transducer on the 3D US scanner can be varied to match the sampling rate to the frame rate of the US machine. The translation distance and speed of the US transducer also affect the 3D US acquisition time. Typically, 3D US images can be acquired in approximately 10 seconds or less.

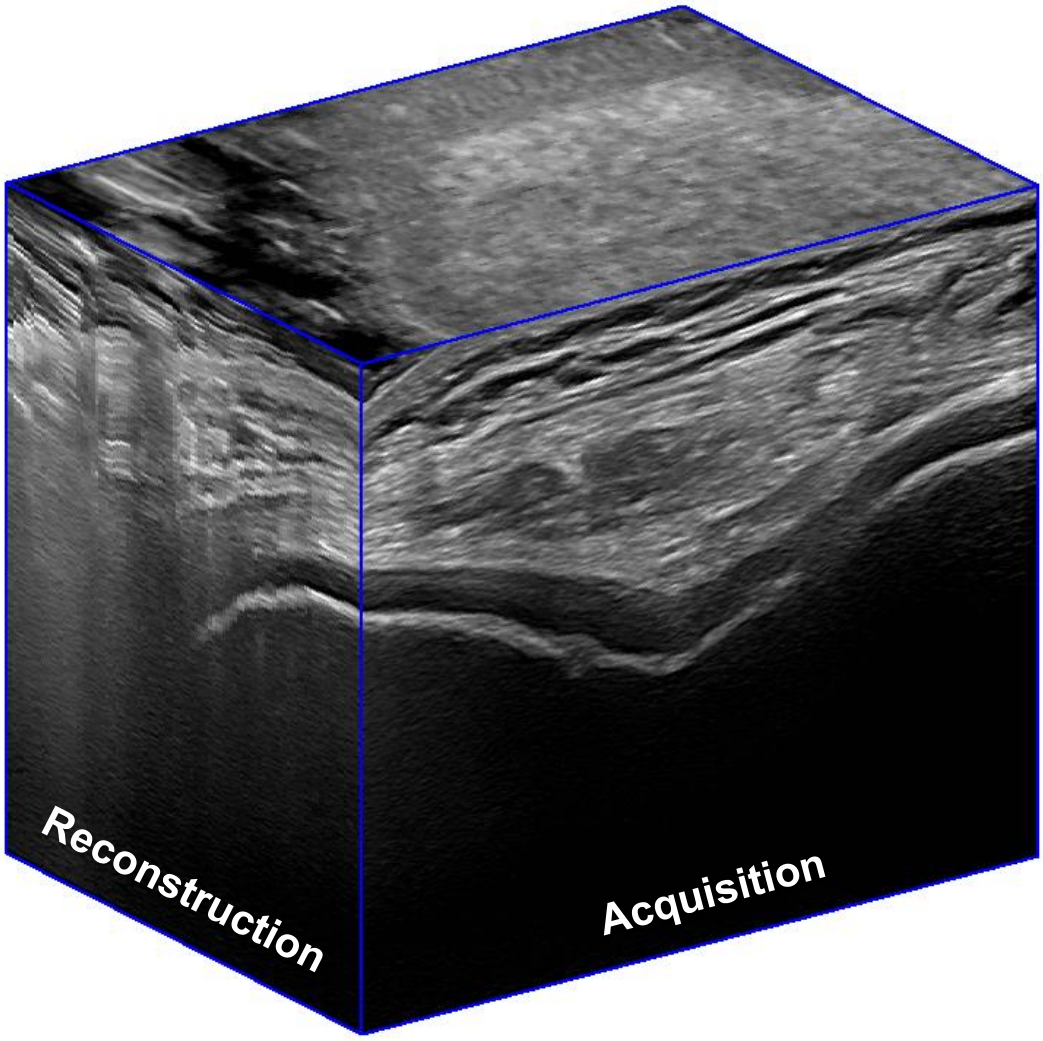

Figure 1.5 3D US image of the trochlear FAC from a healthy knee with labelled acquisition and reconstruction planes.

With mechanical 3D US acquisition, the drive mechanism's housing can be designed to allow for easy, ergonomic handheld positioning and manipulation. Because of the

flexibility in design, the transducer mounting attachment can be designed to conform to any transducer, making 3D US compatible with any US machine. Additionally, since 3D US acquisition forms images using consecutive 2D US images, it can be implemented in any application where 2D US is used. 3D US imaging also reduces variability and user dependency when measuring tissue volumes and provides the ability to select any arbitrary imaging plane for disease diagnosis and monitoring.

1.4 Medical image processing and analysis

1.4.1 Segmentation

Image segmentation, also referred to as labelling or contouring, is the process of identifying image pixels or defining boundaries for all pixels within a given group or region that share a common property or belong to the same tissue type or organ.[105] Segmenting anatomical structures from medical images provides a unique visualization of the tissues of interest without the surrounding anatomical information. The gold-standard method for image segmentation is manual segmentation, which is completed manually by tracing regions within an image that belong to the tissue of interest. Becoming proficient in manual image segmentation requires training and practice and the necessary anatomical and medical imaging background knowledge for a given application.[106] Segmentations of FAC are necessary to acquire thickness, surface area, and volume measurements. The quality of the segmentation also directly impacts the accuracy of the measurements.[107,108] However, manually segmenting images is subjective as the individuals performing the task make their own decisions based on prior knowledge and experience, leading to inconsistencies.[109,110]

1.4.2 Registration

In medical imaging, registration is a processing technique that is used to align two or more images or segmentations of the same scene taken at different times, viewpoints, or with different modalities.[111] Image or segmentation registration is used to compare or combine valuable information in multiple images or segmentations. Applications of registration in the medical imaging field include the fusion of anatomical and functional images acquired from different modalities to obtain more information about the tissue of

interest.[112] Registration involves designating one image or segmentation as the reference and applying a geometric transformation to the other image or segmentation to align it with the reference.[113] Comparing segmentation-based measurements of KOA progression, such as FAC volume, provides the ability to assess the performance of new methods for acquiring these measurements.

1.5 Challenges in imaging-based knee arthritis monitoring

1.5.1 Previous work and unmet need

Developing new imaging modalities, or repurposing existing technologies for novel applications, requires rigorous testing and validation before implementation into standard clinical care. When working with new applications, it is crucial to evaluate the workflow for feasibility in a clinical setting and validate the system's measurement capabilities and accuracy. We have previously validated the measurement errors of our tilt and linear 3D US scanning devices with tungsten filament phantoms and volumetric agar phantoms. The linear scanner demonstrated the ability to acquire Euclidean distance and volumetric measurements with errors < 2% compared to the known phantom dimensions.[114] However, measurements made from US images can be subject to intra- and inter-rater variabilities, and idealized phantom images may not represent complex human anatomy. Therefore, a study with human volunteers that possess healthy knees is needed to test the intra- and inter-rater reliabilities of using our 3D US device to measure the volume of FAC and develop an efficient clinical workflow.

1.5.2 Hypothesis

The central hypothesis of this thesis is that 3D US imaging can be used to quantify the volume of FAC with similar reliability and accuracy to the current clinical standard of MRI.

1.5.3 Objectives

The objectives of this thesis are to:

1. Assess the intra- and inter-rater reliabilities of manual FAC segmentations of healthy knees from MRI and 3D US.

2. Assess the validity of segmentation-based FAC volume measurements using 3D US compared to the current clinical standard of MRI in healthy knees.

In this context, validity refers to the degree of similarity between manual segmentation-based FAC volume measurements acquired using 3D US imaging in comparison to FAC volume measurements acquired using MRI in healthy volunteers.

1.6 Thesis outline

This thesis will address the specific objectives in one manuscript (Chapter 2).

Chapter 2: Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume

Chapter 2 describes our work on developing and validating a handheld mechanical 3D US acquisition device that will be used to monitor the progression of KOA. The ability to monitor the progression of KOA at the patient's bedside will improve clinical workflow by enabling clinicians and researchers to obtain more information without added complexity or additional stress and discomfort to patients. This device will be beneficial in longitudinal and interventional studies to detect FAC volume changes over time.

Our handheld mechanical 3D US device demonstrated excellent intra- and inter-rater reliabilities and strong concurrent validity with MRI when acquiring FAC volume measurements from healthy knees. 3D US imaging can decrease the overall costs of KOA monitoring and significantly improve the feasibility of FAC volume measurements during KOA clinical trials and patient care.

Chapter 3: Conclusions and future work

This chapter provides an overall conclusion of the previous chapter and will discuss future work to address the unmet needs from this thesis.

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Chapter 2

2 Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume

Handheld 3D US imaging has the potential to improve clinical workflow and decrease the overall costs of KOA imaging and monitoring at the patient's bedside. The purpose of Chapter 2 is to present the validation of a handheld mechanical 3D US acquisition device for measuring the volume of FAC compared to MRI.

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2.1 Introduction

KOA is a whole-joint disease with a prevalence of 7-17% among adults 45+ years old and is increasing with rising obesity rates and population ageing.[1,2] KOA affects all knee joint tissues, leading to cartilage degradation, subchondral bone remodelling, and muscle atrophy.[3] Cartilage degradation, a hallmark of KOA, has motivated efforts to characterize disease severity through measures of FAC loss, where decreases in FAC quality and quantity are interpreted as increased KOA severity. Semi-quantitative scoring systems, such as the KL grading scale, define the presence of KOA using TF JSN as a surrogate for FAC loss. Most imaging-based KOA scales target TF cartilage because of easy visualization with weight-bearing radiography. Although radiographic JSN may represent FAC loss, radiographic grading has poor sensitivity to detect FAC changes in early-stage KOA.[4] Furthermore, radiographic JSN suffers from limited reproducibility for visualizing 3D features due to variations in knee joint angulation.[5] Additionally, JSN is a composite of meniscal positioning and degeneration, which are not necessarily associated with KOA severity.[6,7]

Limitations of radiographic JSN have motivated MRI investigations of FAC as a discriminative and evaluative KOA tool. The MOAKS, BLOKS, KOSS, and WORMS

are all MRI-based semi-quantitative scales that have shown excellent reliabilities in OA populations.[8,9,10,11] Furthermore, compositional MRI techniques produce quantitative measurements of cartilage biochemistry and have primarily been developed to investigate early-stage KOA. Due to the ability of MRI to assess the status of whole joint cartilage with reasonable spatial resolution, it has been largely accepted as the gold standard for KOA FAC assessments. While MRI has accelerated the scientific and medical communities' understanding of KOA, it has limitations. MRI is not feasible for POC disease classification due to high manufacturing and operating costs, long acquisition times, and inaccessibility to all patients at all times.[12] However, while other modalities may be less expensive and more accessible than MRI, finding individuals that possess the expertise needed to interpret images in under-served areas of the world is challenging.

Conventional 2D US is widely accessible, relatively inexpensive, and overcomes the limitations associated with MRI. 2D US is a high-resolution imaging modality that has been increasingly used for POC assessments of rheumatological diseases.[13,14,15,16] 2D US has been implemented in KOA research via OMERACT US working group's semi-quantitative grading scale.[17] However, this scale has not been formally validated, and conventional 2D US is associated with limitations. Clinicians must cognitively integrate multiple 2D images to mentally reconstruct 3D anatomy, which is inefficient and leads to operator variability.[18] Additionally, 2D US tissue volume calculations require measurements of height, width, and length in two orthogonal views and are associated with low accuracy, high variability, and large operator dependency. Furthermore, sensitivity to change is limited when using ordinal scales with a small dynamic range such as 0-3 in the OMERACT scale. Alternatively, 3D US techniques involve translating a 2D US transducer while continually acquiring images that are reconstructed into a 3D image. 3D US imaging overcomes the limitations of 2D US and may fill the clinical need for an objective imaging-based POC tool for assessing KOA status, progression, and response to treatment.

3D US techniques have been applied to neonatal, gynecological, and vascular applications, among others.[19,20,21] We have developed a handheld mechanical 3D US device to provide POC assessments of trochlear FAC (tFAC). The objectives of this

cross-sectional study were to investigate the intra- and inter-rater reliabilities of our 3D US scanner for measuring tFAC volumes in healthy volunteers and assess its concurrent validity compared to the current clinical standard of MRI. We hypothesized that tFAC volumes measured from 3D US would demonstrate excellent reliability (ICC > 0.90) and be strongly correlated ($\rho > 0.80$) to MRI measurements in the same ROI.

2.2 Methods

Twenty-five volunteers over the age of 18 without a recent history of chronic knee joint pathology (healthy knees) in the year prior to the study were recruited for MR and 3D US knee imaging. The imaging protocol was approved by the Research Ethics Board at Western University Canada, and all volunteers provided written informed consent prior to imaging (Appendix A). Knees were deemed healthy if volunteers denied experiencing knee pain on most days of the weeks prior to this study and had not been diagnosed with any type of knee arthritis. Volunteers with prior knee injuries and/or surgeries that occurred before the year leading up to the study were not excluded from the cohort if they denied experiencing frequent knee symptoms including pain, aching, or stiffness on most days of the weeks prior to this study.

2.2.1 Image acquisition

MRI scans were acquired on a 3.0 Tesla MR system (General Electric Healthcare, Milwaukee, WI, USA) using a 3D Multiple Echo Recombined Gradient Echo (MERGE) sequence in accordance with the OARSI recommendations for KOA imaging clinical trials.[22] The MERGE sequence is a T2*-weighted pulse sequence for musculoskeletal imaging that enables direct visualization of FAC. An HD T/R Knee Array Coil (8 Channels) was used while volunteers were positioned supine with minimal knee flexion. Images were acquired in the sagittal plane with voxel sizes of 0.63 x 0.63 x 0.40 mm^3, an average of 250 slices, a reconstructed matrix size of 256 by 256 voxels, and an FOV of 16 cm. The excitation flip angle was 5° with a repetition time (TR) of 30 ms and an echo time (TE) of 11.71 ms. The MERGE sequence scan time for one knee was 4 minutes and 27 seconds. Total scan time was 45 minutes including both knees.

3D US images were acquired using an Aplio i800 US machine (Canon Medical Systems Corporation, Ōtawara, Tochigi, Japan) equipped with a 14L5 linear transducer with a 58 mm footprint length and an operating frequency of 10 MHz (3.8 MHz – 10.0 MHz). The 2D US transducer was mounted to our 3D US scanner using a custom 3D-printed mould (Fig. 1). Our 3D US device consisted of a motorized drive mechanism that linearly translated the transducer over 4.0 cm along the patient's skin. 2D US images were continually acquired at regular spatial intervals which were reconstructed into a 3D image immediately after scanning via computer software.[18] Our 3D US scanner has previously been validated on tungsten filament phantoms and volumetric agar phantoms, demonstrating the ability to acquire Euclidean distance and volumetric measurements with errors < 2%.[23] For 3D US acquisition, volunteers were positioned supine and instructed to flex their knee to the maximum range of motion without eliciting pain. 3D US images of the tFAC were acquired at the distal end of the femur, proximal to the patella during maximum knee flexion (Fig. 2). 120 2D US images were acquired in the transverse plane with transducer translation along the perpendicular axis. Reconstructed 3D US image voxel sizes were 0.058 x 0.058 x 0.33 mm^3 with 2D US in-plane image dimensions of 968 x 694 voxels. 3D US acquisition time was 15 seconds for one knee. The time period between MRI and 3D US imaging sessions was as short as possible while still accommodating to the individual schedules of the participating volunteers.

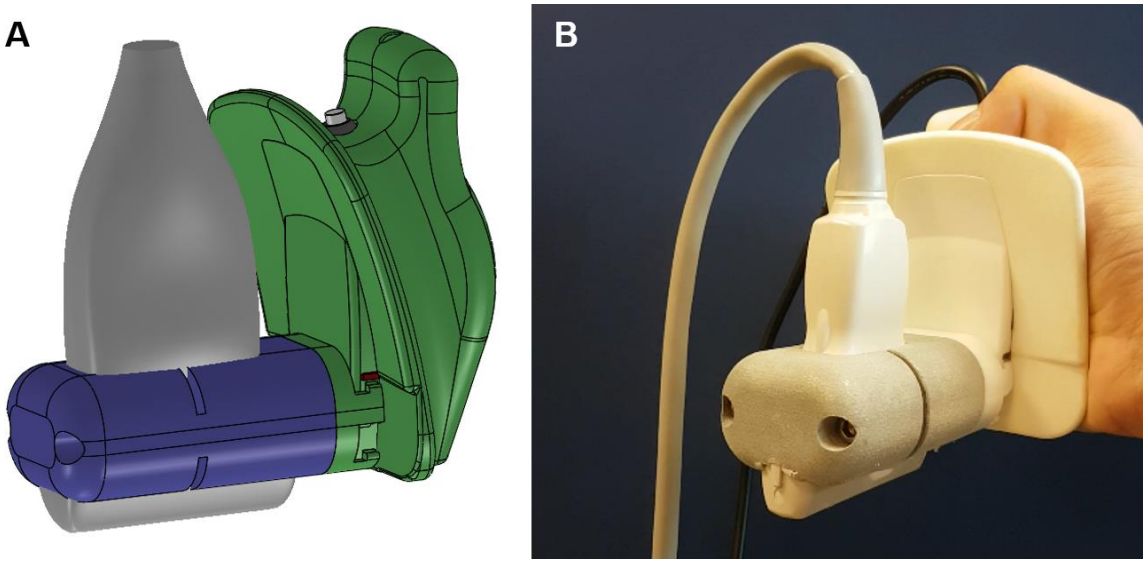

Figure 2.1 (A) Schematic diagram of our handheld mechanical 3D US acquisition device. The conventional US transducer (gray) is mounted to a motorized drive mechanism (green) via a custom 3D-printed transducer mould (purple). Pressing the button located on the top of the device initiates a 3D US acquisition. (B) Image of the 3D US acquisition device in the hand of a user.

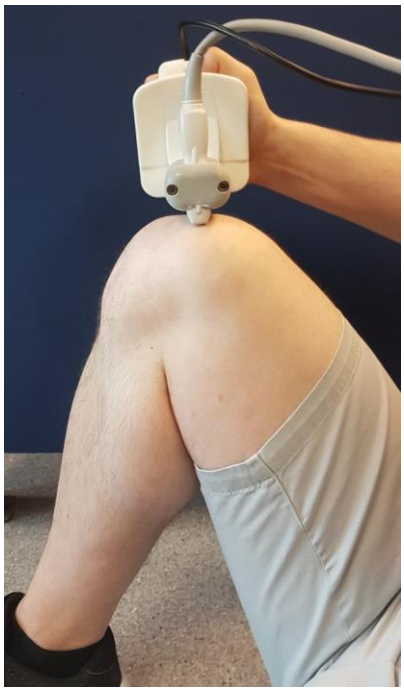

Figure 2.2 Image depicting the knee in full flexion during 3D US image acquisition.

2.2.2 Manual segmentation

MRI voxel resampling was performed to ensure that the segmentation pixel spacings were substantially smaller than the smallest FAC image feature. Voxel resampling was conducted in MATLAB R2019b (MathWorks, Natick, Massachusetts, USA) using the *interp2* function with the spline interpolation method. The resampled voxel size was 0.15 x 0.15 x 0.40 mm^3 to provide a balance between segmentation sensitivity and computation time.

Manual tFAC segmentations were completed by two raters (SP, RD) on MRI and 3D US after receiving training during three formal calibration sessions with a rheumatologist possessing advanced diagnostic and interventional musculoskeletal ultrasonography training (CTA). One rater had no prior experience with medical image segmentation but possesses a medical physics academic background with courses in medical imaging modalities including US and MRI. The other rater is a registered diagnostic medical sonographer with formal training and clinical experience in medical imaging. Segmentations were performed in the open-source software 3D Slicer (3D Slicer 4.11.0 Preview Release) using the segment editor module and were conducted in the sagittal MRI and transverse 3D US planes.[24] Segmentations of both MRI and 3D US were completed using every second 2D image to decrease segmentation time for both modalities without a reduction in sensitivity to tFAC volume changes.[25] Segmented 2D images were interpolated using a morphological contour interpolation algorithm in 3D Slicer, resulting in an average of 146 and 92 segmented 2D images per MRI and 3D US image, respectively.[26] Both raters were blinded to the other imaging modality during segmentations such that MRI segmentations were completed without the help of 3D US image and vice versa. Each rater completed segmentations in a random order on each modality.

During MRI segmentations, the posterior condylar cartilage was excluded by defining the anterior border of the posterior aspect of the lateral and medial menisci as a segmentation border to further reduce segmentation times (Fig. 3a, b). The hyperintense synovial membrane lining Hoffa's fat pad was excluded from MRI segmentations. For 3D US segmentations, the anterior hyperechoic tFAC surface and the hyperechoic border of the

cortex were defined as boundaries for the anechoic cartilage (Fig. 3c, d). With these boundaries and definitions, total segmentation times were approximately 45 to 60 minutes per knee for MRI and 20 to 30 minutes per knee for 3D US. Five knees from separate volunteers were randomly selected by each rater and re-segmented on MRI and 3D US. Repeated segmentations were conducted during sessions separated by a two-week "washout" period to reduce the probability of each rater relying on memory when conducting a repeated segmentation.

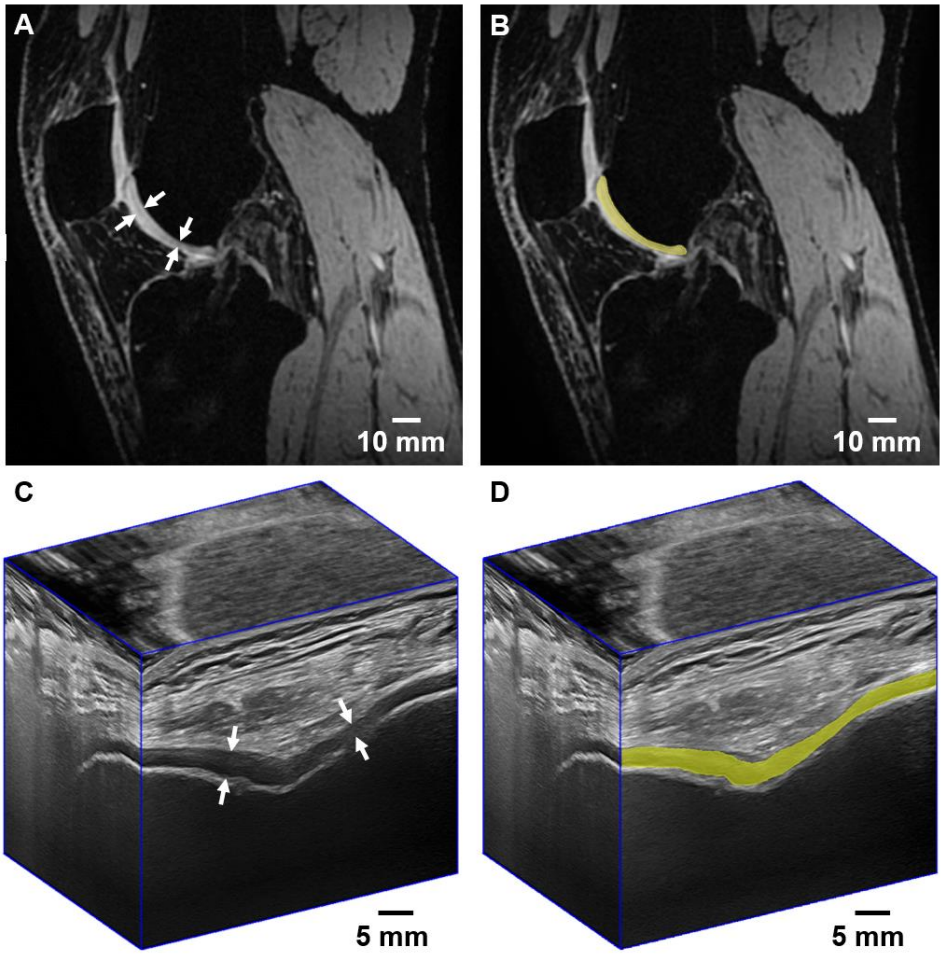

Figure 2.3 MERGE MRI (A) and 3D US (C) images of the trochlear articular knee cartilage outlined by the white arrows in the sagittal MRI and transverse US planes of a healthy volunteer, accompanied by the same images with an overlaid MRI (B) and 3D US (D) slice that has been manually segmented.

2.2.3 Reliability and validation analysis

MRI and 3D US segmentations were registered via manual initialization followed by automated surface-based registration in 3D Slicer (Fig. 4). Initialization involved manipulating 3D US tFAC models using linear transformations and rotations along the three Cartesian axes to align the segmentations with MRI using the intercondylar notch as an anatomical landmark. An automatic surface-based registration method (Jean-Baptiste & Vinicius Boen, University of Michigan) was applied to the segmentations to complete the registration. Intra- and inter-rater reliabilities were assessed using the same registration procedures. Reliability analysis was conducted using the entire segmented area of MRI and 3D US tFAC models, while validation between modalities involved additional trimming of MRI segmentations. MR images captured a larger FAC FOV than 3D US, resulting in segmentations that did not represent identical anatomical ROI when comparing modalities. Therefore, MRI segmentations were manually trimmed using the overlaid 3D US segmentations as guides, ensuring that tFAC models represented the same ROI on both modalities. Registration and trimming were repeated on five knees selected at random during sessions separated by a two-week “washout” period.

Segmentation volumes were computed by 3D Slicer, and the percent differences between MRI and 3D US volumes were calculated. The mean surface distance (MSD), Hausdorff distance (HD), and Dice similarity coefficient (DSC) were computed as these metrics are widely used to compare and evaluate segmentations.[27] MSD represents the mean distance from a point on one surface to the nearest corresponding point on the other surface, while HD is the largest distance from a point on one surface to the closest point on the other surface (Fig 4e). DSC provides a measure of similarity in terms of overlap between segmentations and ranges from 0% (no overlap) to 100% (identical objects). MSD and HD values were computed using the open-source software CloudCompare (CloudCompare v2.11 beta), and DSC values were computed using the segment comparison module in 3D Slicer (Csaba Pinter, PerkLab, Queen’s University, Canada).

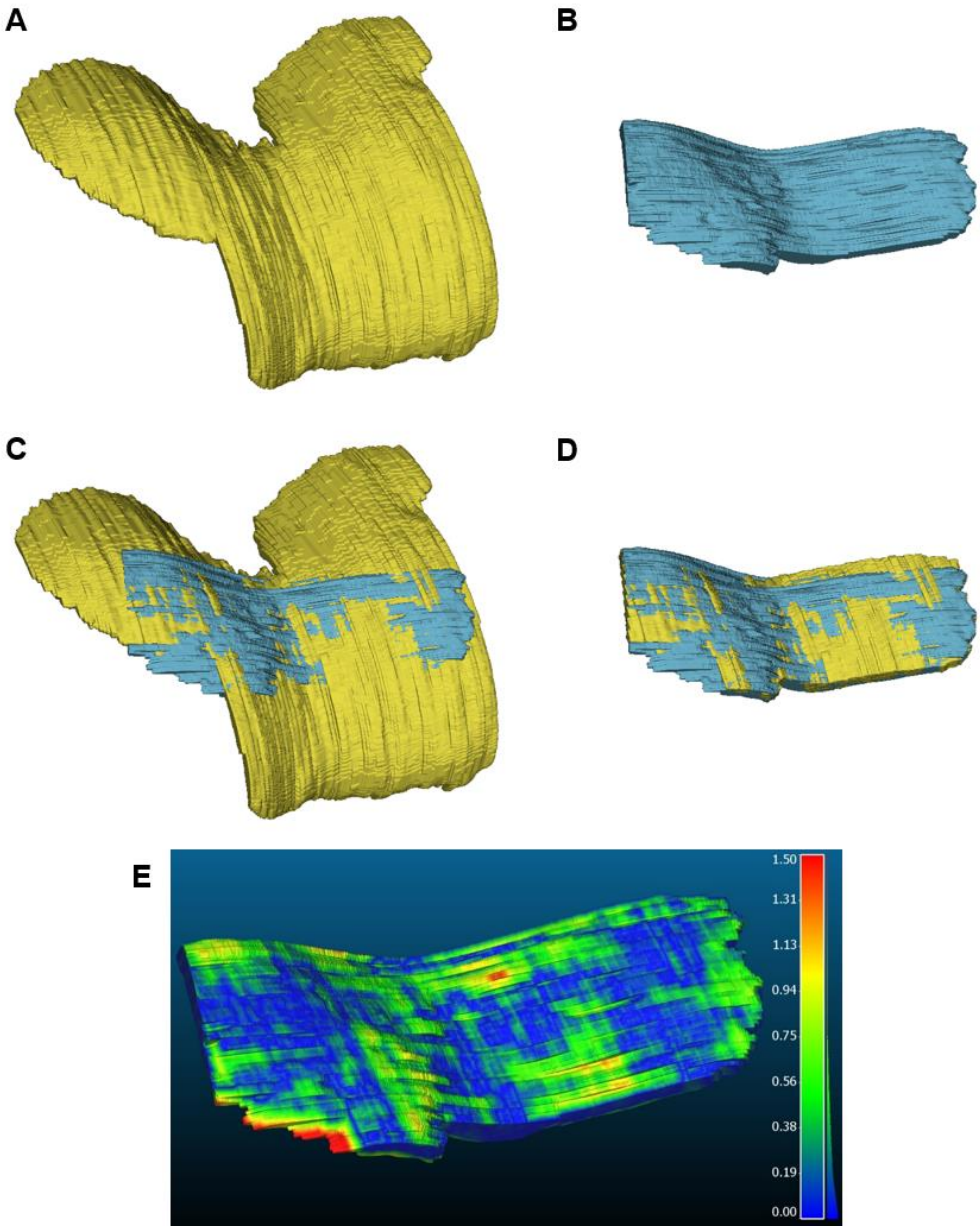

Figure 2.4 Manual segmentations of the FAC from MRI (A) and 3D US (B) images. 3D US segmentations were registered to MRI using a semi-automated surface-based registration algorithm (C). MRI segmentations were then trimmed (D) to ensure both MRI and 3D US segmentations covered the same cartilage region for comparison purposes. (E) Colour map representing the absolute distance (mm) between a given MRI and 3D US segmentation pair from the same knee of a volunteer. The distance map has been overlaid on the 3D US segmentation and represents the distance from each point to the nearest points on the MRI segmentation.

2.2.4 Statistical analysis

Statistical analyses were performed using SPSS (SPSS Statistics v26; IBM, Armonk, NJ). All data were initially tested for normality using the Shapiro-Wilk test. Intra- and inter-rater segmentation reliabilities from MRI and 3D US for both raters were assessed using intraclass correlation coefficients (ICCs). Intra-rater ICCs were based on a single-rating, absolute-agreement, 2-way mixed-effects model, while inter-rater ICCs were based on a single-rating, absolute-agreement, 2-way random-effects model. ICCs were interpreted as less than 0.50 indicating poor reliability, between 0.50 and 0.75 indicating moderate reliability, between 0.75 and 0.90 indicating good reliability, and greater than 0.90 indicating excellent reliability.[28] Bland-Altman plots were used to assess differences between intra- and inter-rater tFAC volumes along with differences between MRI and 3D US segmentations. A cumulative percentile plot was used to observe the relationship of the differences between MRI and 3D US tFAC volumes. Correlations between tFAC volumes calculated as the mean of the two raters from MRI and 3D US segmentations were determined using Spearman Rank-Order Correlation due to the non-normal distribution of data. Linear regression analysis was conducted using MRI segmentation volumes as predictors for 3D US tFAC volumes and the enter method for equation construction.

2.3 Results

The demographic data of the volunteers are shown in Table 1 and was available from 24 of the 25 participants.

Table 2.1 Demographic data of twenty-four out of the twenty-five volunteers.

	Volunteers with healthy knees
% Women	58.3
Age [year] (mean ± SD)	29.9 ± 14.5
Height [m] (mean ± SD)	1.68 ± 0.11
Weight [kg] (mean ± SD)	67.0 ± 14.8
BMI [kg/m^2] (mean ± SD)	23.4 ± 3.3

2.3.1 Reliability

Similar mean segmentation volumes and mean absolute volume differences between intra- and inter-rater comparisons were observed using the same modality for each rater (Table 2, Fig. 5). The smallest ICC was 0.83 (0.48, 0.94) and was observed for the inter-rater comparison of MRI, while the largest ICC was 1.00 (0.98, 1.00) and was observed for the intra-rater 3D US comparison for rater 1 (Table 3). Global mean MSD and HD were smaller for 3D US than MRI for intra- and inter-rater comparisons, while DSC was larger for 3D US than MRI during all comparisons (Table 3).

Table 2.2 Mean volumes ± standard deviations (SDs) for all intra-rater and inter-rater comparisons, along with the absolute volume difference ± SD between MRI and 3D US. The mean volumes and absolute differences for repeated registrations and trimmings of MRI segmentations are also provided.

	Mean Volume [cm^3]	Mean Volume (repeated) [cm^3]	Absolute Difference [cm^3]
Intra-rater (n = 5)			
MRI (rater 1)	4.71 ± 1.18	4.76 ± 1.20	0.232 ± 0.152
MRI (rater 2)	4.56 ± 1.10	4.20 ± 1.04	0.366 ± 0.351
3D US (rater 1)	2.52 ± 1.01	2.53 ± 0.96	0.0516 ± 0.0531
3D US (rater 2)	2.15 ± 0.92	2.17 ± 1.08	0.167 ± 0.111
Inter-rater (n = 25)			
MRI	4.79 ± 1.23	4.38 ± 1.03	0.494 ± 0.465
3D US	2.29 ± 0.72	2.30 ± 0.64	0.155 ± 0.134
Registration & trimming (n = 5)			
Single rater	2.14 ± 0.56	2.13 ± 0.54	0.0173 ± 0.0166

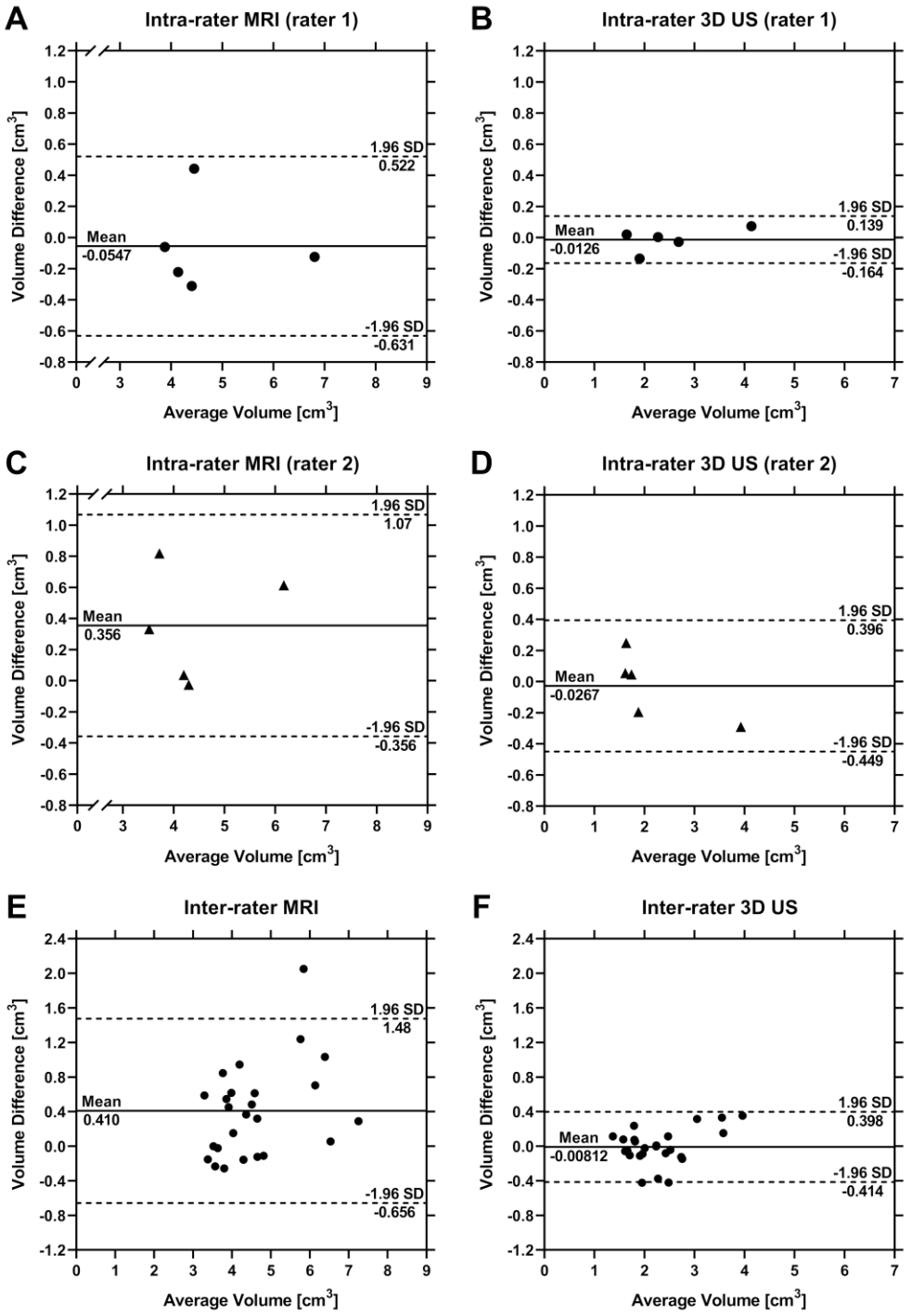

Figure 2.5 Bland-Altman plots assessing intra-rater test/re-test reliability of rater 1 with MRI (A) and 3D US (B), and rater 2 with MRI (C) and 3D US (D). Bland-Altman plots assessing inter-rater reliability between the two raters using MRI (E) and 3D US (F) to complete segmentations. Mean differences in segmentation volumes are indicated by a solid line and mean ±1.96 SD are indicated by dashed lines.

Table 2.3 Intra- and inter-rater reliability ICCs with 95% confidence intervals (CIs) for manual MRI and 3D US segmentations, along with repeated MRI and 3D US registrations and trimmings. The MSD, HD, and DSC values ± SD for all comparisons are also presented.

	ICC (95% CI)	*P* value	MSD [mm]	HD [mm]	DSC [%]
Intra-rater (n = 5)					
MRI (rater 1)	0.97 (0.79, 1.00)	0.001	0.218 ± 0.109	2.88 ± 1.37	87.3 ± 2.8
MRI (rater 2)	0.90 (0.25, 0.99)	0.002	0.499 ± 0.275	6.66 ± 2.76	83.5 ± 4.6
3D US (rater 1)	1.00 (0.98, 1.00)	< 0.0001	0.126 ± 0.024	1.76 ± 0.35	92.9 ± 0.2
3D US (rater 2)	0.98 (0.84, 1.00)	0.0003	0.256 ± 0.143	3.70 ± 2.23	88.1 ± 2.6
Inter-rater (n = 25)					
MRI	0.83 (0.48, 0.94)	< 0.0001	0.274 ± 0.122	3.51 ± 1.77	83.1 ± 3.6
3D US	0.96 (0.90, 0.98)	< 0.0001	0.243 ± 0.133	2.89 ± 1.72	86.4 ± 3.1
Registration & trimming (n = 5)					
Single rater	1.00 (0.99, 1.00)	< 0.0001	0.101 ± 0.090	1.72 ± 0.94	94.3 ± 4.4

2.3.2 3D US to MRI registration and trimming

The mean percent difference between MRI and 3D US volumes averaged across all comparisons including both raters individually, following registration and trimming, was 16.7 ± 12.9 % (n = 50). 3D US tFAC volume measurements were larger than MRI volume measurements in 88% of the comparisons between the two modalities (Fig. 6a, b). Spearman Rank-Order Correlation revealed a strong correlation between MRI and 3D US volumes ($\rho = 0.884$ (0.746, 0.949), $p < 0.0001$), and linear regression resulted in $R^2 = 0.848$ (0.750, 0.950), $p < 0.0001$, and $Y = 1.29 * X - 230$ (Fig. 6c). Global mean MSD, HD, and DSC between registered segmentations averaged between both raters were 0.375 ± 0.071 mm, 2.85 ± 1.18 mm, and 71.2 ± 6.5 %, respectively (n = 25).

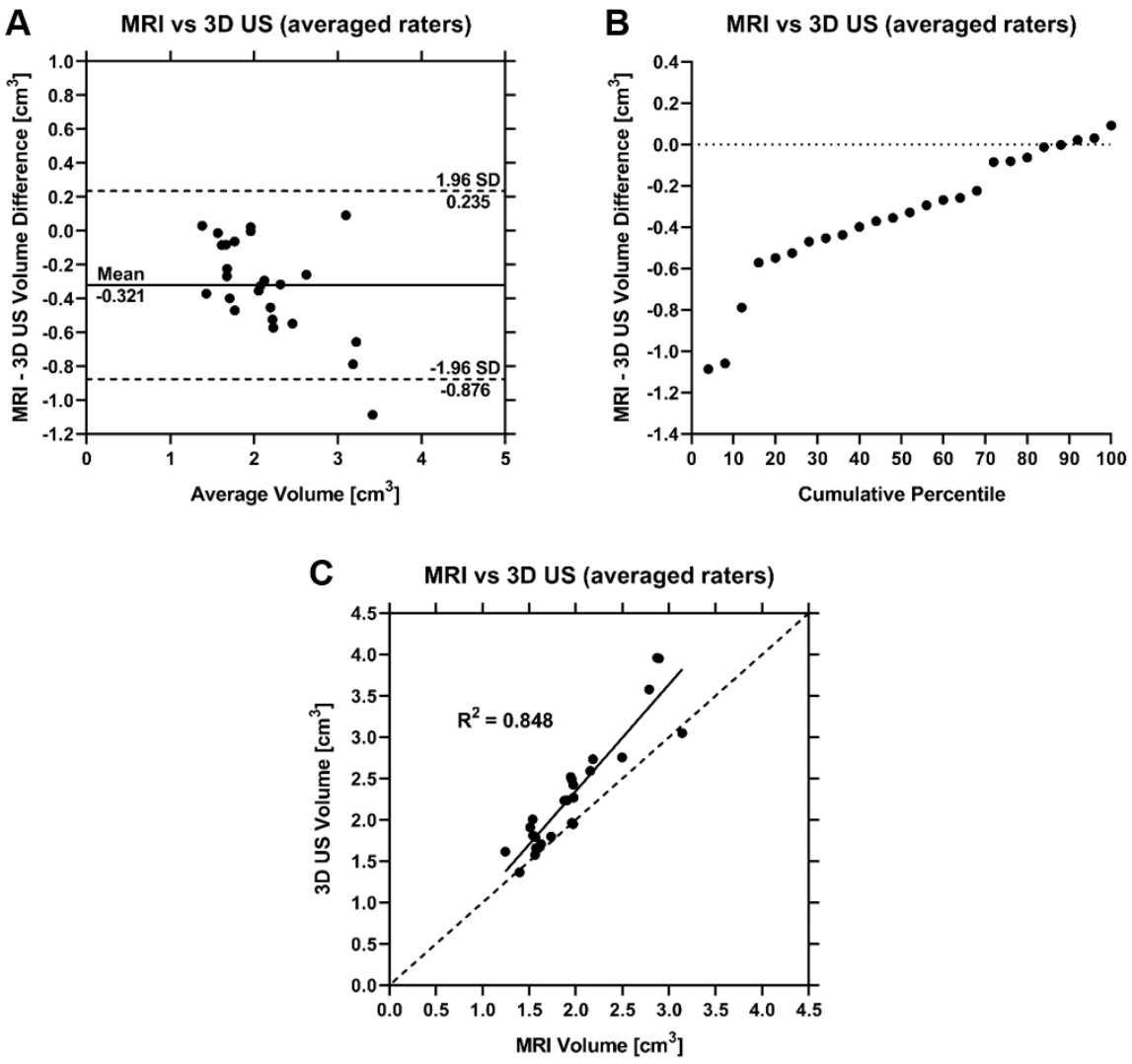

Figure 2.6 (A) Bland-Altman plot assessing the relationship between MRI and 3D US segmentation volumes as the mean for both raters. Mean differences in segmentation volumes are indicated by a solid line and the mean ±1.96 SD are indicated by dashed lines. (B) Cumulative percentile plot depicting the volume difference between MRI and 3D US segmentations averaged between both raters. (C) Linear regression plot of MRI segmentation volumes used as a predictor for 3D US. A line of equality is represented by the dashed line.

2.4 Discussion

This is the first study investigating the reliability and validation of FAC volume measurements using 3D US in healthy volunteers. This study focused on validation of

tFAC volumes, which is important when studying the status and progression of KOA affecting patellofemoral (PF) articulation. Since KOA affects the entire joint, these results are pertinent to the study of nearly all KOA phenotypes. Healthy FAC possesses a relatively smooth and continuous surface without distinct anatomical landmarks that can be used for registering segmentations, besides the intercondylar notch. Therefore, tFAC images that included the intercondylar notch enabled registration of MRI and 3D US segmentations. Additionally, the intercondylar notch can be used as an anatomical landmark during longitudinal studies to ensure repeated measures are taken from the same ROI.

3D US imaging is possible in any application involving 2D US since the only modification required is mounting the 2D US transducer to a 3D US scanning device. Several studies have previously investigated the application of 2D US for evaluating femoral condylar cartilage for KOA assessments[29,30,31,32]. However, quantitative image analysis of non-invasive knee US has only been reported for cartilage thickness measurements but not entire cartilage volumes[33,34,35]. Quantitative image analysis may provide more sensitive information regarding early KOA than semi-quantitative grading scales, which are subjective and potentially susceptible to US operator/rater differences. However, semi-quantitative grading scales are potentially faster than manual quantitative image analysis. Therefore, this study builds on previous work and is easily implemented in similar clinical settings.

Many studies have investigated cartilage thickness measurements for assessing KOA severity[36,37]. However, thickness measurements are highly variable and dependent on the FAC ROI being measured, which can vary within subjects due to US transducer placement and angulation at different time points[38,39,40]. Detecting changes in cartilage loss using thickness measurements requires the ability to sample the same ROI with good test-retest reliability. Volume measurements may overcome these limitations by enabling quantification of cartilage loss in all dimensions and provide a similar metric to average cartilage thickness. Furthermore, 3D US may provide meaningful advantages over MRI for quantifying FAC volume. Our 3D US device is compatible with any commercially available US machine and is associated with low manufacturing and operating costs.

Additionally, the portability of our 3D US device enables FAC volume measurements to be acquired at the patient's bedside.

2.4.1 Reliability

Intra-rater ICCs for MRI and 3D US demonstrated excellent reliabilities (> 0.90). Inter-rater ICC for MRI demonstrated good reliability (0.75 – 0.90) while 3D US ICC demonstrated excellent reliability (> 0.90). Intra- and inter-rater Bland-Altman plots displayed smaller volume difference variations for 3D US compared to MRI in all comparisons (Fig. 5). Additionally, global mean MSD and HD were smaller for 3D US than MRI, and mean DSC for 3D US was higher than MRI for intra- and inter-rater comparisons (Table 3). Collectively, these results suggest that our 3D US system can quantify tFAC volume with similar or perhaps superior reliability and precision than MRI.

The higher spatial resolution of 3D US images acquired with the Canon 14L5 linear transducer compared to 3.0 Tesla MRI may partially account for reliability and precision differences. Resolution differences between modalities were most apparent during MRI segmentations when raters attempted to define the interface between tFAC and the synovial lining of Hoffa's fat pad. Differentiating tFAC from slightly hyperintense synovial lining proved extremely difficult or impossible during MRI segmentations despite manipulating image contrast. Additionally, the TF cartilage interface was difficult to identify on MRI as both cartilage structures were equally hyperintense. The synovial lining of Hoffa's fat pad along with the TF contact point were not within the ROI of 3D US acquisitions since images were acquired during maximum knee flexion. Healthy FAC produced ideal US images with excellent differentiation from surrounding tissues. The difficulties in identifying borders on MRI likely also contributed to higher segmentation times compared to 3D US. The MRI and 3D US resolutions were chosen to match what is routinely used in both patient care and clinical trials for OA to enable comparisons in a clinically relevant context.

2.4.2 Validity

3D US tFAC segmentations possessed larger volumes than MRI segmentations. Considering the higher spatial resolution of US compared to MRI, it is possible that MRI segmentations were not able to capture the true cartilage volume as effectively as 3D US. Medial and lateral portions of the tFAC and condylar cartilage become thin and difficult to delineate from thin adipose tissue and may often not be visible in MRI. Due to the high spatial resolution of 3D US, the thin medial and lateral portions of tFAC were easily identified and therefore included in segmentations. This will be of great importance in clinical studies of joint disease since thinner areas of cartilage are particularly susceptible to damage and loss in KOA. Our 3D US device was able to visualize tFAC and condylar cartilage regions that were difficult or impossible to visualize using MRI, providing a more comprehensive model of the cartilage and improved volume quantifications. Notwithstanding these differences in absolute cartilage volumes, Spearman Rank-Order Correlation and linear regression analyses revealed a strong correlation between MRI and 3D US tFAC measurements and that MRI tFAC volumes can predict 3D US volumes.

2.4.3 Limitations and impact

This study was conducted on volunteers with healthy knees rather than KOA patients. Validating our 3D US system on healthy knees prior to testing with KOA patients was a necessary first step for developing image acquisition, segmentation, and analysis protocols. In KOA patients, FAC characteristically develops fissures, abrasions, and other surface irregularities, whereas healthy cartilage is smooth and continuous. Therefore, before implementing our 3D US device clinically, the measurement properties of this system should also be evaluated in KOA patients. Results from a KOA patient study will enable us to determine if KOA cartilage pathology impacts measurement properties of our system relative to healthy cartilage. However, given the high resolution and excellent soft-tissue contrast of clinical US systems, we anticipate our 3D US system will perform similarly in KOA patients.

Only a portion of FAC was captured in a single pass 3D US acquisition as the FAC cannot be visualized through the patella and tibia using US. Therefore, knees were

scanned in maximum flexion proximal to the patella to capture the greatest portion of FAC possible. However, during maximum knee flexion, the posterior medial and lateral condylar cartilage are in contact with the tibial cartilage and are not visible with 3D US. This limitation can be overcome if the tFAC is used as a non-invasive imaging “biopsy” of knee cartilage, providing clinicians with an indication of FAC status representative of overall joint health. Additionally, manual trimming of MRI segmentations to match the 3D US ROI was only necessary for validating our system against MRI and would not be required when using 3D US independently in future studies. While this procedure may have introduced variability or bias, repeated registrations, along with repeated trimming, revealed nearly perfect reproducibility (Table 3), indicating that our protocol results in very little variability or bias.

The weight-bearing condylar cartilage was able to be visualized using our 3D US device. However, this required additional acquisitions on the medial and lateral sides of the patella during maximum knee flexion. Since MR images of FAC were acquired during minimal knee flexion, variations in patella positioning relative to the FAC surface in MRI compared to 3D US resulted in difficulties registering 3D US condylar cartilage segmentations to MRI. Therefore, this study focused on the tFAC region for validation with MRI, but 3D US could be used for monitoring condylar cartilage volume changes over time without requiring MRI comparisons. Finally, a small subset of patients with severe KOA may experience limited range of motion, which might interfere with visualization of the most inferior aspects of the tFAC.

The greatest advantage of our 3D US system is the ability to acquire images quickly, easily, and comfortably at the patient’s bedside, providing cost-effective and non-invasive assessments of FAC status for reliable longitudinal monitoring. Our 3D US device could alter the workflow of orthopedic, sports medicine, primary care, and arthritis clinics by enabling clinicians and researchers to obtain more information without added complexity or additional stress and discomfort to patients. This technology may be well-suited to longitudinal and interventional clinical studies where detecting changes in cartilage volume is required. In the future, this system will also be useful in a routine clinical care context. Currently, the use of KL grading for assessing KOA progression is

insensitive to change and relies on indirect features of FAC thinning. MRI-based measures of cartilage volume are superior to radiographic measures but are limited by cost, time, accessibility, and patient-related factors, preventing generalized use of quantitative MRI for KOA. Our study demonstrates that cartilage volume measurements acquired using 3D US represent a more feasible method to quantitatively assess tFAC volume with very high reliability and accuracy.

In conclusion, we have demonstrated the reliability and validity of a handheld mechanical 3D US device we developed to quantify tFAC volumes in healthy volunteers. We demonstrated that 3D US segmentations are associated with excellent intra- and inter-rater reliabilities and possess strong agreement with MRI tFAC volume measurements. The tFAC is a vital region of the knee joint for investigating the progression of PF OA and could also be used as a non-invasive imaging “biopsy” of the FAC to monitor KOA progression and response to treatment. Future work will assess the reliability of our 3D US device in KOA patients and the ability to monitor FAC volume changes over time. Further assessment of measurement properties, including sensitivity to change, is necessary before its use can be recommended in clinical trials. Future work will also assess the test-retest reliability of 3D US during image acquisitions separated by time. In addition to longitudinal construct validity, future work will also assess the intra- and inter-rater reliability of 3D US cartilage measurements in a longitudinal study to monitor the progression of tFAC change and degradation for early detection of KOA. 3D US is a promising, inexpensive, and widely accessible imaging modality for POC assessments of KOA and will enable clinicians and researchers to obtain additional information without added complexity or discomfort to patients.

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Chapter 3

3 Conclusion and future directions

This chapter revisits the overarching aims of this thesis and summarizes the findings from Chapter 2. This chapter also explores the limitations of this work with potential solutions and discusses directions for future work.

3.1 Overview and research objectives

KOA is one of Canada's most common chronic health conditions and causes patients to suffer from debilitating pain, disability, and a decreased quality of life.[1,2] X-ray radiography and MRI are the current clinical standards for diagnosing and monitoring the progression of KOA and its response to treatment. However, radiographic grading has poor sensitivity for detecting FAC changes in early KOA and has poor soft-tissue contrast for visualizing FAC.[3] MRI is not feasible for POC KOA assessments due to its high manufacturing and operating costs, long acquisition times, and inaccessibility to all patients at all times.[4] Conventional 2D US is an alternative, widely accessible, and more cost-effective imaging modality for monitoring KOA at the patient's bedside. However, there are several critical limitations associated with 2D US. Operators must cognitively reconstruct the necessary 3D anatomy through several 2D images, leading to variability. Additionally, tissue volume measurements using 2D US are associated with low accuracy, high variability, and large operator dependency.[5] Alternatively, 3D US imaging techniques involve translating a 2D US transducer while continually acquiring consecutive images that are reconstructed into a 3D image following an acquisition. 3D US imaging has the potential to overcome the limitations associated with 2D US and may fill the clinical need for a POC imaging tool to monitor KOA progression and response to treatment.

The purpose of this work was to investigate the application of 3D US imaging for measuring FAC volume without the limitations associated with x-ray radiography and MRI. The central hypothesis of this thesis was that 3D US imaging could be used to quantify the volume of FAC with similar reliability and accuracy to the current clinical

standard of MRI. This thesis sought to test this hypothesis through the following objectives:

1. Assess the intra- and inter-rater reliabilities of manual FAC segmentations of healthy knees from MRI and 3D US.

2. Assess the validity of segmentation-based FAC volume measurements using 3D US compared to the current clinical standard of MRI in healthy knees.

3.2 Summary

In Chapter 2, the reliability and validity of our handheld mechanical 3D US imaging device were tested by comparing manual FAC volume quantifications against MRI. Bilateral knee images of 25 healthy volunteers were acquired with MRI and our 3D US scanner. MRI scans were acquired using a 3.0 Tesla General Electric Healthcare system with a 3D MERGE acquisition sequence. 3D US scans were acquired using a Canon Medical Systems Aplio i800 US machine equipped with a 14L5 linear transducer. Two raters manually segmented the tFAC from both MRI and 3D US after receiving training from a rheumatologist with advanced diagnostic and interventional musculoskeletal ultrasonography experience. Each rater repeated segmentations on five cases during separate sessions to assess intra-rater reliability. 3D US and MRI segmentations were registered using a semi-automated surface-based registration algorithm. The MRI segmentations were trimmed to match the same FAC ROI from 3D US to enable direct volume comparisons. Intra- and inter-rater reliabilities were assessed using ICCs calculated from the segmentation volumes. Spearman correlation and linear regression were used to evaluate the relationships between MRI and 3D US tFAC volumes.

MRI intra-rater ICCs were 0.97 (0.79, 1.00) and 0.90 (0.25, 0.99) for each rater, with an inter-rater ICC of 0.83 (0.48, 0.94). 3D US intra-rater ICCs were 1.00 (0.98, 1.00) and 0.98 (0.84, 1.00) for each rater, with an inter-rater ICC of 0.96 (0.90, 0.98). Spearman correlation and linear regression revealed a strong correlation $\rho = 0.88$ (0.75, 0.95) and regression $R^2 = 0.85$ (0.75, 0.95). These results indicate that 3D US is associated with excellent intra- and inter-rater reliabilities and strong concurrent validity with MRI when

quantifying healthy tFAC volume with manual segmentations. 3D US imaging has the potential to greatly improve feasibility for quantifying knee cartilage volume during KOA clinical trials and patient care.

3.3 Limitations

This study was conducted on volunteers with healthy knees and not patients diagnosed with KOA. In diseased patients, the FAC develops surface abnormalities such as fissures, abrasions, divots, and other irregularities. Therefore, the measurement properties of our 3D US device need to be evaluated in KOA patients before clinical implementation. Additionally, 3D US imaging possesses a smaller FOV than MRI, making it difficult to visualize the entire FAC in a single 3D US image. It is possible to visualize the weight-bearing femoral condylar cartilage using 3D US with additional acquisitions. However, variations in the patella position relative to the cartilage surface in MRI compared to 3D US resulted in difficulties registering condylar cartilage segmentations between modalities.

Due to the large acoustic impedance mismatch between soft tissue and bone, US imaging cannot visualize the FAC through the patella and tibia. Therefore, knees were imaged during maximum flexion with 3D US to reveal the largest possible region of FAC without obstruction by the tibia. The bore size of MRI scanners cannot accommodate legs under full knee flexion, making it impossible to acquire MR images of the knee in the same orientation as 3D US images. The differences in the degree of knee flexion between MRI and 3D US acquisitions result in variations in the patella position along the trochlear groove. These variations introduced complications when identifying the intercondylar notch for registering MRI and 3D US segmentations. However, registering FAC segmentations between MRI and 3D US is only necessary for validating our 3D US device against MRI. When using 3D US independently in the clinic and future studies, multi-modality registrations will not be required.

3.4 Future directions

The results of this work highlight the potential of 3D US for use as an objective, imaging-based POC tool to assess KOA status, progression, and response to treatment. In Chapter 2, FAC volume measurements were acquired using our handheld mechanical 3D US device and validated against MRI in healthy volunteers. A study investigating the reliability and validity of our 3D US device for quantifying FAC volume in patients diagnosed with KOA will be conducted to expand beyond healthy volunteers and provide further evidence for clinical feasibility. Longitudinal studies using 3D US to monitor FAC volume changes in healthy volunteers and KOA patients should also be conducted to evaluate 3D US's sensitivity to cartilage volume changes.

Future studies will also investigate the application of our 3D US device for monitoring knee synovitis. Synovitis and the resultant pro-inflammatory mediators are essential components in the pathogenesis of KOA.[6,7] Synovitis may also be linked to heightened pain sensitivity through sensitization and activation of sensory neurons.[8,9] Monitoring changes in synovial volume with 3D US may provide insight into the complex relationship between synovitis, pain, and KOA. However, synovitis can cause the synovium to expand to several times the size of its healthy state, making it difficult to visualize the entire synovium in a single 3D US image. Furthermore, there is an absence of rigid anatomical landmarks in the suprapatellar synovium region, making it challenging to register several images. To address these challenges, we have developed a counterbalanced POC system that can track the position of 3D US acquisitions in 3D space. The tracking information enables merging multiple 3D US acquisitions to visualize the entire suprapatellar synovium in a single image. The POC system features a multi-jointed arm linkage with electromagnetic encoders at each joint to compute the position and orientation of our 3D US device using forward kinematics. The tracking accuracy of the POC system was validated using an external optical tracking system, demonstrating an overall mean absolute tracking error of 3.08 ± 2.01 mm with no difference between the two tracking systems (p = 0.965).[10] Future work will decrease the POC system's tracking error and test the image registration capabilities using volumetric agar phantoms before imaging volunteers and KOA patients.

Another direction for future work is to develop automatic cartilage segmentation algorithms with deep learning. Several studies have investigated the application of deep learning for automatic knee cartilage segmentations.[11,12,13] Manual 3D US cartilage segmentations are time-consuming and subject to operator dependencies. Automatic segmentation will enable clinicians to measure FAC volume directly at the patient's bedside using 3D US. Future studies will also investigate monitoring synovitis using 3D US and deep learning.

3.5 Conclusion

In conclusion, this thesis investigates applying a handheld mechanical 3D US device for monitoring KOA progression and response to treatment at the patient's bedside. The study described in this thesis demonstrates that 3D US FAC volume measurements are associated with excellent reliability and strong concurrent validity with the current clinical standard of MRI. 3D US imaging is a promising, widely accessible imaging modality for POC assessments of KOA and will enable clinicians and researchers to obtain valuable information without added discomfort to patients.

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9. Stoppiello LA, Mapp PI, Wilson D, Hill R, Scammell BE, Walsh DA. Structural Associations of Symptomatic Knee Osteoarthritis. *Arthritis & Rheumatology*. 2014;66(11):3018-3027. doi:https://doi.org/10.1002/art.38778

10. Papernick S, Orlando N, Park CK, et al. Spatially tracked three-dimensional ultrasound imaging for monitoring the synovial membrane in knee arthritis. In: *Proc. SPIE 11602, Medical Imaging: Ultrasonic Imaging and Tomography.* 2021;116020D. doi:10.1117/12.2580772

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12. Hou W, Zhao J, He R, et al. Quantitative measurement of cartilage volume with automatic cartilage segmentation in knee osteoarthritis. *Clin Rheumatol*. Published online October 7, 2020. doi:10.1007/s10067-020-05388-7

13. Norman B, Pedoia V, Majumdar S. Use of 2D U-Net Convolutional Neural Networks for Automated Cartilage and Meniscus Segmentation of Knee MR Imaging Data to Determine Relaxometry and Morphometry. *Radiology*. 2018;288(1):177-185. doi:10.1148/radiol.2018172322

Appendices

Appendix A: Research ethics board approval letter

Western Research

Date: 4 April 2019

To: Dr. Aaron Fenster

Project ID: 113477

Study Title: 3D Ultrasound Acquisition of Cartilage of the knee joint for Deep Learning Development

Application Type: HSREB Initial Application

Review Type: Full Board

Meeting Date: 26/Feb/2019

Date Approval Issued: 04/Apr/2019

REB Approval Expiry Date: 04/Apr/2020

Dear Dr. Aaron Fenster

The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above mentioned study as described in the WREM application form, as of the HSREB Initial Approval Date noted above. This research study is to be conducted by the investigator noted above. All other required institutional approvals must also be obtained prior to the conduct of the study.

Documents Approved:

Document Name	Document Type	Document Date	Document Version
Data_collection_form_Jan-16-2019-v1.0	Other Data Collection Instruments	16/Jan/2019	1.0
Email Script - 05-Mar-2019	Email Script	Received April 1, 2019	
Letter of Info - 28-Feb-2019	Written Consent/Assent	28/Feb/2019	1.1
Protocol - 28-Feb-2019-1.1	Protocol	28/Feb/2019	1.1

Documents Acknowledged:

Document Name	Document Type	Document Date
CIHR-funding-approval	Other	01/Aug/2017

No deviations from, or changes to, the protocol or WREM application should be initiated without prior written approval of an appropriate amendment from Western HSREB , except when necessary to eliminate immediate hazard(s) to study participants or when the change(s) involves only administrative or logistical aspects of the trial.

REB members involved in the research project do not participate in the review, discussion or decision.

The Western University HSREB operates in compliance with, and is constituted in accordance with, the requirements of the TriCouncil Policy Statement: Ethical Conduct for Research Involving Humans (TCPS 2); the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline (ICH GCP); Part C, Division 5 of the Food and Drug Regulations; Part 4 of the Natural Health Products Regulations; Part 3 of the Medical Devices Regulations and the provisions of the Ontario Personal Health Information Protection Act (PHIPA 2004) and its applicable regulations. The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

Please do not hesitate to contact us if you have any questions.

Sincerely,

Karen Gopaul, Ethics Officer on behalf of Dr. Joseph Gilbert, HSREB Chair

Note: This correspondence includes an electronic signature (validation and approval via an online system that is compliant with all regulations).

Appendix B: Permission for reproduction of scientific article

Copyright agreement for the journal *Osteoarthritis and Cartilage Open* (Chapter 2)

From: …
Date: February 22, 2021 8:14 AM
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Subject: Obtain permission request – Journal (1136468) [210219-018764]

Dear Mr. Samuel Papernick,

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Anita
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Date: February 19, 2021 6:03 PM
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Subject: Submission Confirmation: Obtain Permission – request

Submission ID: 1136468
Date: 19 Feb 2021 6:03 PM

Dear Mr. Papernick,

Thank you for submitting the Permission request form at https://www.elsevier.com/authors/permission-request-form. The following data have been recorded:

Name: Mr. Samuel Papernick
Institute/company: Western University Canada
Address: …
Post/Zip Code: …
City: …
State/Territory: …
Country: …
Telephone: …
Email: …

Type of Publication: Journal

Title: Osteoarthritis and Cartilage Open
Authors: S Papernick, R Dima, DJ Gillies, CT Appleton, A Fenster
Year: 2020
From page: 100127
To page: 100127
ISSN: 2665-9131
Volume: 2
Issue: 4
Article title: Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume

I would like to use: Full article / chapter

I am the author of the Elsevier material: Yes
Involvement: First author and corresponding author of article publication.

In what format will you use the material: Print and Electronic
Translation: No

Proposed use: Reuse in a thesis/dissertation

High-res figures: Yes ^notempty:

Additional Comments / Information:

Curriculum Vitae

EDUCATION

2019-present **Master of Science (MSc) in Medical Biophysics**
Western University Canada, London, Ontario
Supervisors: Dr. Aaron Fenster, PhD, FCCPM and Dr. Tom Appleton, MD, PhD, FRCPC
Thesis title: "Three-dimensional ultrasound imaging for quantifying knee cartilage volume"

2015-2019 **Bachelor of Medical Science (BMSc) Honours in Medical Biophysics**
Honours Specialization in Medical Biophysics (Clinical Physics Concentration)
Schulich School of Medicine and Dentistry, Western University Canada, London, Ontario
Supervisor: Dr. Aaron Fenster, PhD, FCCPM
Thesis title: "Three-dimensional ultrasound use for diagnosis of knee rheumatoid arthritis and osteoarthritis"

AWARDS AND HONOURS

2021 **1st Place Oral Presentation Award – ImNO Conference**
Imaging Network Ontario, London, Ontario
Awarded for scientific oral presentation
Provincial

2020 **Ontario Graduate Scholarship (OGS)**
Government of Ontario
Merit-based scholarship awarded for academic achievement and research excellence
Provincial ($15,000)

2020 **Western Graduate Research Scholarship**
Department of Medical Biophysics, Western University Canada
Awarded to graduate students who maintain an average of 80% or more
Institutional ($5,000)

2020 **1st Place Oral Presentation Award – Robarts Research Retreat**
Robarts Research Retreat, Western University Canada
Awarded for scientific oral presentation

Institutional

2020 **1st Place Abstract Award – Resident Research Day**
Department of Medicine, Western University Canada
Awarded for best scientific abstract for MSc, MD, or undergrad students
Institutional ($500)

2019-2020 **Frederick Banting and Charles Best Canada Graduate Scholarships-Master's (CGS-M)**
Canadian Institutes of Health Research (CIHR)
Awarded to high-caliber students based on academic merit and research achievements
National ($17,500)

2019 **Western Graduate Research Scholarship**
Department of Medical Biophysics, Western University Canada
Awarded to graduate students who maintain an average of 80% or more
Institutional ($5,000)

2019 **Medical Biophysics Top Up Award**
Department of Medical Biophysics, Western University Canada
Awarded to students who hold an external tri-council national scholarship
Institutional ($3,000)

2019 **The University of Western Ontario Gold Medal**
Schulich School of Medicine and Dentistry, Western University Canada
Awarded to the student with the highest average in the courses required for their respective module/program
Institutional

2019 **Kikuchi Best Poster Award**
The International Society for Computer Aided Surgery (ISCAS) – sub-conference of Computer Assisted Radiology and Surgery (CARS)
Awarded for scientific poster presentation
International

2019 **Faculty of Medical Sciences Distinction**
Schulich School of Medicine and Dentistry, Western University Canada

Awarded to students who have achieved an overall average of 80% and no grade lower than 70% on the entire program with no failed courses
Institutional

2019 **Volunteer of the Month**
Let's Talk Science, Western University Canada
Awarded for outstanding volunteer work
Institutional

2019 **Strik Couprie Inch Cancer Research Course Prize**
Department of Medical Biophysics, Western University Canada
Awarded to the student receiving the highest mark in Medical Biophysics 4467A/B: Radiation Biology with Medical Applications
Institutional ($300)

2019 **Dr. G. E. Hall Scholarship**
Department of Medical Biophysics, Western University Canada
Awarded to the student with the highest average in third year of the Medical Biophysics undergraduate program
Institutional ($500)

2019 **Alan C. Burton Course Prize in Medical Biophysics**
Department of Medical Biophysics, Western University Canada
Awarded to the student who receives the highest average in Medical Biophysics courses 3501F, 3503G, 3505F, 3507G, and 3970Z
Institutional ($750)

2018 **Undergraduate Student Research Award (USRA)**
Natural Sciences and Engineering Research Council of Canada (NSERC)
Department of Medical Biophysics, University of Toronto
Merit-based award to stimulate interest and develop potential for research in the natural sciences or engineering in an academic setting
National ($4,500)

2018 **Richard Konrad Scholarship in Science**
Department of Medical Biophysics, Western University Canada
Awarded to a full-time student in year 3 or year 4 in the Faculty of Science based on academic performance
Institutional ($1,500)

2015-2019 **Western Continuing Admission Scholarship**
Western University Canada

Awarded to students with entering averages of 95% at time of admission to undergraduate studies
Institutional ($10,000)

2015-2019 **Dean's Honour List**
Schulich School of Medicine and Dentistry, Western University Canada
Full-time students who completed a minimum of 4.0 courses during the previous fall/winter session and earned an average of 80% or more with no failed courses
Institutional

RESEARCH EXPERIENCE

2019-present **Robarts Research Institute**
Department of Medical Biophysics, Western University Canada, London, Ontario
Supervisors: Dr. Aaron Fenster, PhD, FCCPM and Dr. Tom Appleton MD, PhD, FRCPC
Project: Three-dimensional ultrasound imaging for monitoring arthritis-induced knee cartilage degradation and synovial inflammation

2019 **Sunnybrook Health Sciences Center**
Department of Medical Biophysics, University of Toronto, Sunnybrook Hospital, Toronto, Ontario
Supervisor: Dr. Christine Démoré, PhD

2018-2019 **Robarts Research Institute**
Department of Medical Biophysics, Western University Canada, London, Ontario
Supervisor: Dr. Aaron Fenster, PhD, FCCPM
Project: Validating 3D ultrasound measurements of the knee synovium for diagnosis of rheumatoid arthritis

2018 **Sunnybrook Health Sciences Center**
Department of Medical Biophysics, University of Toronto, Sunnybrook Hospital, Toronto, Ontario
Supervisor: Dr. Christine Démoré, PhD
Project: Development of a combined micro-ultrasound and photoacoustic imaging system for photothermal therapy guidance in patients with prostate cancer

2017-2018 **Lawson Health Research Institute**

Department of Medical Biophysics, Western University Canada, London, Ontario
Supervisor: Dr. Neil Gelman, PhD
Project: Monitoring breast cancer response to radiotherapy using pharmacokinetic modelling

TEACHING EXPERIENCE

Fall 2020 — **Graduate Teaching Assistant (GTA) in Biology**
Course title: Biology 1001, First-Year Labs
Department of Biology, Western University Canada, London, Ontario
Supervisor: Winona Gadapati

Winter 2020 — **Graduate Teaching Assistant (GTA) in Physics & Astronomy**
Course title: Physics 1029, Physics 1302, Physics 1402, Physics 1502, First-Year Physics Labs
Department of Physics & Astronomy, Western University Canada, London, Ontario
Supervisor: Dr. Shailesh Nene

COMMITTEE PARTICIPATION

2018-2021 — **Committee Member, Medical Biophysics Undergraduate Research Day**
Department of Medical Biophysics, Western University Canada, London, Ontario

2018-2019 — **President, Medical Biophysics Students' Association**
Department of Medical Biophysics, Western University Canada, London, Ontario

2017-2018 — **Outreach Executive, Medical Biophysics Students' Association**
Department of Medical Biophysics, Western University Canada, London, Ontario

2015-2018 — **Vice President: Coordination, Western Guitar Club**
Western University Canada, London, Ontario

VOLUNTEERING

2021 — **Medical Biophysics Student Research Symposium abstract reviewing**

Western University Canada, London, Ontario

2020-2021 **National Scholarship Review and Ranking**
Western University Canada, London, Ontario

2020-2021 **Let's Talk Science**
Western University Canada, London, Ontario, Canada

2020-2021 **Let's Talk Cancer Symposium**
Let's Talk Science, Western University Canada, London, Ontario, Canada

2020 **St. John's Hospitality Services – food bank/soup kitchen volunteer**
St. John the Evangelist Anglican Church, London, Ontario

2019 **All-In for Arthritis Poker Gala**
The Arthritis Society, London, Ontario, Canada

2019 **Undergraduate Student Mentor**
Western University Canada, London, Ontario
Number of mentees: 5

2017-2019 **Western Fall Preview Day**
Schulich School of Medicine and Dentistry, Western University Canada, London, Ontario

2017-2019 **Western Spring Open House**
Schulich School of Medicine and Dentistry, Western University Canada, London, Ontario

2015-2018 **Guitar Teacher, Western Guitar Club**
Western University Canada, London, Ontario

PROFESSIONAL MEMBERSHIPS

2021-2022 **American Institute of Ultrasound in Medicine (AIUM)**
Maryland, USA
Student member

2019-2021 **International Society of Photo-optical Instrumentation Engineering (SPIE)**
California, USA
Student member

2019-2020 **Biomedical Imaging Research Center (BIRC)**
Western University Canada, London, Ontario
Student member

PUBLICATIONS & PRESENTATIONS

Peer-reviewed Journal Manuscripts:
(1 published; 1 first-author)

1. **S. Papernick**, R. Dima, D.J. Gillies, C.T. Appleton, A. Fenster, "Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume" *Osteoarthritis and Cartilage Open*. 2020;2(4):100127. doi:10.1016/j.ocarto.2020.100127

Peer-reviewed Conference Proceedings: Published Manuscripts and Abstracts
(3 published; 3 first-author)

1. **S. Papernick**, R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume" Osteoarthritis and Cartilage. 1 April 2021. 29:S341. doi:10.1016/j.joca.2021.02.444 (International; Virtual)

2. **S. Papernick**, N. Orlando, C.K. Park, R. Dima, D.J. Gillies, J. Bax, L. Gardi, K. Barker, T. Appleton, A. Fenster, "Spatially tracked three-dimensional ultrasound imaging for monitoring the synovial membrane in knee arthritis" *Proc. SPIE 11602, Medical Imaging 2021: Ultrasonic Imaging and Tomography, 116020D.* 15 February 2021. doi:10.1117/12.2580772 (International; Virtual)

3. **S. Papernick**, D. Gillies, T. Appleton, A. Fenster, "Three-dimensional ultrasound for monitoring knee inflammation and cartilage damage in osteoarthritis and rheumatoid arthritis" *Proc. SPIE 11315, Medical Imaging 2020: Image-Guided Procedures, Robotic Interventions, and Modeling, 113150E*. 16 March 2020. doi:10.1117/12.2549624 (International; Houston, Texas, USA)

Peer-reviewed Conference Abstracts/Presentations
(14 total; 12 first-author; 6 international conferences)
* indicates presenting author.

Abstracts (1)

1. **S. Papernick***, R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Validation of 3D ultrasound segmentation reliability compared to MRI for assessing knee cartilage degradation in osteoarthritis" *Resident Research Day, Schulich School of Medicine*

and Dentistry, Western University Canada. 15 May 2020. (Regional; London, Ontario; **Best Abstract Award**)

Oral Presentations (9)

2. **S. Papernick***, R. Dima, D.J. Gillies, C.T. Appleton, A. Fenster, "Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume" *American Institute of Ultrasound in Medicine (AIUM) Annual Integrative Ultrasound Meeting.* 10-14 April 2021. (International; Virtual)

3. **S. Papernick***, R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Reliability and concurrent validity of 3D ultrasound for quantifying knee cartilage volume" *Imaging Network Ontario (ImNO)*. 23-24 March 2021. (Provincial; Virtual; **Best Oral Presentation Award**)

4. V. Sainani*, C.K. Park, **S. Papernick**, D. Tessier, K. Barker, L. Gardi, A. Fenster, "Optimization of three-dimensional ultrasound acquisition parameters for diagnostic evaluation of thyroid nodules" *Imaging Network Ontario (ImNO)*. 23-24 March 2021. (Provincial; Virtual)

5. **S. Papernick***, N. Orlando, C.K. Park, R. Dima, D.J. Gillies, J. Bax, L. Gardi, K. Barker, T. Appleton, A. Fenster, "Spatially tracked three-dimensional ultrasound imaging for monitoring the synovial membrane in knee arthritis" *Society of Photographic Instrumentation Engineers (SPIE) Medical Imaging: Ultrasonic Imaging and Tomography*. 15 February 2021. (International; Virtual)

6. **S. Papernick*,** R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Validation of handheld mechanical 3D ultrasound for bedside monitoring of cartilage degradation and synovium inflammation in knee osteoarthritis and rheumatoid arthritis" *American Association of Physicists in Medicine (AAPM) and Canadian Organization of Medical Physicists (COMP) Joint Conference*. 12-16 July 2020. (International; Virtual)

7. **S. Papernick*,** R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Validation of 3D ultrasound segmentation reliability for quantifying trochlear knee cartilage degradation" *Robarts Research Retreat, Western University Canada*. 19 June 2020. (Regional; Virtual; **Best Oral Presentation Award**)

8. **S. Papernick***, R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Validation of 3D ultrasound for quantifying trochlear knee cartilage loss" *Canadian Bone and Joint Conference (CBJC)*. 12 June 2020. (National; Virtual)

9. **S. Papernick*,** R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Validation of 3D ultrasound for bedside monitoring of osteoarthritis-induced synovium inflammation and cartilage degradation" *Imaging Network Ontario (ImNO)*. 27 March 2020. (Provincial; Virtual)

10. **S. Papernick*,** D. Gillies, T. Appleton, A. Fenster, "Three-dimensional ultrasound for monitoring knee inflammation and cartilage damage in osteoarthritis and rheumatoid arthritis" *Society of Photographic Instrumentation Engineers (SPIE) Medical Imaging: Image-Guided Procedures, Robotic Interventions, and Modeling*. 16 February 2020. (International; Houston, Texas, USA)

Poster Presentations (4)

11. **S. Papernick***, R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Reliability and concurrent validity of three-dimensional ultrasound for quantifying knee cartilage volume" *Osteoarthritis Research Society International (OARSI) Virtual World Congress on Osteoarthritis*. 29 April - 1 May 2021. (International; Virtual)

12. **S. Papernick*,** R. Dima, D.J. Gillies, T. Appleton, A. Fenster, "Validation of 3D ultrasound for bedside monitoring of osteoarthritis-induced synovium inflammation and cartilage degradation" *Western Research Forum, Western University Canada*. 19 March 2020. (Regional; Virtual)

13. **S. Papernick*,** D.J. Gillies, K. Barker, L. Gardi, A. Fenster, "Validating three-dimensional ultrasound measurements of the synovium for diagnosis of rheumatoid arthritis" *Imaging Network Ontario (ImNO)*. 28-29 March 2019. (Provincial; London, Ontario, Canada)

14. A. Fenster, J. Rodgers*, D. J. Gillies, J. Kishimoto, **S. Papernick,** N. Kakani, "Development of mechanical 3D ultrasound scanning devices for image-guided interventions" *Computer Assisted Radiology and Surgery (CARS)/International Society for Computer Aided Surgery (ISCAS)*. 17-21 June 2019. (International; Couvent des Jacobins, Rennes, France; **Kikuchi Best Poster Award**)