MRI software measurement of osteophyte volume in knee osteoarthritis: a longitudinal validation study

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Thesis

MRI SOFTWARE MEASUREMENT OF OSTEOPHYTE VOLUME IN KNEE OSTEOARTHRITIS:
A LONGITUDINAL VALIDATION STUDY

by

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MRI SOFTWARE MEASUREMENT OF OSTEOPHYTE VOLUME IN KNEE OSTEOARTHRITIS: A LONGITUDINAL VALIDATION STUDY

MING YIN
Boston University School of Medicine, 2016

ABSTRACT

Osteoarthritis (OA) currently affects 41 million Americans, and knee OA (KOA) alone causes the highest risk of mobility disability of any medical condition in people 65 years and older. There are no current treatments to reverse the degenerative changes of KOA, and research is aimed at finding biomarkers of KOA progression to aid in the development of effective therapies.

Osteophytes are a hallmark feature of KOA and may act as a biomarker of joint space loss and pain progression. MR imaging, which is an accurate and non-invasive method to monitor KOA disease status, may aid in clarifying the role of osteophytes in KOA, especially using semi-automated quantitative software methods to accurately and efficiently calculate osteophyte volume in longitudinal studies.

This study investigated the association of osteophyte volume change with joint space narrowing and pain progression in a randomized sample of 505 subjects from the FNIH OA Biomarker Consortium Project, a case-control study based on a larger
longitudinal study of patients with KOA. We also aimed to further validate a software method that measured osteophyte volume in MRI.

We found a moderate and significant association with osteophyte volume and joint space narrowing, but no significant association with pain progression. The software was further validated as responsive and efficient method to measure KOA osteophyte volume change.
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LIST OF ABBREVIATIONS

ACL....................................................................................................................... anterior cruciate ligament
BLOKS.......................................................................................................................... Boston-Leeds Osteoarthritis Knee Score
BML............................................................................................................................... bone marrow lesion
CI................................................................................................................................. confidence interval
COL2A1......................................................................................................................... collagen, type II, alpha 1
DMOAD .......................................................................................................................... disease-modifying OA drug
ECM................................................................................................................................. extracellular matrix
FNIH............................................................................................................................... Foundation for the National Institutes of Health
ICC................................................................................................................................. intraclass correlation coefficient
IL-1................................................................................................................................. interleukin-1
JSL................................................................................................................................. joint space loss
JSN................................................................................................................................. joint space narrowing
JSW................................................................................................................................. joint space width
KOA............................................................................................................................... knee osteoarthritis
LF................................................................................................................................. lateral femur
LT................................................................................................................................. lateral tibia
MF................................................................................................................................. medial femur
MMP............................................................................................................................. metalloproteinase
MOAKS......................................................................................................................... MRI Osteoarthritis Knee Score
MRI............................................................................................................................... magnetic resonance imaging
MT..........................................................................................................................medial tibia
NIH..........................................................................................................................National Institutes of Health
NSAID......................................................................................................................nonsteroidal anti-inflammatory drug
OA.............................................................................................................................osteoarthritis
OAI............................................................................................................................Osteoarthritis Initiative
OARSI..............................................................Osteoarthritis Research Society International
PCSK6......................................................................................................................proprotein convertase subtilisin/kexin type 6
PG..............................................................................................................................proteoglycan
TIMP........................................................................................................................tissue inhibitor of metalloproteinase
TNF-α....................................................................................................................tumor necrosis factor-α
ΔV.............................................................................................................................change in volume
WOMAC..................................................................................................................Western Ontario and McMaster Universities Arthritis Index
WORMS................................................................................................................Whole-Organ Magnetic Imaging Score
INTRODUCTION

1.a. Osteoarthritis: overview

There are an estimated 41 million Americans affected by osteoarthritis (OA), and societal trends in the population indicate the number of people affected by OA will increase by 50% of the next 20 years, partially due to an increase of obesity rates (Johnson & Hunter, 2014). Currently, OA is one of the leading causes of disability among non-institutionalized adults, with symptomatic OA affecting 10% of the adult population in the US, and knee OA (KOA) alone causing the highest risk of mobility disability of any medical condition in people 65 years and older (Johnson & Hunter, 2014). 80% of patients with OA have some limitation of mobility, while one-fourth cannot perform major activities of daily living (Guccione et al., 1994).

Economically, OA costs the US over $100 billion annually in direct and indirect costs (Lozada, 2015). In severe cases of knee or hip arthritis, total knee replacements (TKRs) or total hip replacements (THRs) are required, signaling the end-stage of the disease. OA is indicated in 95% of TKR and THR procedures, costing over 42 billion dollars in hospital expenditures in 2009 (Murphy & Helmick, 2012). Mortality from other diseases is also affected. Compared to the general population, adults with OA have nearly a twofold increase in mortality from cardiovascular disease and dementia (CDC, 2015).

Given the high individual and societal disease burden, research into OA is a high priority. OA, or degenerative joint disease, is defined as progressive, focal loss of joint hyaline cartilage with associated bony changes (Medline, 2016). The most commonly affected areas are the knee, hip, and hand joints. Biologically, the process of OA involves
the gradual loss of articular cartilage, narrowed joint space, the growth of bone spurs called osteophytes, and nonspecific synovial inflammation. In patients, OA is diagnosed by structural signs (e.g. radiographic evidence of joint space narrowing, osteophytes, and bony sclerosis) and clinical symptoms (e.g. pain, swelling, and stiffness) (CDC, 2015). This study will focus on knee OA, or KOA.

The knee, defined as the area where the femur in the upper leg meets the tibia on the lower leg, actually contains two joints: the tibiofemoral joint and the patellofemoral joint, which work together to form a modified hinge joint that can bend and rotate slightly (Figure 1). Given that our knees support 1.5 times our body weight when we walk and 8 times our body weight when we squat, these joints bear enormous pressure loads (Schmidler, 2016).

The points where the bones touch each other are covered with articular cartilage (i.e. hyaline cartilage), a smooth connective tissue that allows the bones to move freely against each other. It is in this tissue where the main degeneration of KOA occurs. Articular cartilage is found on the ends of the femur, the top of the tibia, and on the back of the patella. Against the articular cartilage of the femur and tibia are the crescent-shaped menisci, which act as shock absorbers that spread weight-bearing force over a larger area (Schmidler, 2016). Menisci are also affected by KOA. Finally, surrounding these cartilaginous structures is the joint capsule, containing outer fibrous capsule layer and the inner synovial layer, held together by ligaments. The synovium produces synovial fluid that provides lubrication for the knee.
KOA is the result of the wearing-down of the articular and meniscal cartilage on either knee joint, although most research is focused on the weight-bearing region of the tibiofemoral joint. Cartilage at pressure points wears down over time and has limited repairing ability due to its lack of blood vessels and very low cell proliferation rate. This is the root of the problem of any type of OA: once damage is done to the cartilage, there is currently no effective way to reverse it.

In broad strokes, the course of KOA starts with worn down cartilage that leads to a narrowed joint space width (JSW), or as it is sometimes called, joint space loss (JSL) or joint space narrowing (JSN). This injury causes inflammation of the synovium and capsule, bony outgrowths at the joints called osteophytes, and in severe cases, the damage

Figure 1. Healthy knee and osteoarthritic knee structures. KOA is characterized by a thickened and stretched capsule, worn down cartilage, osteophyte growth, a thickened and inflamed synovium, narrowed joint space, and thinner bone. (Bupa, 2015)
to the femoral or tibial bone structures (Figure 1). Both local and systemic factors contribute to the development of KOA. Local factors include injuries to the knee and developmental disorders that affect the musculoskeletal system, such as congenital hip dysplasia (Baker-LePain et al., 2010). Systemic factors include older age, obesity, gene polymorphisms such as COL2A1 that code for a type of collagen in bone, and decreased estrogen levels, leading to a higher incidence of OA in post-menopausal women (Hämäläinen et al., 2009, Roman-Blas et al., 2009).

1.b. Development of OA

Development of OA is progressive due to the poor ability of cartilage to self-repair. The etiopathogenesis can be divided into three stages: stage I, normal cartilage; stage II, aging/damaged cartilage; and stage III, osteoarthritic cartilage (Cannon, 2001). In stage I, normal cartilage is characterized by chondrocytes that maintain an extracellular matrix (ECM) with strong tensile strength. This healthy ECM contains molecules such as collagens type II, IX, and XI, proteoglycans such as aggrecan, and glycosaminoglycans like chondroitin sulfate and keratan sulfate, all of which retain water and form the biomechanical basis of articular cartilage’s load-bearing capacity (Fox et al., 2009). Incidentally, some of these molecules are being investigated as possible clinical therapies. (Uebelhart et al., 2004; Pomin, 2015),

Chondrocytes, the cells of the articular cartilage, maintain the ECM by balancing the rate of synthesis and degradation of the structural components. Degradation is accomplished by chondrocyte secretion of matrix metalloproteinases (MMPs), which are
enzymes that degrade ECM components (Cannon, 2001). Synthesis is promoted by the secretion of tissue inhibitors of MMPs (TIMPs), which in turn are upregulated by proinflammatory factors such as interleukin-1 (IL-1) and tumor necrosis factor-α (TNF-α) (Cannon, 2001). Also, synthesis is promoted by growth factors such as transforming growth factor (TGF)-β and bone morphogenetic proteins (BMPs), which are among the same factors responsible for endochondral ossification during fetal development (Sandell and Aigner, 2001).

Stage II, the passage of normal cartilage into aging/damaged cartilage, is caused by the failure of chondrocytes to maintain appropriate turnover of ECM components necessary to compensate for the joint’s mechanical stresses, instability, or matrix destruction (Cannon, 2001). Initiating variables include decreased ligament stability, excessive weight-bearing forces, decreased peripheral neuroprotective responses over time, and increased microfractures in the subchondral bone, for instance from a knee injury (Lane Smith et al., 2000). Subchondral microfractures are especially relevant to osteophyte development, since increased cartilage degeneration causes the development of a subchondral sclerosis zone, which may progress into osteophyte growth (Cannon, 2001).

Sandell and Aigner describes five categories of cellular reaction patterns to the osteoarthritic disease process, as seen in Figure 2: 1) proliferation and cell death (apoptosis), 2) changes in synthetic activity, 3) changes in degradation, 4) phenotypic modulation of the articular chondrocytes, and 5) formation of osteophyte (2001).
First, a low level of chondrocyte proliferation is a distinctive hallmark of OA, since normal chondrocytes very rarely regenerate. Some apoptosis occurs as well, although rates of cell death are still undetermined. Second, chondrocytes increase their synthesis of ECM components, but paradoxically, a net loss of PG content is one of the hallmarks of the entire OA cartilage degeneration process.

Third, chondrocytes increase their synthesis of degradative enzymes, particularly MMPs. Nearly all OA cells were found to contain elevated levels of MMP-3, 8, and 13. Fourth, chondrocytes change their phenotype by dedifferentiating to an early, fibroblast-like cell type, which synthesizes different types of ECM that do not help the growth of healthy adult cartilage. Functional chondrocytes produce collage type II and aggrecan, while dedifferentiated chondrocytes produce collagens type I and III. Finally, osteophytes develop, which will be described in the next section.

**Figure 2: Chondrocyte response to injury.** a) Types of injuries and responses. b) Chondrocyte modulation of gene expression resulting in recapitulation of collagen production found during
development, dedifferentiation of fibroblasts, cartilage growth plate hypertrophy, apoptosis, or regeneration of mature cartilage. (Sandell and Aigner, 2001)

1.c. Osteophytes

Osteophytes are one of the most visible diagnostic features of OA on radiographs, and the most common MRI-detected knee abnormality found in non-diagnosed adults over the age of 50 (Guermazi et al., 2012).

Osteophytes develop from new cartilage and bone growth on joint margins. They may form independently of OA due to normal aging or other types of disease (Cedars Sinai, 2016). For example, osteophytes can form in the back of the spine as a person ages, and may be asymptomatic or only cause pain if they impinge on a nerve. Diffuse idiopathic skeletal hyperostosis can cause bone ossification along the spine that has the appearance of “melted wax” (Ghosh et al., 2004). However, osteophytes are the main feature of OA that distinguishes it from other arthritic diseases (Sandell & Aigner, 2011).

In the knee, it is theorized that osteophytes form to stabilize the joint by increasing bone surface area, distributing pressure more evenly across the bone and overcoming abnormal cartilage loading (Felson et al., 2005). Studies have demonstrated that, after an induced anterior cruciate ligament (ACL) tear, osteophytes form in a way that limits pathological translocation of the femur on the tibia, compensating for ligament damage (Felson et al., 2005). Osteophytes also form near sites of KOA cartilage loss (Felson et al., 2005). However, it is still unclear if osteophyte formation after OA progression is related to the disease process, or if it is a marker for nearby cartilage loss.
One aim of this study is to examine a possible correlation between osteophyte volume change and JSL in subregions of the knee.

The development process of osteophytes is also still not fully clear, although animal and histological studies have illuminated crucial stages. Osteophytes are defined as fibrocartilage-capped bony outgrowths arising in the connective tissue overlying the bone, the periosteum (van der Kraan et al., 2007). Osteophytes develop in a process similar to endochondral ossification, and mesenchymal stem cells are thought to be the main cellular precursors of osteophytes (van der Kraan et al., 2007). In a murine model of OA, osteophytes formed after repeated injections of TGFB-1 in the knee (Menkes and Lane, 2004).

Figure 3 shows a histological cross-section of a murine experimental model for KOA, with major areas of marginal osteophyte formation located at the lateral and medial articular surfaces of the tibia and femur (van der Kraan et al., 2007). Osteophytes may also form in other locations, for instance at the site of attachment of the joint capsule or ligaments (i.e. enthesophytes), but in this study we focus on marginal osteophyte growth.

Although osteophytes are hypothesized to stabilize OA knees, they are still associated with worse JSW (Muraki et al., 2011; Felson et al., 2005), increased pain (Sowers et al., 2011), and decreased physical functioning (Muraki et al., 2011). This is why it is crucial to clarify the association of osteophytes to KOA, as we attempt to do in this study by following volumetric osteophyte change in a longitudinal study.
Figure 3. Histological schematic of a murine knee joint. Stars mark areas where osteophytes develop during experimental OA. T – tibia, P – patella, F – femur, L – ligament, M – meniscus, C – capsule. (van der Kraan et al., 2007)

1.d. Pain

One of the key clinical outcomes of KOA is pain. A specific grading scale, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), a 24-item index used to assess pain, stiffness, and physical function in patients with KOA or hip OA (Bellamy, 2002). The domain scores range from 0 to 20 for pain, 0 to 8 for stiffness, and 0 to 68 for physical function (Bellamy, 2014). Pain is based on patient descriptors of pain level during five activities: walking, using stairs, sitting in bed, lying in bed, and standing (Bellamy, 2014).

While it may seem straightforward to correlate the severity of the disease with the severity of pain, almost half of people with knee pain have no radiographic OA...
(Guermazi et al., 2012). Conversely, patients with diagnosable KOA features such as cartilage defects may not report any pain (Sowers et al., 2011).

Nonetheless, it is valuable to investigate if and which biomarkers have a greater correlation with higher WOMAC pain scores, given the clinical significance of joint pain on disability and quality of life (Muraki et al., 2011). With the availability of clinical Osteoarthritis Initiative (OAI) data, a longitudinal cohort study of KOA, we have an opportunity to investigate a connection between pain scores and osteophyte size.

The conception of pain itself is a complex neurological process that can be influenced by depression, gender, race, and education (Sharma, 2016). Pain is sensed peripherally by nocireceptors, and although articular cartilage does not contain nocireceptors, adjacent structures such as the bone, meniscus, and fat pad are innervated and respond to tissue damage (Jones et al., 2013). Certain symptoms of KOA are more strongly associated with knee pain: BMLs, cartilage defects, osteophytes, and synovitis/effusion, which indicates local inflammation (Jones et al., 2013). On the other hand, there has been generally consistent evidence that knee bone size, subchondral bone density, and meniscal extrusion are not associated with pain (Jones et al., 2013).

On a more systemic level, obesity is a very strong correlate of knee pain, with BMI contributing 10-25% of the increase in knee pain in participants of a 20-year KOA research study (Jones et al., 2013). Weight loss is often recommended as part of a treatment plan for KOA, although weight gain is more strongly associated with worsening pain than weight loss with improvements in pain, suggesting limited reversibility of symptoms (Jones et al., 2013).
Finally, pain perception differs among individuals based on peripheral and central nervous system differences. A lower pressure-pain threshold was associated with pain severity but not OA presence, severity, or duration, so pain experience and KOA disease trajectories do not always align (Sharma, 2016). Depression is often linked to pain experiences for all rheumatic disease, higher self-efficacy is inversely correlated with KOA pain, and a tendency to catastrophize (viewing a situation as considerably worse than it is) is positively associated with pain severity, possibly explaining the higher pain levels reported by women (Jones et al., 2013). Knee pain is heritable as well, with a variant in PCSK6 associated with protection against pain in KOA (Jones et al., 2013).

Isolating the role of osteophytes in KOA pain severity has been difficult, especially since studies often use composite scores such as the K/L scale, masking the effects of individual symptoms.

1.e. KOA biomarkers and clinical treatment

Ultimately, one of the key objectives in KOA research is finding biomarkers that predict who is at higher risk of developing the disease or having a more severe disease sequelae, with hopes of discovering clinical interventions that target earlier stages of the disease. The KOA disease process may begin 20 years before JSN is clinically detectable, and much earlier molecular and preradiographic biomarkers are detectable before radiographic evidence indicates the presence of disease (Figure 4). By the time visible JSN structural changes occur, KOA is, at the time of publication, irreversible due to the articular cartilage’s inability to regenerate (Sharma, 2016).
Clinical treatment currently focuses on pain management and maintenance of function. Examples include intraarticular injections of hyaluronic acid, glucosamine sulfate, physical therapy, NSAIDs, and arthroplasty (Cannon, 2001).

Research into clinical disease modifying OA drugs (DMOADs) are looking to reduce structural pathology of joint tissue in conjunction with beneficial clinical outcomes (Eckstein et al., 2014). In particular, imaging methods such as radiography and MRI are important ways to find and monitor structural pathology, so improving imaging methodology and utilizing imaging results is a promising avenue of research into KOA mechanisms and therapies.
2.a. Imaging: overview

Medical imaging visualizes interior structures of the body for diagnosis and treatment, and its major forms include x-rays (a.k.a. radiography), computed tomography (CT) scans, magnetic resonance imaging (MRI) scans, and ultrasound. Clinical monitoring and research on KOA has mainly used radiography and MRI as imaging modalities, although CT scans may be used on patients who cannot tolerate MRI (Medscape, 2016). MRI offers the benefit of 3-dimensional imaging, visualization of detailed soft tissue structures, and no x-ray radiation hazards.

An overview of magnetic resonance imaging (MRI) is useful for our discussion of KOA imaging. In a body, hydrogen protons are found in fat and water, where they spin on an axis to produce a north-south pole like a bar magnet. In an MRI scanner, a strong magnetic field (usually 1.5-3 T) aligns the protons’ axes and produces a magnetic vector along the MRI axis (Berger, 2002). Receiver coils detect the emitted signal and the signal intensity is plotted on a grayscale, creating the MRI scan.

However, image contrast needs differ based on which tissue is being visualized. Using different parameters, MRI scans can emphasize certain tissues (e.g. cartilage or bone for musculoskeletal imaging) or suppress the signal from other tissues (e.g. fat). This is especially important for MR imaging for KOA, given the range of musculoskeletal tissues involved in the disease.

2.b. KOA imaging and grading systems

In KOA, both soft and hard tissue structures are important to visualize.
Radiographs are the cheaper, more common method of detecting and assessing change in KOA, and features such as JSW, sclerosis, and osteophytes are visible, as seen in Figure 5.

MRI scans, while more expensive, allow for cartilage and soft tissue visualization, so that features such as cartilage defects and BMLs are only observed through MRI scans. Compared to the 2-dimensional imaging of x-rays, a 3-dimensional view of the joint structure can be invaluable. Radiographs are also projection images that are dependent on position, which could cause inconsistent osteophyte imaging. MR imaging has been shown to accurately assess long-term KOA structural changes in dog experimental models (Boileau et al., 2008). Also, MRI scans may find JSN that radiographic images cannot (Howell, 2010). Figure 6 shows a clinical case in which a patient over 40 presented with cartilage loss in a knee despite being diagnosed with normal JSW with a radiograph (Howell, 2010). This changed the orthopedist’s treatment recommendation and prevented an unnecessary arthroscopic surgery to fix the meniscal tear, which turned out not to be the source of the patient’s pain.

![Radiograph of an osteoarthritic tibiofemoral knee joint.](image)

**Figure 5: Radiograph of an osteoarthritic tibiofemoral knee joint.** The joint shows the presence of osteophytes, reduced JSW, and bony sclerosis. (Howell, 2010)
With these imaging modalities come grading systems that allow objective assessments of disease presence and progressions. KOA grading systems are scales that assess the severity of the disease. The most common clinically used systems are qualitative and ordinal; for example, grading the severity of KOA from a scale of 0-4. Newer grading systems have been developed to take advantage of computer-assisted quantitative measurements, where factors like JSW are measured as continuous variables.

The first and most established grading system is the Kellegren-Lawrence (K/L) grading scale, proposed in 1957 and still used as the “gold standard” for KOA diagnosis. It uses knee radiographs to observe the presence of four main KOA features. The grades range from 0, a knee with no radiographic features of KOA, to 4, where the knee contains large osteophytes, marked JSN, severe sclerosis, and definite bony deformity (Kellegren, 1957).
Grading scales can isolate the progression of specific KOA symptoms. One limitation of the K/L scale is the inability to individually assess the severity of KOA features. This was addressed by Osteoarthritis Research Society International (OARSI), which created a radiographic atlas that allows osteophytes and JSN to be separately assessed in the medial and lateral tibiofemoral compartments (OARSI, 2001).

Other scales measure different imaging modalities. Of interest to this thesis are the MRI grading scales, which focus on KOA features and subregions (Table 1). They include Whole-Organ Magnetic Resonance Imaging Score (WORMS), Knee Osteoarthritis Scoring System (KOSS), Boston Leeds Osteoarthritis Score (BLOKS), and MRI Osteoarthritis Knee Score (MOAKS) (Kornaat et al., 2005, Hunter et al., 2008, Hunter et al., 2011, Peterfy et al., 2005).

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<th>Scored features (grades)</th>
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<td><strong>Whole joint</strong></td>
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<tr>
<td><strong>WORMS:</strong> Peter et al. (2004)</td>
<td>Cartilage (0–6); BMLs (0–3); subchondral cysts (0–3); bone attrition (0–3); effusion and synovitis (0–3); periarticular cysts (0–3); bursitides (0–3); loose bodies (0–3); osteophytes (0–7); meniscal tear (0–4); cruciate and collateral ligaments (0–1)</td>
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<tr>
<td><strong>KOSS:</strong> Kornaat et al. (2005)</td>
<td>Cartilage size and depth (0–3); BMLs (0–3); subchondral cysts (0–3); osteophytes (0–3); effusion (0–3); meniscal tear (0–3); meniscal extrusion (0–3); popliteal cysts (0–3); synovial thickening (0–1)</td>
</tr>
<tr>
<td><strong>BLOKS:</strong> Hunter et al. (2008)</td>
<td>Cartilage size and depth (0–3, plus extent of any cartilage loss at specified point); BMLs (0–3, for each lesion); osteophytes (0–3); effusion (0–3); meniscal extrusion (0–3); synovitis (in Hoffa's fat pad 0–3 and at 5 additional sites* 0–1); meniscal status (0–1 for intramensical signal, tears, maceration, meniscal cyst, each scored individually); ligaments (0–1); periarticular cysts/bursitis (0–1); loose bodies (0–1)</td>
</tr>
<tr>
<td><strong>MOAKS:</strong> Hunter et al. (2011)</td>
<td>Cartilage size and depth (0–3); BMLs (0–3, for each lesion); osteophytes (0–3); effusion-synovitis (0–3); Hoffa synovitis (0–3); meniscal extrusion (0–3); meniscal status (0–1, for intramensical signal, tears, maceration, meniscal cyst, hypertrophy; scored individually); ligaments (0–1); periarticular cysts/bursitides (0–1, scored individually); loose bodies (0–1)</td>
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</tbody>
</table>

**Table 1:** Summary of KOA whole joint semiquantitative MRI scoring systems. These include WORMS, KOSS, BLOKS, and MOAKS. (Guermazi et al. 2013)
2.c. KOA semi-automated quantitative MRI software

Given the thousands of MRI scans that may need to be analyzed in a single KOA study, it can be difficult for an expert reader such as a radiologist to complete data collection within a reasonable amount of time. Qualitative WORMS, KOSS, BLOKS, and MOAKS scoring systems are thorough, but require evaluation of 8+ KOA features within a whole knee joint scan. Although they are more specific than grading systems (such as the K/L) that subsume all KOA features into one score, current qualitative MRI grading systems still grade based on an ordinal rather than continuous scale. Also, grading may be affected by reader bias.

The introduction of software able to automate this process is a crucial addition to keeping KOA research inexpensive and responsive, as well as allowing the measurement of continuous variables such as cartilage and osteophyte volumes. Semi-automated software is based on algorithms that do the bulk of the measurements (for instance, by detecting the bone-cartilage border based on grayscale values), requiring only a trained reader to fine-tune the measurements. A radiologist completes the process with a final quality assurance step. Multiple software methods have been developed to measure cartilage loss, BML volume, and osteophyte volume in KOA (Iranpour-Boroujeni et al., 2011; Duryea et al., 2014; Hakky et al., 2015; Stehling et al., 2011).

Specific aims

One objective of this study is to validate the responsiveness of a software method that calculates marginal osteophyte volume in subjects with diagnosed KOA. Previous
studies show that this software demonstrates good inter- and intra-reader reliability, strong responsiveness to average change in osteophyte volume over time, and concurrent validity with the MOAKS osteophyte score (Hakky et al., 2015). With the addition of datasets of 505 patients from the Osteoarthritis Initiative (OAI), a prospective cohort study of men and women at risk of KOA or with symptomatic KOA, we are now able to reexamine the responsiveness of this software to osteophyte volume measurement.

This study will also aim to use these osteophyte volume measurements to investigate possible associations with cartilage degeneration and pain scores. Since these are both clinically important factors of KOA progression and impact patient quality of life, finding a significant correlation could allow osteophytes to serve as an imaging biomarker for clinical, research, and therapeutic KOA research.

1. To further validate the responsiveness of semi-automated software for measuring osteophyte volume change
2. To examine a possible association between KOA marginal osteophyte volume change and JSW over 24 months
3. To examine a possible association between KOA marginal osteophyte volume change and pain over 24 months
METHODS

Study sample

We assessed knee MRI scans from the Foundation for the National Institutes of Health (FNIH) OA Biomarker Consortium Project dataset, drawn from the larger National Institutes of Health (NIH) Osteoarthritis Initiative (OAI) study (UCSF, 2013). The OAI is a public domain, longitudinal observational study aimed to help researchers understand incident and progressional KOA. 4,796 men and women ages 45-79 were enrolled from February 2004 to May 2006, recruited based on their symptomatic disease status or high risk of developing KOA. The seven-year project maintains a database of clinical evaluation data, radiological images, and biospecimens from the OAI participants over four years of follow-up. Annual visits every 12 months, were completed through 48 months, with two additional time points at 72 and 96 months.

The FNIH OA Biomarker Consortium Project is a separate public-private research partnership that uses data from the first four years of the OAI, using a nested case-control study (194 cases and 406 controls) to determine the validity and responsiveness of biomarkers with KOA progression (Nevitt, 2015). KOA progression was measured based on radiographic (x-ray) and pain progression outcomes from baseline (BL) compared to 24 month through 60 month OAI clinic visits. Imaging and biochemical marker changes were examined between BL and 12 month through 24 month visits.
X-ray progression was defined as medial minimum JSW loss (JSL) that was ≥0.7 mm from BL to 24, 36 or 48 months. This was the study-specific smallest detectable change determined from OAI images (Nevitt, 2015). Subjects with lateral KOA JSN at BL were excluded.

Pain progression was defined as a persistent increase in the total WOMAC pain score above the minimal clinically important difference (MCID), compared to BL (Angst et al., 2001). The MCID WOMAC pain score is ≥9 change on a 0-100 scale, since it is the score associated with the smallest detectable difference (SDD) in patient outcomes (Angst et al., 2001). All eligible knees started at a K/L score of 1-3 at BL.

Subjects were divided into four case-control groups based on x-ray and pain progression (Figure 7). The primary case definition was 1) an x-ray + pain (or JSL-only, as used in this thesis) progressor, characterized by a knee that had both radiographic and pain progression. The primary control definition was a knee that did not reach criteria for both endpoints, leading to three control groups: 1) an x-ray-only progressor, 2) a pain-only progressor, and 3) a non-progressor, defined as a knee with neither X-ray nor pain progression. The case-control groups were also frequency matched based on baseline BMI and K/L grade, creating a better balance among the groups for covariate adjustment.

<table>
<thead>
<tr>
<th>X-ray and Pain progressor (Case)</th>
<th>X-ray only progressor</th>
<th>Pain only progressor</th>
<th>Neither X-ray nor pain progression (Non-progressor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>194 (194)</td>
<td>103 (103)</td>
<td>103 (103)</td>
<td>200 (200)</td>
</tr>
</tbody>
</table>

**Figure 7: FNIH OA Project study sample.** This figure displays the selected subjects and total number of (knees). Case group: 1) X-ray + pain progressors (n = 194). Control groups: 2) X-ray-only progressors (n = 103), 3) pain-only progressors (n = 103), and 4) non-progressors (n = 200). (Nevitt, 2015)
In this study, we randomly selected 505 subjects from the 600 subjects in the FNIH Study. Our study sample was distributed as JS + pain progressors (n = 140), JS-only progressors (n = 97), pain-only progressors (n = 88) and non-progressor (n = 180). An earlier preliminary analysis with this software method was done using 289 FNIH Study subjects and showed statistically significant results (Yin 2016).

Table 2 and 3 summarize the baseline subject and knee characteristics of the participants selected for the FNIH Study.

<table>
<thead>
<tr>
<th></th>
<th>X-ray + pain progressor</th>
<th>X-ray only progressor</th>
<th>Pain only progressor</th>
<th>Non-progressor</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (SD)</td>
<td>62.0 (8.8)</td>
<td>63.1 (8.3)</td>
<td>58.0 (8.7)</td>
<td>61.5 (9.1)</td>
<td>0.011</td>
</tr>
<tr>
<td>Male</td>
<td>43%</td>
<td>55%</td>
<td>35%</td>
<td>35%</td>
<td>0.003</td>
</tr>
<tr>
<td>Nonwhite</td>
<td>20%</td>
<td>12%</td>
<td>28%</td>
<td>22%</td>
<td>0.029</td>
</tr>
<tr>
<td>Pain meds for knees mst days, past yr</td>
<td>32%</td>
<td>21%</td>
<td>36%</td>
<td>28%</td>
<td>0.088</td>
</tr>
<tr>
<td>Glucosamine mst days, past mo</td>
<td>33%</td>
<td>33%</td>
<td>29%</td>
<td>26%</td>
<td>0.290</td>
</tr>
</tbody>
</table>

Table 2: Baseline subject characteristics. Age, gender, race, pain medication usage in the past year, and glucosamine usage in the past month. (Nevitt, 2015)
Table 3: **Baseline index knee characteristics.** History of knee injury (*based on self-report of knee injury causing difficulty walking for >=2 days), WOMAC score, and presence of grade 2 medial JSN (vs. grade 0-1). (Nevitt, 2015)

MRI

Double echo steady state (DESS) 3D sagittal images were obtained and reformatted into a coronal series (0.365 mm x 0.7 mm, 0.73 mm slice thickness) for osteophyte readings.

**Osteophyte measurements**

Osteophyte volume was measured at four central weight-bearing regions: medial femoral condyle (MF), medial tibial plateau (MT), lateral tibial plateau (LT), and lateral femoral condyle (LF). The readers viewed and analyzed the scans paired for BL and 24-month follow up, but blinded to order of visit and case-control status. A radiologist later reviewed the accuracy of the readings and suggested changes when needed.
Figure 8. Screen capture of the semi-automated quantitative software used to measure osteophyte volume. The bone outline is automatically detected with an algorithm, while a reader creates the lines closing off the osteophyte areas. Corner #0 = MF, #1 = MT, #2 = LF, #3 = LT.

Figure 8 shows a screen capture of a single slice that is fully “segmented” (i.e. outlined) by a reader. Two readers, a post-doctoral senior radiology resident and a research assistant, were trained in the use of the software and assessed for inter- and intra-reader reliability. A previous study found reader reproducibility high, with an intraclass correlation coefficient (ICC) of 0.98 and an inter-reader ICC of 0.97 (Hakky et al., 2015).

A reading began with locating the standardized starting point on the image, roughly within a 2.5 cm region anterior to the intercondylar line. At this point, the femoral condyles are no longer separate bony structures (Figure 9). This slice was marked the starting point of the series of 18 that were analyzed.
We limited measurements to 2.5 cm anterior of the intercondylar line rather than the whole tibiofemoral joint, since previous studies have shown this is the crucial weight-bearing area and a reliable assessment of KOA effects on the joint (Glaser et al., 2003). Limiting osteophyte volume measurements to 18 slices ensures a fast reading time, roughly 10 minutes per reader, without sacrificing precision (Hakky et al., 2015).

Next, a second slice was located 17 slices anterior to the first slice at the intercondylar line. The joint margin was also found, indicating the location of the soft...
tissue adjacent to the bone. Each tibiofemoral joint compartment was then measured separately. As shown in Figure 9, the knee joint was divided into four compartments ("corners") for separate analysis. Corner #0 was located the MF, corner #1 at the MT, corner #2 at the LT and corner #3 at the LF.

Figure 10 shows the software graphical user interface (GUI) for segmenting corners. Once the first and second slices are marked for a corner, the software runs an edge detection algorithm that delineates the bone edges by differentiating structures along a gray-scale gradient. Bone is darkest, while cartilage and fluid are a few of the lightest areas. If a given bone edge contains an osteophyte, the reader will “close it off” by drawing a line along the assumed bone contour, isolating the osteophyte area for the final volume calculation (Figure 10). This process is repeated for the next 17 slices, then for the other three knee joint compartments. Finally, the software measures the total osteophyte volume in each region as a sum of the osteophyte areas on all 18 slices.
Figure 10: Software GUI. The corners outlined in yellow are completed; osteophytes are segmented in corner #0 and #1. The corner outlined in light blue is being edited by the user. On the bottom of the screen, “Quit” leaves the GUI, “Prev” navigates to the previous slice, “<” and “>” adjusts the blue outline by increasing or decreasing the threshold sensitivity for greyscale, and “Hide” temporarily removes the GUI to show the original scan.

Readers were blinded to case-control status and time point. Each scan was segmented for osteophytes at one time point, made into a duplicate image, and shown as a side-by-side image with image from a second time point, also segmented, to ensure consistency. Finally, a radiologist performed a quality assurance step.
**Statistical analysis**

For each subject group (JSL+pain, JSL-only, pain-only, and non-progressor), we analyzed the mean osteophyte volume change from baseline to 24 months (ΔV) and 95% confidence interval (95% CI) for the entire knee. We then found the ΔV, standard deviation for ΔV (SD), and standardized response mean (SRM) for each anatomical region (MF, MT, LT, LF), as well as the medial compartment (M = MF+MT), lateral compartment (L = LF+LT), femoral compartment (F = LF+MF), and tibial compartment (T = LT+MT), and total knee (Total = MF+MT+LF+LT).

SRM defines the responsiveness of the software to change to osteophyte volume measurement, assuming that osteophytes increase in volume over time. It is calculated by mean of ΔV divided by the standard deviation of ΔV (ΔV/SD), and reflects the sensitivity of a measurement instrument to detect change within groups between two points in time (i.e. responsiveness) (Middel and van Soderen, 2002). This calculation acts as an effect size index (ES), where thresholds can be interpreted as follows (Middel and van Soderen, 2002):

[1] SRM < 0.20 = trivial  
[2] 0.20 ≤ SRM < 0.50 = small  
[3] 0.50 ≤ SRM < 0.80 = medium  
[4] SRM ≥ 0.80 = large

Finally, we found with odds ratio (OR) and 95% CI for case/control predictors, comparing the relative odds of osteophyte volume change given the exposure (JSL + pain, JSL-only, and pain-only). For adjusted ORs, we used logarithmic regression with
univariate models, adjusted for covariates of baseline age, sex, BMI, race, K/L grade, WOMAC pain score, pain medication use, and minimum JSW. This allows a comparison of osteophyte volume change between three separate case/control status groups:

[1] primary case/control analysis: **radiographic + pain progressors** (JSL+pain) versus **non radiographic + pain progressors** (all other groups)

[2] **radiographic progressors** (JSL+pain and JSL) versus **non radiographic progressors** (pain only and non-progressor)

[3] **pain progressors** (JSL+pain and pain only) versus **non pain progressors** (JSL only and non-progressor)
RESULTS

Results are shown in Table 4 - 6. Table 4 is summary of whole knee osteophyte volume changes over 24 months, showing the sample size, ΔV, and 95% CI for each subject group. Average reader time was 10 minutes.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>ΔV (mm³)</th>
<th>95% CI (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JSL + Pain</td>
<td>140</td>
<td>118.1</td>
<td>89.25 - 147.04</td>
</tr>
<tr>
<td>JSL</td>
<td>97</td>
<td>132.2</td>
<td>96.57 - 167.79</td>
</tr>
<tr>
<td>Pain</td>
<td>88</td>
<td>37.6</td>
<td>26.11 - 56.84</td>
</tr>
<tr>
<td>Non-progressor</td>
<td>180</td>
<td>41.5</td>
<td>18.62 - 56.64</td>
</tr>
</tbody>
</table>

Table 4: Average osteophyte volume change and 95% confidence interval for total knee, by group.

Several trends are of interest. First, as explained earlier, subject groups had different sample sizes, but effects are significant and trends follow the findings described in this section (Yin 2016).

Second, both JSL groups showed a significant higher volume change (JSL+pain ΔV = 118.1 mm³, JSL-only ΔV = 132.2 mm³) than non-JSL groups (pain-only = 37.6 mm³, non-progressor = 41.5 mm³). This was the main finding in the preliminary investigation into this cohort.

Third, pain-only progressors showed the least osteophyte volume change, which followed initial findings that showed low to no association of osteophyte growth with pain (Yin et al., 2016). This result could support the hypothesis that osteophytes stabilize knee by redistributing irregular forces caused by articular cartilage loss.
Table 5 shows $\Delta V$, SD, and SRM for each knee region and compartment, divided by subject group. The first column displays results for all the groups combined, while the next four columns show results for the four case-control groups.

<table>
<thead>
<tr>
<th>Region</th>
<th>All Groups $\Delta V$ (+/- SD) (mm$^3$)</th>
<th>SRM</th>
<th>JSL + Pain $\Delta V$ (+/- SD) (mm$^3$)</th>
<th>SRM</th>
<th>JSL-only $\Delta V$ (+/- SD) (mm$^3$)</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>24.8 (+/- 54.1)</td>
<td>0.46</td>
<td>40.4 (+/- 69.0)</td>
<td>0.59</td>
<td>38.8 (+/- 65.2)</td>
<td>0.60</td>
</tr>
<tr>
<td>MT</td>
<td>16.4 (+/- 46.2)</td>
<td>0.36</td>
<td>21.3 (+/- 46.2)</td>
<td>0.46</td>
<td>37.1 (+/- 71.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>LF</td>
<td>24.9 (+/- 38.3)</td>
<td>0.41</td>
<td>36.3 (+/- 83.2)</td>
<td>0.43</td>
<td>35.9 (+/- 59.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>LT</td>
<td>13.3 (+/- 61.0)</td>
<td>0.35</td>
<td>20.2 (+/- 48.0)</td>
<td>0.42</td>
<td>20.4 (+/- 39.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>F</td>
<td>49.7 (+/- 97.7)</td>
<td>0.51</td>
<td>76.7 (+/- 127.6)</td>
<td>0.60</td>
<td>74.7 (+/- 109.6)</td>
<td>0.68</td>
</tr>
<tr>
<td>T</td>
<td>29.7 (+/- 67.8)</td>
<td>0.44</td>
<td>41.5 (+/- 72.4)</td>
<td>0.57</td>
<td>57.4 (+/- 91.2)</td>
<td>0.63</td>
</tr>
<tr>
<td>M</td>
<td>41.3 (+/- 83.5)</td>
<td>0.49</td>
<td>61.7 (+/- 93.6)</td>
<td>0.66</td>
<td>75.9 (+/- 115.1)</td>
<td>0.66</td>
</tr>
<tr>
<td>L</td>
<td>38.2 (+/- 84.0)</td>
<td>0.45</td>
<td>56.4 (+/- 107.8)</td>
<td>0.52</td>
<td>56 (+/- 85.0)</td>
<td>0.66</td>
</tr>
<tr>
<td>Total</td>
<td>79.5 (+/- 145.7)</td>
<td>0.55</td>
<td>118.1 (+/- 172.9)</td>
<td>0.68</td>
<td>132.2 (+/- 176.7)</td>
<td>0.75</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region</th>
<th>Pain-only $\Delta V$ (+/- SD) (mm$^3$)</th>
<th>SRM</th>
<th>Non-progressor $\Delta V$ (+/- SD) (mm$^3$)</th>
<th>SRM</th>
</tr>
</thead>
<tbody>
<tr>
<td>MF</td>
<td>11.9 (+/- 30.2)</td>
<td>0.39</td>
<td>11.6 (+/- 35.5)</td>
<td>0.33</td>
</tr>
<tr>
<td>MT</td>
<td>2.2 (+/- 22.4)</td>
<td>0.10</td>
<td>8.4 (+/- 30.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>LF</td>
<td>14.2 (+/- 38.2)</td>
<td>0.37</td>
<td>15.4 (+/- 46.4)</td>
<td>0.33</td>
</tr>
<tr>
<td>LT</td>
<td>9.3 (+/- 33.9)</td>
<td>0.28</td>
<td>6.1 (+/- 28.6)</td>
<td>0.21</td>
</tr>
<tr>
<td>F</td>
<td>26.0 (+/- 57.3)</td>
<td>0.45</td>
<td>29.9 (+/- 66.9)</td>
<td>0.40</td>
</tr>
<tr>
<td>T</td>
<td>11.6 (+/- 43.9)</td>
<td>0.26</td>
<td>14.5 (+/- 50.5)</td>
<td>0.29</td>
</tr>
<tr>
<td>M</td>
<td>14.1 (+/- 40.8)</td>
<td>0.35</td>
<td>20.0 (+/- 55.7)</td>
<td>0.36</td>
</tr>
<tr>
<td>L</td>
<td>23.5 (+/- 61.6)</td>
<td>0.38</td>
<td>21.5 (+/- 65.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Total</td>
<td>37.6 (+/- 89.7)</td>
<td>0.42</td>
<td>41.5 (+/- 104.4)</td>
<td>0.40</td>
</tr>
</tbody>
</table>

Table 5: Average osteophyte volume change, standard deviation, and standardized response mean for each knee region and compartment, by group.

There are several trends in this table:

[1] **JSL groups versus non-JSL groups:** again, the trend of increased $\Delta V$ in JSL groups compared to non-JSL group is reflected in almost every anatomical region and compartment for each case/control group. The JSL groups also had a higher
average SRM (SRM = 0.42 – 0.75) compared to non-JSL groups (SRM = 0.10 – 0.45), implying that the software had higher responsiveness to osteophyte volume change in groups that showed structural cartilage loss.

[2] **Pain groups versus non-pain groups:** pain groups in general showed lower ΔV compared to non-pain groups as well as lower responsiveness (e.g. JSL-only total ΔV = 132.2 mm$^3$ and SRM = 0.75, versus pain-only total ΔV = 37.6 mm$^3$ and SRM = 0.42). The pain-only group had equal or lower ΔV compared to non-progressors in every region and compartment, although this effect may not be significant.

[3] **Medial versus lateral:** Intriguingly, medial and lateral compartments in almost all groups show similar osteophyte ΔV and SRMs, despite subjects being selected based on medial JSL and specifically excluded for lateral JSL at BL. Given the higher cartilage structural damage in the medial compartment at BL, it would be expected that the medial compartment would show significantly greater osteophyte ΔV than lateral compartment. However, all subject groups show a similar medial ΔV and lateral ΔV, with perhaps the exception of JSL-only progressors. The JSL + pain and JSL-only groups are more consistent with the earlier trend of increased osteophyte ΔV in areas with JSL, but the ΔV and SRMs are fairly close (e.g. JSL+pain medial ΔV = 61.7 mm$^3$ compared to JSL+pain lateral ΔV = 56.4 mm$^3$, with only ~5 mm$^3$ difference in volume).

[4] **Femoral versus tibial:** the femoral regions and compartments showed higher ΔV and somewhat higher SRM compared to the tibia (e.g. all groups femoral ΔV =
49.7 mm$^3$ and SRM = 0.51, versus tibial $\Delta V = 11.6$ mm$^3$ and SRM = 0.44) but also a larger SD.

[5] **SRM:** The results of all groups, JSL-only group, and JSL+pain group showed moderate to moderate-high responsiveness to change (all groups SRM = 0.35 – 0.55, JSL-only SRM = 0.52 – 0.72, and JSL+pain SRM = 0.42 – 0.68). Pain-only and non-progressor groups showed low to low-moderate SRMs (pain-only SRM = 0.10 – 0.45 and non-progressor SRM = 0.21 – 0.40).

Finally, Table 6 shows the adjusted OR, 95% CI, and p-value for the three case/control statuses.

<table>
<thead>
<tr>
<th>Region</th>
<th>Radiographic + pain vs. no radiographic + pain progression</th>
<th>Radiographic vs. non-radiographic progression</th>
<th>Pain vs. no pain progression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
<td>Adjusted OR (95% CI)</td>
</tr>
<tr>
<td>MF</td>
<td>1.53 (1.23-1.90)$^1$</td>
<td>2.12 (1.60-2.80)$^1$</td>
<td>1.22 (1.00-1.49)$^2$</td>
</tr>
<tr>
<td>MT</td>
<td>1.18 (0.97-1.44)</td>
<td>1.72 (1.35-2.19)$^1$</td>
<td>0.96 (0.79-1.16)</td>
</tr>
<tr>
<td>LF</td>
<td>1.32 (1.08-1.62)$^2$</td>
<td>1.52 (1.22-1.89)$^2$</td>
<td>1.12 (0.93-1.36)</td>
</tr>
<tr>
<td>LT</td>
<td>1.26 (1.04-1.53)$^1$</td>
<td>1.54 (1.23-1.93)$^1$</td>
<td>1.13 (0.94-1.36)</td>
</tr>
<tr>
<td>M</td>
<td>1.44 (1.17-1.76)$^2$</td>
<td>2.25 (1.70-2.97)$^2$</td>
<td>1.11 (0.91-1.34)</td>
</tr>
<tr>
<td>L</td>
<td>1.37 (1.12-1.67)$^1$</td>
<td>1.68 (1.34-2.11)$^1$</td>
<td>1.15 (0.96-1.40)</td>
</tr>
<tr>
<td>T</td>
<td>1.49 (1.21-1.83)$^1$</td>
<td>1.91 (1.70-2.90)$^1$</td>
<td>1.13 (0.95-1.40)</td>
</tr>
</tbody>
</table>

**Table 6:** Adjusted odds ratios and 95% confidence interval for three case/control statuses: 1) radiographic + pain vs. no radiographic + pain progression, 2) radiographic vs. no radiographic progression, and 3) pain vs. no pain progression. $^1$ p < 0.001, $^2$ p < 0.05

[1] **Radiographic + pain progression versus no radiographic + pain progression:**

$\Delta V$ is moderately associated with cartilage degeneration and pain together.

Femoral regions (MF OR = 1.53, LF OR = 1.32) show a stronger effect than tibial regions (MT OR = 1.18, LT OR = 1.26). Medial (OR = 1.44) and lateral (OR =
1.37) compartments again have similar outcomes, and are closer to the total knee
OR (OR = 1.49) than the separate knee regions.

[2] **Radiographic progression versus no radiographic progression:** $\Delta V$ is most
strongly associated with radiographic progression alone, and all ORs were
significant. Medial regions (MF OR = 2.12, MT OR = 1.72, M OR = 2.25) show
the highest association of osteophyte volume change with cartilage degeneration,
which is again expected given subjects were chosen by medial JSL.

[3] **Pain progression versus no pain progression:** $\Delta V$ has almost low or no
statistically significant association with pain progression. MF $\Delta V$ showed a low
significant association with pain progression (OR = 1.22).

[4] **Total knee $\Delta V$:** ORs are reflective of overall effect of the predictor in each
group. Pearson correlation coefficients (not shown in table) revealed a good
association of total knee $\Delta V$ with the individual knee regions, with these results:
MF ($r = 0.77$), MT ($r = 0.69$), LF ($r = 0.79$), and LT ($r = 0.65$) $\Delta V$. 
DISCUSSION

This study addressed three objectives: 1) providing further longitudinal validation of a semi-automated software tool by finding good responsiveness and reader time, 2) discovering a statistically significant association between an increase in osteophyte volume and JSL, and 3) finding no statistically significant association between an increase in osteophyte volume with pain progression.

Software method validation

Based on SRM values (Table 5), we found moderate to moderate-high responsiveness of the software for osteophyte volume change to all the combined subjects, as well as specifically to the JSL-only and JSL+pain groups. We found lower but still meaningful responsiveness for the pain-only and non-progressor groups. Trends include increased sensitivity to femoral locations over tibial locations, as well as similar results in the lateral and medial compartments.

Additionally, the semi-automated nature of the software made analysis rapid compared to non-software methods. That average reader time per scan was 10 minutes. Given that this study examined 18 slices per scan of the tibiofemoral joint at two time points for 505 subjects, this amounted to 18,180 slices finished over several months.

These results further validate the efficacy of a semi-automated quantitative knee MRI software method, which may have utility in future studies that require fast and efficient quantification of osteophyte volume for KOA research.
**Osteophyte volume change and JSL**

Overall, joint space loss was moderately and significantly associated with osteophyte volume change. JSL-only groups showed the highest change in osteophyte volume, and radiographic groups compared to the non-radiographic groups revealed the strongest adjusted OR values.

Several patterns emerged. First, it is noteworthy that, although subjects for this cohort were selected based on the presence of medial JSL, since lateral compartment osteophyte ΔV and SRM were showed similar values to medial compartment osteophyte ΔV and SRM. Since we found the earlier trend of increased osteophyte ΔV correlating with increased cartilage loss, it is remarkable that the lateral knee compartment – which had a lower BL JSN than the medial compartment given the subject selection process – had almost equal osteophyte growth as the medial compartment, challenging the hypothesis that JSL on one side of the knee causes ipsilateral osteophyte growth (i.e. stabilizing the knee on the side where there is loss of articular cartilage) (Faschingbauer et al., 2015). Still, the JSL-only group is consistent the earlier trend of increased ΔV in areas with JSL.

Given that a previous study found higher osteophyte scores increased risk of ipsilateral cartilage JSL progression (e.g. lateral osteophytes increased risk of lateral JSL) and decreased the risk of contralateral JSL progression, this is an interesting finding (Felson et al., 2004). However, these associations were attenuated by the presence of knee varus-valgus malalignment (Felson et al., 2004). It would be fruitful to further investigate the effect of KOA osteophyte presence and size based on knee compartment.
Second, the osteophyte $\Delta V$, SRM, and ORs for the JSL+pain group were consistently the same or less than the JSL-only group. The presence of pain progression dilutes the moderately strong association of osteophyte growth with joint space narrowing, which could include both articular and meniscal cartilage loss. This is intriguing since clinically, cartilage loss combined with knee pain is a more severe form of KOA than cartilage loss alone, which makes it difficult to use osteophyte volume change as a unilateral marker of increased KOA severity.

Third, femoral knee regions showed greater $\Delta V$ and SRM but larger SD than tibial compartments, indicating a higher magnitude and range of osteophyte volume change over time. Knowing the higher responsiveness and sensitivity to change of the femoral change may allow future studies to concentrate measurements in that compartment as a substitute for the entire joint.

Fourth, the total knee results for $\Delta V$, SRM, and OR were reflective of results in other knee compartments and regions. As indicated by the correlation coefficients, total knee change was a good stand-in for MF, MT, LF, and LT regions ($r = 0.65 – 0.79$). Also, total knee measurements tended to fall in the middle of other values, so it may be useful as a summary measurement on its own.

**Osteophyte volume change and pain progression**

It is interesting to note that the pain-only progressor group showed the least total $\Delta V$ out of all the groups, including the control non-progressor group, although the difference is only clearly significant between the pain-only group and JSL groups. Overall, both pain progressor groups showed no positive association with increased
osteoophyte ΔV. Non-progressors, by definition, showed less KOA clinical progression than all other groups, but they did not have the smallest amount of osteophyte growth. This may support a hypothesis that osteophytes may only act as a marker of nearby cartilage loss, and other factors are more directly responsible for causing or alleviating knee pain during KOA progression.

Pain progression also showed low or no statistically significant association with osteophyte volume growth based on adjusted ORs. Given some contradictory evidence from previous studies, it is difficult to infer the role of osteophytes in knee pain, the many factors influencing the presence and perception of pain by patients with KOA.

**Conclusion**

In conclusion, these results may shed light on the role of osteophytes in OA cartilage degeneration. We found that osteophyte volume is moderately associated with structural worsening of KOA, but less so with pain progression. Also, it is osteophyte growth in the lateral compartment of the tibiofemoral weight-bearing region is associated with JSL in the medial compartment, showing a contralateral rather than ipsilateral association between osteophytosis and JSL.

There were several limitations to this study. First, software calculations of osteophyte volume were localized to a 2.5 cm weight-bearing area in the knee joint.

Although this area was shown to be sensitive to whole-joint osteophyte growth, some KOA-related volume change may be unaccounted for. However, given that we used data from a longitudinal study and measured the same knee joint location in baseline and
24-months, the relative change in osteophyte volume between subregions and compartments should not be affected. Second, the current analysis in this thesis is based on 505 subjects out of the 600 subjects in FNIH OA Project case-control sample. However, these findings show significant results that are similar to an earlier preliminary analysis of 289 subjects from the same study sample (Yin 2016).

Further research using this quantitative MRI software would help clarify the role of osteophyte growth in KOA, given that this software allows for a more granular and sensitive measurement of osteophyte volume. A more highly-powered study examining the correlation between osteophyte volume, articular cartilage loss, and knee pain could further elucidate the function of osteophytes in KOA and their status as a possible imaging biomarker for the disease.
REFERENCES


Yelin, Edward, Louise Murphy, Miriam G. Cisternas, Aimee J. Foreman, David J. Pasta, and Charles G. Helmick. 2007. “Medical Care Expenditures and Earnings Losses among Persons with Arthritis and Other Rheumatic Conditions in 2003, and

CURRICULUM VITAE

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EDUCATION

Boston University School of Medicine – Boston, MA
Master of Science in Medical Sciences, 2016
(anticipated)

University of California, Berkeley – Berkeley, CA
Bachelor of Arts in Integrative Biology, May 2014
Bachelor of Arts in Public Health, May 2014

PUBLICATIONS


RESEARCH
Harvard Medical School / Brigham and Women’s Hospital – Department of Radiology  
**Research Assistant**  
*Boston, MA*  
**Sept 2015 – July 2016**  
- Acted as reader using MRI semi-automated software for knee osteoarthritis by measuring osteophyte volume, cartilage volume, and bone mass lesion volume.
- Acted as reader using MRI semi-automated software for rheumatoid arthritis by segmenting bone erosion volume in wrist bones.
- Aided in several abstracts as co-author and was first author in a study on longitudinal changes of osteophyte volume in knee osteoarthritis.

Boston University School of Medicine – Pharmacology and Experimental Therapeutics Department  
**Research Assistant**  
*Boston, MA*  
**May 2011 – Aug 2011**  
- Assisted in Dr. Libin Cui’s research of dysmyelination in Huntington’s disease using mouse models.
- Utilized laboratory techniques: maxiprep, PCR, spinal cell culture, agarose gel electrophoresis, Western blot, and fluorescence microscopy.

Shanghai Jiao Tong University School of Medicine - Neurological Research Institute in Ruijin Hospital  
**Research Assistant**  
*Shanghai, China*  
**Dec 2011**  
- Assisted Dr. Jianqing Ding’s research of microtubule-related pathogenesis of Parkinson’s disease.
- Utilized laboratory techniques: maxiprep, neuron cell culture, and fluorescent microscopy visualization.
- Aided in editing grant proposals.

CLINICAL

Children’s Hospital of Oakland  
**Welcome Wagon Volunteer**  
*Oakland, CA*  
**Nov 2013 – May 2014**  
- Assisted patients and families in the Medical Unit with bedside visits, e.g. relieving parents during mealtimes.
• Supported unit nursing staff during rounds, especially in the post-natal ward, e.g. feeding babies.

**Marin Sonoma Urology Associates**  
*Novato, CA*  
*Shadowing in Urology*  
*July 2013*

• Observed the physician in Dr. Peter Bretan, M.D., FACS in his outpatient urology clinic, where half the time he worked with the prison population.
• Observed the physician in the role of a medical expert witness and in his role as a member of the CMA (California Medical Association).

**Shanghai First People’s Hospital**  
*Shanghai, China*  
*Shadowing in Neurology*  
*Dec 2010*

• Observed Dr. Jun Liu, M.D. in neurology outpatient rounds, mainly with Alzheimer patients.
• Learned the dynamics of working in a large city hospital.

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**LEADERSHIP**

**American Medical Students Association - Berkeley Chapter**  
*Berkeley, CA*  
*Community, Environmental, & Global Health Committee Chair*  
*Aug 2009 – May 2011*

• Presented monthly educational meetings on aspects of community, environmental, and global medicine to 40-60 AMSA members.
• Coordinated travel, activities, and fundraising for the yearly service trip to New Orleans for 30 members.
• Coordinated with other chairs in monthly meetings and liaised with the national AMSA board

**Suitcase Clinic**  
*Berkeley, CA*  
*Women’s Clinic Health Supplies Coordinator*  
*Aug 2010 – May 2011*

• Distributed health and hygiene supplies to women in the Suitcase Clinic homeless shelter weekly.
• Oversaw activities of 2 other volunteers in the Health Supplies division.
• Coordinated city and campus-wide fundraisers for donations bimonthly.
Phi Delta Epsilon, CA Iota Chapter  
**Berkeley, CA**

*Academic Committee / Recruitment Committee*  
Jan 2010 – May 2013

- Currently act as a mentor for new members.
- Established a new MCAT resource for future members.
- Coordinated Rush Week and pledging activities every semester.
- Facilitated the admissions and interviewing process for new members.
- Volunteered in biweekly community service events, e.g. an annual Children’s Miracle Network banquet that raises ~$5,000 per year for Children’s Hospital of Oakland.

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**COMMUNITY SERVICE**

Global Water Brigades  
*Los Liquidambos, Honduras*

*Volunteer*  
June 2013

- Dug trenches and laid pipework for a clean water infrastructure with the Los Liquidambos community.
- Developed lesson plans and educated children in the community about water sanitation and safety.

Berkeley Humane Society  
*Berkeley, CA*

*Cat Foster Volunteer*  
May 2013 – May 2014

- Fostered 8 shelter cats, including kittens too young to be adopted.
- Promoted adoption efforts through written descriptions and photos of the animals.

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**SKILLS**

- **Laboratory**: maxiprep, PCR, spinal cell culture, neuron cell culture, agarose gel electrophoresis, Western blot, and fluorescence microscopy visualization.
- **Computers**: Microsoft Word, Microsoft Powerpoint, RefWorks, PubMed
- **Other**: CITI RCR certified, CPR-AED certified