MRI ANALYSIS OF KNEE OSTEOARTHRITIS PATHOLOGY

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To my husband, with love

Contents

Statement of author

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Abstract

Knee osteoarthritis (OA) represents a substantial burden to older individuals and the community. It is a common disease causing significant pain and disability. New insights into the structural pathology and causes of pain at all stages of this disease are required to allow further development of novel interventions. Magnetic resonance imaging (MRI) provides a non-invasive method of assessing both intra- and extra-articular structures around the knee in osteoarthritis.

The work presented in this MD thesis has provided novel information about the structural pathology, sources of pain and the natural history of knee OA, using data from the Boston Osteoarthritis of the Knee Study (BOKS). This cohort study assessed 381 participants with painful knee OA and 77 subjects without knee pain with MRI and plain radiography.

Data presented in each chapter represents a substudy of BOKS to investigate the prevalence and associations of knee effusions, periarticular lesions, cruciate ligament integrity, synovitis and bone marrow lesions in those with and without symptomatic knee OA. These studies represented the largest MRI studies, at the time, to look at the relationship between these features and pain in knee OA, and to look at the longitudinal relationships between synovitis and pain, and bone marrow lesions and radiographic changes.

Data presented in Chapter 2 demonstrates that moderate or larger effusions were common in those with knee pain and radiographic knee OA (55%), and were present less often in those without knee pain (14.6%), suggesting that effusion and capsular distention are sources of pain in knee OA.

Data presented in Chapter 3 demonstrates that peripatellar lesions occurred with similar frequency amongst participants with radiographic knee OA with or without knee symptoms (9.8% vs 15.7%). However, other periarticular lesions (e.g. anserine bursitis) were seen more frequently amongst those with both radiographic OA and knee pain (14.9%), compared to 3.9% in those with radiographic OA but no knee pain. Neither peripatellar or other periarticular lesions were seen in those with neither knee pain or radiographic OA. These results demonstrate that periarticular lesions

are common in people with symptomatic knee OA and need consideration as alternative sources of pain.

Data presented in Chapter 4 demonstrates the significant prevalence of complete anterior cruciate ligament (ACL) rupture in people with knee OA (23%), compared to those without symptomatic knee OA (2.4%). Only half of those with a complete ACL rupture could recall a significant knee injury, suggesting that ACL rupture in these patients may be the result of ligament degeneration rather than traumatic rupture.

Longitudinal data presented in Chapter 5 demonstrates a relationship between changes in synovitis score and changes in pain score over time, such that an increase of one unit in summary synovitis score resulted in a 3.15-mm increase in VAS pain score (0–100 scale). However, no association was seen between changes in synovitis score and cartilage loss over time. Of the 3 locations for synovitis, changes in the infrapatellar fat pad were most strongly related to pain change. Synovitis was not associated with cartilage loss in either tibiofemoral or patellofemoral compartment. This work suggests that treatment of pain in knee OA needs to consider treatment of synovitis.

Data on bone marrow lesions outlined in Chapter 6 demonstrated for the first time that bone marrow lesions identified on MRI were associated with knee pain. Bone marrow lesions were present in 77.5% of painful knees, compared with 30% of those without knee pain. Longitudinal analysis of BOKS data demonstrated that bone marrow lesions were associated with radiographic OA progression in the corresponding compartment, showing that these lesions are potent risk factors for structural deterioration in knee OA.

The work presented in this MD thesis has demonstrated the association of moderate to large knee effusions, periarticular lesions, synovitis and bone marrow lesions to pain in knee OA, the high prevalence of complete anterior cruciate ligament rupture amongst those with symptomatic knee OA and the longitudinal relationships between synovitis and pain; and bone marrow lesions and radiographic progression. This has contributed to the knowledge of structural pathology, sources of pain and the natural history of knee OA and opened up further avenues of research and potential targets for interventions in this common and disabling disease.

Chapter 1

1.1 Introduction

Osteoarthritis (OA) is the major cause of disability in older Australians and associated costs account for 1-2.5% of GDP (March 1997). By 2050, OA is projected to be the most prevalent arthritic condition affecting 3.1 million Australians (Access Economics 2007). The prevalence of radiographic knee OA is around 37% and symptomatic knee OA affects 12% of those over 60 (Dillon 2006). As a result of this high prevalence, knee OA is a major cause of disability and accounts for more difficulties walking and climbing stairs than any other chronic disease (Guccione 1994), and is the commonest indication for knee joint replacement surgery. Due to the aging of the Australian population and increased burden of knee OA, the number of knee joint replacements performed in Australia is increasing rapidly (AOA NJR Annual Report 2008). These facts have led to 2000-2010 being labelled internationally as the Bone and Joint Decade and musculoskeletal disorders being recognised as a National Health Priority by the Australian Government in 2002. Knee OA represents a significant personal and societal burden to the Australian community.

It is a disease of uncertain aetiology that results in deterioration of the structure and function of articular cartilage. Nonetheless, understanding of this disease has been greatly hampered by limitations in non-invasive assessment. Current treatment for knee OA is confined to conservative measures involving symptom control with paracetamol and/or nonsteroidal anti-inflammatory drugs, as well as physical therapies, or joint replacement surgery. To date, no specific targeted therapy for OA has been marketed. Although some treatments aimed at chondroprotection have been trialed, many of these have failed to meet expectations. Therefore, improved knowledge of the structural changes and causes of pain in knee OA are essential to advance the treatment of this increasingly common disease.

The research work constituting this MD thesis seeks to contribute to this knowledge using magnetic resonance imaging (MRI).

The initial chapter of this MD thesis will provide the background to this research work focusing on the risk factors for knee OA, sources of pain in knee OA, the role of MRI, and give an outline the methodology of the Boston Osteoarthritis Study (BOKS) from which the data for this thesis arose.

1.2 Risk factors

Although no single aetiological cause has been found, previous epidemiological studies have identified risk factors for both incidence and progression of knee OA. These have helped inform and focus further study into structural pathology and potential causes of pain.

Systemic risk factors:

1. Age: Age remains the strongest risk factor for OA with increasing prevalence with age. (Lawrence 2008).
2. Gender: Female gender is a risk factor for knee OA with a recent meta-analysis of population based studies finding that women had both more incident and prevalent knee OA as well as more severe disease than men (Srikanth 2005).
3. Race/ethnicity: The prevalence of knee OA appears to differ between races. Despite lower rates of hip and hand OA, Chinese women had a higher prevalence of knee OA than white women, and this could partially be explained by high prevalence of prolonged squatting amongst elderly Chinese women (Zhang 2001, Zhang 2004)
4. Genetics: Knee OA has a heritable component but appears to be less pronounced than either hip or hand OA (Spector 1996, Valdes 2008). This area is under intense investigation at present with several genome-wide association studies underway and the possibility of determining genetic associations with specific radiographic or MRI features of OA (Valdes 2008). Zhai and colleagues (2006a) have recently demonstrated the heritability of MRI features of knee OA including bone marrow lesions.
5. Obesity: Obesity is a significant risk factor for incident and progressive knee OA (Felson 1998). It is likely to be more complex than just absolute weight as a recent MRI studies in non-OA subjects demonstrated a beneficial effect of fat-free mass and a deleterious effect of fat mass on knee cartilage volume and defects (Wang 2007). Weight loss has also been demonstrated to be associated with decreased risk of developing radiographic knee OA. In the obese with established knee OA, weight loss is associated with improved pain and disability (Christensen 2007).
6. Dietary factors: Numerous dietary factors (vitamins C, D, E, K, antioxidants) have been examined in knee OA (Zhang 2008). However, the interaction between dietary factors and knee OA appears to be complex and results have been conflicting. For example, low vitamin D levels appear to be a risk factor for progressive but not incident radiographic knee OA (McAlindon 1996a), but more recent combined data from 2 cohort studies showed no association between risk of

joint space or cartilage loss in knee OA (Felson 2007a). In addition, 2 randomized clinical trials of vitamin E and K supplementation in knee and hand OA, respectively, demonstrated no effect on disease progression (Wluka 2002, Neogi 2008).

7. Smoking. Smoking appears to be an independent risk factor for knee cartilage loss. A recent study using MRI outcomes in males demonstrated that smokers sustain more severe cartilage loss and have more severe pain than non-smokers (Amin 2007). Ding and colleagues (2007) showed that smoking was related to increased knee cartilage loss and this was more pronounced in those with a family history of severe primary knee OA.

Local risk factors

1. Injury: Knee OA is significantly more common after knee injuries which include mensical tear requiring meniscectomy, anterior cruciate ligament injury and fractures including the joint surface (Roos 2001, Lohmander 2004, Englund 2004). In addition, NHANES I data revealed that history of previous knee injury was a strong predictor of symptomatic knee OA (Davis 1989).

2. Physical activity: There are conflicting results with regard to the association between knee OA and physical activity. Elite long distance runners and soccer players are at increased risk of knee OA (Zhang 2008). However, the association with regard to leisure physical activity is less clear. Framingham data suggests that elderly people with higher levels of physical activity, such as leisure walking and gardening, had higher risk of developing radiographic OA over 8 year period than sedentary people (McAlindon 1999). Other work has not demonstrated increased risk of knee OA with recreational long distance running (Lane 1993).

3. Occupation: Occupation work load is a risk factor for incident knee OA, particularly in men with occupations that involve both carrying and kneeling or squatting in mid-life are twice as likely to develop knee OA (Felson 1991). This risk is compounded in those whose job also involves lifting (weights >25kg) or who are obese (Coggon 2000).

4. Muscle strength: Most studies have focussed on quadriceps strength. It may play a role in incident disease as quadriceps weakness is present in both asymptomatic Caucasian and Chinese with radiographic knee OA (Slemenda 1997, Baker 2004), and reduced quadriceps strength may be a risk factor for progressive radiographic knee OA (Brandt 1999). However, the relationship is likely to be complex as Sharma (2003) has also demonstrated greater quadriceps strength at baseline was associated with increased likelihood of tibiofemoral OA progression in malaligned and lax knees after 18 months of follow-up.

5. Alignment: The alignment of the knee (hip-knee-ankle angle) influences load distribution at the knee. There is consistent evidence for the association of malalignment with an increased risk of OA progression and decline in physical function, but the association with incident knee OA is conflicting. Sharma and colleagues (2001) first demonstrated in 2001 that varus alignment increases the risk of medial OA progression and valgus alignment increases the risk of lateral OA progression in a prospective cohort study followed for 18 months. Subsequent work from the BOKS study (presented in this MD thesis) has also demonstrated the significant influence of knee joint malalignment on the size and progression of bone marrow lesions and on cartilage loss. Cicuttini (2004) also found an association between baseline knee angle and rate of cartilage loss in knee OA. With regard to incident knee OA, the Rotterdam Study (1501 subjects) demonstrated an increased risk of incident knee OA in knee with varus or valgus deformity, compared to normally aligned knee and this association was most pronounced in obese or overweight subjects (Brouwer 2007). In contrast, work by Zhai and colleagues (2007) found that, in a prospective cohort study of 315 predominantly non-OA subjects, baseline knee alignment was not associated with subsequent loss of cartilage volume or progression of chondral defects over 2 years. Cerejo and colleagues (2002) found that, although there was some effect of malalignment at all stages of radiographic knee OA, the impact of varus or valgus malalignment on OA progression over 18 months was greater in knees with moderate (K/L grade 3) OA at baseline. Most recently, four measures of alignment (the anatomic axis, the condylar angle, the tibial plateau angle, and the condylar tibial plateau angle) were found not to be associated with incident radiographic tibiofemoral knee OA in the Framingham cohort (Hunter 2007). These authors suggest that malalignment is a marker of disease severity and progression, rather than a risk factor for knee OA.

6. Laxity: Varus-valgus laxity has been demonstrated to be increased in the contralateral uninvolved knee of OA subjects, suggest that some degree of laxity may predate OA (Sharma 1999). Cross-sectional studies of OA subjects at different disease stages have suggested that antero-posterior laxity may be increased in mild disease, and may decline with increasing severity of disease (Wada 1996, Brage 1994). Like malalignment, laxity may be altered by the disease itself and indeed may be associated with malalignment (van der Esch 2005). At this stage, there is a paucity of longitudinal data.

1.3 Sources of pain in knee osteoarthritis

Determining the structural sources of pain in knee OA is the major focus of this MD thesis. Pain is the major and most disabling symptom of knee OA, but the causes of this pain have remained elusive as the primary site of pathology in OA, cartilage, is both aneural and avascular. Evolving concepts of knee OA have expanded our view beyond cartilage to consider knee OA as disease entity affecting the entire joint including subchondral bone, synovium, menisci and ligaments (Felson 2000). A better understanding of the causes of pain in knee OA are essential to advance the treatment of OA for which there are no specifically targeted therapies.

The experience of pain in knee OA is complex and combines biologic, psychological and social factors (Dieppe 2005). This MD focuses on structural pathology and sources of pain in knee OA within and around the knee joint and does not seek to cover the important contribution of central mechanisms and psychological aspects to pain in knee OA (Keefe 2002, Hunter 2008).

An enlightening study of pain-sensitive structures within the knee was undertaken by Dye and colleagues (1998). A conscious subject underwent arthroscopy of both his normal knees without anaesthetic, probing found that the most pain sensitive areas in the knee were the insertion sites of the cruciate ligaments, synovium, Hoffa's fat pad, and the joint capsule. There was no pain when the articular cartilage was probed (Dye 1998).

Creamer and colleagues (1996) demonstrated that in subjects with painful knee OA, injection of intra-articular anaesthetic relieved pain in 6/10 patients, suggesting an intraarticular cause for pain in 60% of OA subjects.

Nociception in the knee

The predominant nociceptive fibres in the knee joint are the Type III (Aδ) fibres which are thin and myelinated with terminal unmyelinated ending and Type IV (C) fibres which are unmyelinated. These slow conducting fibres have a higher threshold than the other fibres and generally only respond to noxious mechanical stimuli (McDougall 2006a). Abnormal joint movements cause the firing rate of the afferent nerve to increase dramatically and this is interpreted by the central nervous system as pain (McDougall 2006a).

These nociceptive fibres are richly present in the capsule, ligaments, fat pad, menisci, periosteum and subchondral mineralized bone (especially in areas of increased mechanical load) (McDougall 2006a, Schaible 1993). However, nociceptive fibres have not been found to be present in the articular cartilage. These findings are consistent with the clinical findings of Dye outlined above.

Although normal hyaline cartilage does not possess pain fibres, the situation may differ in diseased cartilage such as OA. A study of natural occurring animal model of OA, using osteoarthritic metacarpophalangeal joints of the horse, demonstrated substance P nociceptive fibres in abnormal cartilage such as erosion channels which connect the bone marrow through the tidemark of the cartilage into the cartilage substance itself (Fortier 1997). More recent work by Suri and colleagues (2007) has demonstrated the presence of both sensory and sympathetic nerves in the vascular channels in articular cartilage in both mild and severe cases of tibiofemoral knee OA. However, as Hunter and colleagues (2008a) commented, although this may be interpreted as cartilage being the source of tibiofemoral pain in these subjects, this has so far not been demonstrated electrophysiologically. Work outlined below by Zhai (2006b) also demonstrates that presence of tibial chondral defects on MRI were independently associated with knee pain in older adults.

Given the rich innervation of capsule, ligaments, fat pad, menisci, periosteum and subchondral bone, it is likely that nociceptive stimuli emanate from one of these structures in those with knee OA.

Role of inflammation

Biopsies of patients with both early and late knee OA have shown low grade chronic synovitis with production of pro-inflammatory cytokines (Myers 1990, Smith 2003, Benito 2005). During inflammation, major plasticity changes occur in the peripheral and central nervous systems which cause a lowering of the pain threshold (McDougall 2006a). This can occur in 2 ways via peripheral sensitization and 'silent nociceptors'.

Peripheral sensitization occurs when the activation threshold of joint nociceptors and afferent nerves become hyper-responsive to both normal and noxious movements (McDougall 2006a). Studies in animal models have shown induction of acute synovitis increases the firing frequency of type III and IV fibres with both normal and

abnormal joint movements (Schaible 1985, Coggeshall 1983). These findings of reduced mechanical thresholds and increased afferent discharge rates have also been noted in adjuvant-induced chronic arthritis and animal models of OA (McDougall 2006a).

Inflammatory mediators within the joint lower the firing threshold making the nociceptive fibres more responsive to both normal and noxious stimuli. In addition, accumulation of mediators within the joint may lead to a self-perpetuating pain generation (Hunter 2008a). These inflammatory mediators include neuropeptides (substance P, calcitonin gene-related peptide, and vasoactive intestinal peptide), eiconasoids, cytokines and histamine (Pelletier 2001, Hunter 2008a). The initial studies examined the role of vasoactive intestinal peptide (VIP) in OA pain. VIP has been isolated from synovial fluid and serum of patients with inflammatory arthritis (Lygren 1986). More recently, local administration of VIP into rat knees has been shown to cause pain by sensitizing joint afferents with reduction of pain and reduced peripheral sensitization with use of VIP-antagonist in both normal and OA rat knees (McDougall 2006b). Therefore, the manipulation of these inflammatory mediators which cause peripheral sensitization requires further investigation as a means of controlling OA pain.

'Silent nociceptors', nociceptors that are quiescent in a normal joint, may become active and send nociceptive information to the central nervous system following tissue injury or development of inflammation within the joint (McDougall 2006a). These can make a major contribution to pain in an arthritic joint (Schaible 2006). With inflammation, type III and IV fibres show increased sensitivity to movement. Approximately 50% of type III and 70% of type IV fibres are classed as high threshold units (Schaible 1993). This group of nerve fibres that, in normal situations are not mechanosensitive, become sensitized and may respond even to movements within the normal range, whilst the lower threshold group show increased response to joint movements (Hunter 2008a).

Knowledge about the innervation of the knee joint and the role of inflammation in lowering the pain threshold informs and progresses further investigation of structural causes of pain in knee OA.

1.4 Role of Magnetic Resonance Imaging (MRI)

Plain radiography remains the mainstay of diagnostic imaging of OA in clinical practice. However, plain radiography has inherent difficulties in studies investigating the origins of knee pain and structural pathology in OA and as a structural outcome measure in intervention trials. Its images are largely limited to bone. Therefore, in knee OA, information is confined to osteophytes, subchondral bone sclerosis and cysts, and joint space narrowing. Although the prevalence of knee pain increases with radiographic severity, there is significant discordance between plain radiographic changes and symptoms (Summers 1988, Salaffi 1991, Hannan 2000).

Use of plain radiography has limitations in the research setting. Of radiographic features, osteophytes are associated most closely with knee pain (Lanyon 1998, Spector 1993). However, joint space narrowing is less consistently associated with knee pain (Lanyon 1998, Spector 1993, Lethbridge-Cejku 1995). The joint space was previously believed to represent cartilage, and hence decreasing joint space was thought to correspond to increasing severity of cartilage loss in knee OA. MRI has demonstrated that initial joint space narrowing in knee OA seen on plain radiography is secondary to meniscal extrusion and degeneration, rather than loss of articular cartilage (Adams 1999, Hunter 2006a). This example demonstrates the advantages of MRI in evaluation of knee OA.

Other data regarding the structural pathology of knee OA in humans has come from study of autopsy specimens, surgical specimens (usually at the time of knee joint replacement surgery) and observations at arthroscopy. Each of these approaches has inherent limitations in the study of this disease. In general, little premorbid clinical information about pain or other symptoms is available for autopsy specimens. Surgical specimens are generally confined to end-stage knee OA by the very nature of when this type of surgery is performed, so provides little information about earlier stages of knee OA. In addition, as generally little more than the cartilage surfaces are removed during knee arthroplasty, it provides little insight into non-articular structures around the joint. With the advance of arthroscopy, more research using this modality has been performed in knee OA. However, it only provides data on intra-articular structures and may not fully visualize the posterior portion of the joint and, due to its invasive nature, cannot be repeated frequently (Conaghan 2004). A longitudinal study in knee OA comparing plain radiographs, arthroscopy and MRI found that MRI was the most sensitive to changes in chrondropathy over a one year period. Neither

plain radiographs or arthroscopy demonstrated any change after 1 year (Pessis 2003).

MRI has many advantages in the research setting for the study of knee OA. It is non-invasive and gives low radiation exposure. It allows imaging in 3 dimensions and assessment of multiple structures both within and adjacent to the knee, including synovium, cartilage, menisci, subchondral bone and periarticular structures such as bursa. These are all structures known to be rich in nociceptive nerve fibres and all potential sources of pain in knee OA.

The studies in this MD thesis represent one of the earliest cohort studies of subjects with knee OA, using MRI to define structural pathology and sources of pain in knee OA.

1.5 Boston Osteoarthritis of the Knee Study (BOKS)

The data used in this MD is derived from the Boston Osteoarthritis of the Knee Study (BOKS), a prospective cohort study investigating the natural history of symptomatic knee OA, with the innovative use of MRI as one of the principle outcome measures. The lead investigator for this study was Professor David Felson of Boston University. He was responsible for the study conception, design, funding applications and coordination of the study. The cohort was initially assembled in 1997.

All participants were evaluated at baseline. However, only those with knee pain at baseline were again evaluated at 15 and 30 months.

Participant selection: Male participants were drawn from the Veterans Health Study, a prospective cohort study of 2425 men receiving care at regional area Veterans Affairs (VA) medical centers, designed to evaluate the relationship between chronic diseases and health status outcomes (Kazis 1998). Female participants were drawn from clinics at Boston Medical Center and the VA Medical Center, from advertisements in local newspapers and from a study of women veterans, the VA Women's Health Project (n=800) that was designed to describe the health status of women veterans using ambulatory services. The minimum age for entry into the study was 45 years for men and 50 years for women. (Entry age for women was older to lessen the chance of inadvertently obtaining radiographs on pregnant women). The human studies committee and the institutional review board approved protocols. Informed consent was obtained from all participants.

Classification of participants To look at contribution of various factors on their roles in knee pain in OA, participants both with and without knee pain were enrolled. To allow classification into participants as having 'knee pain' and 'no knee pain', all participants were surveyed about knee symptoms. They were asked two questions: "Do you have pain, aching or stiffness in one or both knees on most days?", and "Has a doctor ever told you that you have knee arthritis?" In a follow-up interview, those answering positively to both questions were asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified in the interview, then the individual was eligible for recruitment as a person with knee pain.

Importantly, participants without knee pain from among those who answered in the negative to both of the above screening questions were also recruited. So in addition to the above questions which allowed us to classify participants as with or without knee pain, we also administered a question that asked participants to evaluate the severity of pain in each knee which was scored 0-100 on a 100 mm visual analog

scale. Participants filled out the WOMAC questionnaire, a validated questionnaire that assesses knee pain and disability during various activities (Bellamy 1988). Of all the participants with knee pain, a subset of 324 who entered a natural history study, either initially or after inclusion into the study, were examined by a rheumatologist (DT Felson) who confirmed that, in all cases, patients had clinical knee OA rather than isolated tenderness only at sites of localized bursitis or tendinitis (e.g., quadriceps tendinitis) or referred pain from the hip. Participants with only isolated periarticular tenderness or evidence of hip OA as a source of knee pain were excluded.

Radiographic evaluation: All participants underwent weight-bearing posteroanterior (PA) radiographs using the protocol of Buckland-Wright weight-bearing skyline and weight-bearing lateral radiographs (Buckland-Wright 1995; McAlindon 1996). For the PA view, the knee was positioned and radiographed under fluoroscopy so that the anterior and posterior medial tibial plateaus were superimposed so as to optimize the measurement of joint space. Radiographs were read for the presence of definite osteophytes and other features by one radiologist using an atlas. If a definite osteophyte was present in a symptomatic knee on any one of the three views, the subject was characterized as having OA (this includes the patella). This definition met the American College of Rheumatology criteria for knee OA (Altman 1986). We identified too few symptomatic individuals without a radiographic osteophyte to include these as a separate study group (n=4).

As Kellgren & Lawrence grades were developed for the AP (PA) view, we scored Kellgren & Lawrence (0-4) grades on this view only. In addition, PA, lateral and skyline views were scored for individual radiographic features, osteophytes (0-3), joint space narrowing (0-3), cysts (0-1) and sclerosis (0-3) using the Framingham Osteoarthritis Study atlas (Felson 1997). Reproducibility for readings of these features and of Kellgren & Lawrence scale was high (Chaisson 2000). Long line leg films were also obtained at the first follow-up examination to measure mechanical alignment. This was measured in degrees on continuous scale, with values less than 0 representing valgus alignment, value of 0 representing neutral alignment and values greater than 0 representing varus alignment.

MRI evaluation. All participants underwent MRI of a single knee. For those with knee pain, the more symptomatic knee was selected for imaging. For those without knee pain, the dominant knee was selected for imaging. All studies were performed on a GE Signa 1.5 Tesla MR (GE Medical Systems, Milwaukee, Wisconsin) using a phased array knee coil. A positioning device for the ankle and knee was used to

ensure uniformity between patients. The MR protocol for each subject included coronal, sagittal and axial images. The imaging protocol included: sagittal spin echo proton density and T2 weighted images (TR2200 TE 20/80) with a slice thickness of 3 mm, a 1 mm interslice gap, 1 NEX, field of view 11-12cm, and a matrix of 256x192, and coronal and axial spin echo fat saturated proton density and T2 weighted images (TR 2200 TE 20/80) with a slice thickness of 3 mm, a 1 mm interslice gap, 1 NEX, field of view 11-12 cm and a matrix of 256x128.

Participant evaluation

Weight (using a balance beam scale) and height were measured on the day of the MRI scan to allow calculation of body mass index. Participants were also asked "Have you ever had a knee injury requiring the use of crutches or a cane? If so, which knee?"

Knee examination:

A subset of 59 participants with knee pain were examined by myself to determine if there were any associations with location of knee pain and structural changes seen on MRI. To enable this, a drawing, dividing the knee into 12 areas with grid lines was devised so that each grid area approximated an anatomic area in the knee and also corresponded to areas scored on the MRIs for lesions (Hill 2003, Figure 1). Participants were asked to demonstrate on their own knee the location of pain in each knees. The location of the pain was marked by myself on a standard drawing of the knee (Figure 1).

The participants were examined by a rheumatologist (myself) who was blinded to the results of MRI findings, which were performed on the same day as the examination in a different location in the hospital by a MRI technician. Prior to study commencement, 2 rheumatologists (myself, DT Felson) performed several examinations together to devise the protocol and to ensure standardization of the knee examination. A dolorimeter was used prior to each examination to ensure that the examiner was exerting regular amounts of pressure in eliciting tenderness. This was designated as 3kg force. Prior to examination, the examiner used the dolorimeter to calibrate finger pressure to 3kg force on 5 occasions, similar to those used by a previously published protocol (Smythe 1998). Then 5 further blinded repetitions were done. If blinded repetitions were greater than 0.5kg from 3kg baseline on greater than 2 occasions, calibration was repeated. The examiner then pressed over each of the 11 anterior areas and popliteal fossa for tenderness. The knee was palpated in a fully extended position for areas overlaying the femur and patella and at 90 degrees of flexion for the infrapatellar region, areas overlying tibia

and popliteal fossa. Participants were asked to indicate to the examiner after each palpation whether the area was non-tender, tender or very tender. To maximize accuracy, the palpation was repeated in areas that were indicated to be painful. Results were recorded on the similar figure to the location of knee pain and was graded as 0 for no tenderness, 1 mildly tenderness, 2 very tender. Areas were characterized as tender only when so designated by participants on both occasions. Tenderness location was noted on the same knee diagram. Based on the locations of tenderness in our knee diagram, we evaluated correlations of the locations with respective pathology as follows: medial tenderness (areas 4, 8, 11) was correlated with the presence of anserine bursitis, semimembranosus-TCL bursitis. Anterior tenderness (areas 5,7,9) was correlated with the presence of patellar lesions (prepatellar bursitis, superficial and deep infrapatellar bursitis). Lateral tenderness (areas 3,6,10) was correlated with the presence of iliotibial band syndrome and areas 6 and 10 for tibio-fibular cyst. Posterior tenderness (area 12) was correlated with presence of popliteal cysts.

Participant characteristics

For this study, 381 participants (259 male, 122 female) with knee pain and 77 participants (46 male, 31 female) with no knee pain were recruited. Overall, all the participants had body mass index (BMI) at least in the overweight range with those with knee pain being slightly heavier. Mean age was slightly younger in the 'no knee pain' groups. In those with knee pain, there was a range of radiographic grading, ranging from Kellgren & Lawrence (K-L) grade 0 to 4 (72 participants with Knee pain/OA, who had K-L grade of 0 due to normal postero-anterior views, were defined as having radiographic OA due to definite osteophytes in patellofemoral joint. In those with no knee pain/XROA, the median K-L grade of 0 (range 0-2) was less than the knee pain group.

The numbers of participants varies slightly between studies as participants may have been have excluded from a particular substudy if, for instance, their MRI was not readable for that feature. One example would be an exclusion from the cruciate ligament paper if MRI was unreadable for cruciate ligament integrity due to movement artifact.

Table 1.

	Knee pain (n=381)		No Knee pain (n=77)			
	Knee pain/XROA		No knee pain/XROA		No knee pain/no XROA	
	Male	Female	Male	Female	Male	Female
Number	259	122	29	23	17	8
Age, yrs, mean (SD)	68.2 (9.4)	65.0 (9.0)	66.8 (9.9)	65.8 (8.4)	63.3 (11.3)	66.6 (8.1)
BMI, kg/m2, mean (SD)	30.8 (4.9)	32.4 (7.1)	28.5 (4.6)	29.0 (6.5)	28.3 (4.9)	29.0 (5.1)
K-L grade, median (range)*	2 (0-4)	2 (0-4)	0 (0-2)	0 (0-2)	0 (0-1)	0 (0-1)
Pain (100mm VAS), mean (SD)	46.4 (25.5)	42.8 (23.8)	0.9 (1.7)	2.2 (2.3)	0 (0)	1.3 (2.5)

*72 participants with Knee pain/OA, who had K-L grade of 0 due to normal postero-anterior views were defined as having radiographic OA due to definite osteophytes in patellofemoral joint.

1.6 Summary

In summary, knee OA represents a substantial burden to older individuals and the community. It is a common disease, causing significant pain and disability, without known aetiology or targeted treatments. New insights into the structural pathology and causes of pain at all stages of this disease are required to allow further development of new treatments. MRI provides a non-invasive method of assessing both intra- and extra-articular structures around the knee in osteoarthritis, thus, provides an ideal method of assessing the structural pathology and sources of pain in knee OA.

Chapter 2

Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, Felson DT. Knee effusions, popliteal cysts and synovial thickening: Association with knee pain in those with and without osteoarthritis Journal of Rheumatology 2001;28:1330-7.
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Joint effusion, synovitis and popliteal cysts are well-known to accompany knee OA, however, the exact prevalence was uncertain as radiographs were unable to identify these components and previous studies relied on clinical examination and by visualization via arthroscopy or arthrography.

One previous MRI study of 52 patients with clinical and radiographic OA compared to 40 age- and sex-comparable participants without knee symptoms found an increasing prevalence of knee effusion with increasing radiographic disease (Fernandez-Madrid 1994). Our larger cohort with comparison groups of participants without knee pain with or without radiographic OA allowed more precise investigation of the prevalence of knee effusions, synovial thickening and popliteal cysts. The conception and design of this substudy was by myself. I performed the MRI reading of effusions and popliteal cysts, with aid from Dr D Gale (who performed the synovial thickening MR reading). I undertook the analysis and interpretation of data and preparation of manuscript, with support from Professor Felson and other co-authors (see Appendix).

Low grade chronic synovitis has been shown in both early and late knee OA (Ostergaard 1997, Smith 2003, Benito 2005). Previous work demonstrated that gadolinium-enhanced synovium correlated with microscopic inflammation in knee OA (Ostergaard 1997). Therefore, synovitis was of interest as a potential source of pain in knee OA. Gadolinium was not available for use in the BOKS participants due to ethical and safety concerns and time constraints, however, a previous study by Fernandez-Madrid and colleagues (1995) demonstrated that synovial thickening on non-contrast MRI, typically located in or near the intercondylar region of the knee, in the infrapatellar fat pad, or in the posterior joint margin represented mild chronic synovitis on arthroscopic biopsy. Their results suggested that non-contrast MRI could be used to evaluate the extent of synovitis, observed as synovial thickening, in patients with knee OA. The location of synovitis is of relevance as the infrapatellar fat pad has subsequently been found to be densely innervated and a rich source of

cytokines (Ushiyama 2003). As such we utilized a system to score synovial thickening in a subset of participants with knee pain in the 3 regions; the infrapatellar fat pad, intercondylar space and anterior horn of the lateral meniscus.

This study demonstrated that moderate or larger effusions were common in those with knee pain and radiographic knee OA (55%), and were present less often in those without knee pain (16% with radiographic knee OA, 11% with no radiographic knee OA), suggesting that effusion and capsular distention are sources of pain in knee OA. In contrast, popliteal cysts appeared to be associated with radiographic but not symptomatic OA as they were equally common amongst those with radiographic knee OA with or without pain (33% v 28%, respectively) and much less common in those without pain or radiographic changes (9%). In a subset in which synovial thickening was read at the infrapatellar fat pad, intercondylar space and anterior horn of the lateral meniscus, synovial thickening was associated with pain severity (independent of effusion).

Knee Effusions, Popliteal Cysts, and Synovial Thickening: Association with Knee Pain in Osteoarthritis

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ABSTRACT. ***Objective.*** To evaluate the association of effusions, popliteal cysts, and synovial thickening with knee symptoms in older persons with and without radiographic (XR) osteoarthritis (OA), using magnetic resonance imaging (MRI).

Methods. Subjects with and without knee symptoms were recruited from Veterans Affairs and community sources. All had weight-bearing knee radiographs. Subjects were divided into 3 groups: Knee pain/XROA group had knee symptoms and radiographic OA; No knee pain/XROA group had no knee symptoms and radiographic OA; and No knee pain/no XROA group had no knee symptoms and a normal radiograph. A single knee was imaged using a 1.5 T MR scanner using T1 and T2 weighted and proton density SE imaging sequences. MRI were read for effusion, popliteal cysts, and synovial thickening.

Results. The mean age of subjects was 67.0 years (66.6% male). We studied 381 subjects with Knee pain/XROA, 52 with No knee pain/XROA, and 25 with No knee pain/no XROA. The prevalence of moderate or larger effusions was: Knee pain/XROA 54.6%, No knee pain/XROA 15.6%, and No knee pain/no XROA 11.1%. Popliteal cysts were present in 33.0% of Knee pain/XROA subjects, 28.0% No knee pain/XROA, and 9.1% No knee pain/no XROA. After adjusting for the severity of radiographic OA, there was a difference between those with and without knee pain in prevalence of moderate or larger effusions ($p < 0.001$) and synovial thickening, independent of effusion ($p < 0.001$), but not in the prevalence of popliteal cysts. Further, among those in Knee pain/OA group, synovial thickening was associated with the severity of knee pain.

Conclusion. Effusions and popliteal cysts are common in middle aged and elderly people. After adjusting for the degree of radiographic OA, moderate or large effusions and synovial thickening were more frequent among those with knee pain than those without pain, suggesting these features are associated with the pain of knee OA. In those with knee symptoms, synovial thickening is uniquely associated with the severity of knee pain. (J Rheumatol 2001;28:1330–7)

Key Indexing Terms:
KNEE OSTEOARTHRITIS EFFUSION POPLITEAL CYST SYNOVITIS

Pain is the predominant feature of clinical knee osteoarthritis (OA). However, the cause of pain in knee OA remains enigmatic. Cartilage loss, considered the primary pathological lesion in OA, could occur without pain, as hyaline cartilage contains no pain fibers[1]. Many other structures around the knee have been shown to contain pain fibers including the joint capsule, the periosteum and other bone sites, insertion sites of ligaments and muscles, and possibly the synovium[1]. We showed that periarticular bone marrow lesions identified on magnetic resonance imaging (MRI) are more common in those with symptomatic knee OA than those with asymptomatic OA[2]. However, these lesions were not present in all subjects with symptomatic OA, and given that the joint capsule and bursae have pain fibers, distention of the capsule or inflammation of periarticular structures or synovium could also contribute to the pain of knee OA[3]. The prevalence of effusions, popliteal cysts, and synovial changes in those with and without clinical knee OA is unknown and their association with knee symptoms has not been studied[4]. Low grade synovial inflammation has been described in knee OA[5]. In addition, synovial thickening around the infrapatellar fat pad evaluated using noncontrast enhanced MRI has been shown on biopsy to represent mild chronic synovitis[6].

Joint effusions and popliteal cysts are recognized to

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accompany knee OA[7,8]. MRI studies have revealed knee effusions in OA that increase in prevalence with increasing radiographic severity, ranging from 25% in those with mild radiographic disease to 100% in those with severe radiographic disease[7]. In addition, using ultrasound, popliteal cysts have been detected in 42% of subjects with OA[7]. Studies using MRI have generally used subjects referred for knee symptoms and not those without symptoms. Consequently, there is scant information on the prevalence of effusions and periarticular lesions in asymptomatic persons and middle aged and elderly persons in particular. MRI studies of the spine have shown frequent abnormalities unassociated with symptoms, raising the possibility that this may also be true of the knee[9].

We examined the association of effusions, popliteal cysts, and synovial thickening with symptom occurrence by comparing the prevalence of these lesions in 3 groups: (1) those with frequent knee symptoms and presence of radiographic OA; (2) those without knee pain and presence of knee OA; and (3) those without knee pain and absence of radiographic knee OA. Any lesions that occurred predominantly in those with knee pain and rarely in those without pain may be associated with pain.

MATERIALS AND METHODS

Participant recruitment. The minimum age for entry into the study was 45 years for men and 50 years for women. Entry age for women was older to lessen the chance of inadvertently obtaining radiographs on pregnant women. Male subjects were drawn from the Veterans Health Study, a prospective cohort study of 2425 men receiving care at regional VA medical centers, designed to evaluate the relationship between chronic diseases and health status outcomes[10]. Female subjects were drawn from clinics at Boston Medical Center and the VA Medical Center, from advertisements in local newspapers, and from a study of women veterans, the VA Women's Health Project (n = 800) that was designed to describe the health status of women veterans using ambulatory services. The human studies committee and the institutional review board approved the protocols. Informed consent was obtained from all subjects.

All subjects were surveyed about knee symptoms. They were asked 2 questions: "Over the past 4 weeks, have you had pain, aching or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" In a followup interview, those answering positively to both questions were asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified in the interview, then the individual was eligible for recruitment as a person with knee pain. In total, 120 subjects with knee pain were examined by a rheumatologist (DTF), who confirmed that in all cases there was tenderness in or around the knee. We attempted to match those without knee symptoms roughly in age and sex to those with knee symptoms.

We recruited subjects without knee pain from among those who answered in the negative to both the screening questions. In addition to the above questions, which allowed us to classify subjects as with or without knee pain, we also asked subjects to evaluate the severity of pain in each knee, which was scored 0–100 on a 100 mm visual analog scale (VAS).

Radiographic evaluation. Weight-bearing anteroposterior (AP) and skyline radiographs (Buckland-Wright protocol) and weight-bearing lateral radiographs (Framingham Study protocol) were obtained from all subjects[11]. Radiographs were read for the presence of definite osteophytes by one radiologist (DRG) using an atlas[12]. If a definite osteophyte was present in a symptomatic knee on any of the 3 views, the subject was characterized as having radiographic OA (this included the patella). This definition meets American College of Rheumatology criteria for knee OA[13]. Symptomatic individuals without a definite radiographic osteophyte were excluded from study because of small numbers (n = 4), although as noted below many participants with knee symptoms had evidence of minimal radiographic OA. Radiographic severity was measured by Kellgren-Lawrence (K-L) grade on AP view only (for which reproducibility has been reported[14]). Thus, some of those characterized as having radiographic OA had patellofemoral disease, and K-L grade could be less than 2.

MRI evaluation. Each subject underwent MRI of a single knee. In those subjects with knee symptoms, this was the most symptomatic knee. For those subjects without knee symptoms, the dominant knee was selected for imaging. All studies were performed on a GE Signa 1.5 Tesla MR machine (GE Medical Systems, Milwaukee, WI, USA) using a phased array knee coil. An anchoring device was used for the ankle and knee to ensure uniform position between subjects. The imaging protocol included sagittal spin echo proton density and T2 weighted images (TR 2200, TE 20/80) with a slice thickness of 3 mm, a 1 mm interslice gap, 1 NEX, field of view 11–12 cm, and a matrix of 256 × 192; and coronal and axial spin echo fat saturated proton density and T2 weighted images (TR 2200, TE 20/80) with a slice thickness of 3 mm, a 1 mm interslice gap, 1 NEX, field of view 11–12 cm, and a matrix of 256 × 128.

Two readers (CLH, DRG) developed a semiquantitative scale to evaluate knee joint effusions and popliteal cysts. Effusion was read on T2 weighted axial images. The effusion scoring system specified that grade 0 was physiological amount of fluid, grade 1 small (Figure 1A), grade 2 moderate (Figure 1B), grade 3 large (Figure 1C). Grade 3 had evidence of capsular distention with bulging of extensor retinaculum. Popliteal cysts were scored grade 0 for absent, grade 1 for small, grade 2 for moderate, grade 3 for large, on T2 weighted images using axial and sagittal views (Figure 2). One reader (CLH) read all films for effusions and presence of popliteal cysts with a random subset reread for intraobserver reproducibility (weighted kappa for effusions = 0.94, for popliteal cysts = 0.67) and a further random subset was read by second reader (DRG) for interobserver reproducibility (weighted kappa = 0.61 for effusions, for popliteal cysts = 0.59).

To evaluate synovial thickening and its association with effusion and with knee pain in those with and without effusion, we randomly sampled 150 knees with varying degrees of effusion, oversampling the most informative knees with no or small effusions that had pain or no pain. Synovial thickening was scored in 3 contiguous areas, the infrapatellar fat pad, intercondylar space, and anterior horn of the lateral meniscus, on sagittal T2 and proton density weighted images, using a described method (Figure 3)[6]. The absence of synovial thickening was scored as grade 0 and presence as grade 1. Synovial thickening was read by one reader (DRG). A further random subset of these films was reread for intraobserver reproducibility (kappa for synovial thickening = 0.77).

For reading for this study, MRI of subjects from each of the 3 study groups were ordered randomly, and the reader was unaware of the group status of the subjects.

Definition of study groups. For the purposes of this study, we defined 3 study groups: (1) A person who responded positively to the screening knee symptom question and had a radiograph (XR) showing a definite osteophyte was classified as a subject with Knee pain/XROA (Group 1). (2) Subjects who did not report knee symptoms but had a definite osteophyte on radiograph were grouped as No knee pain/XROA (Group 2). (3) Subjects who did not report knee symptoms and had no definite osteophyte on their knee radiograph were defined as No knee pain/no XROA (Group 3).

Analysis. Only one knee per subject was studied by MRI, and thus analyses were knee- and subject-specific. Differences between proportions were assessed using chi-square, or by Fisher's exact test if expected values were < 5. Differences in continuous measures between the 3 groups were examined using ANOVA. P values reported are 2 sided.

To determine if effusions or popliteal cysts were associated with pain severity in those with knee pain, we performed linear regression analyses for those in Group 1 alone, using pain (by VAS) as the dependent variable and testing for effusion or popliteal cyst and radiographic severity (using K-L

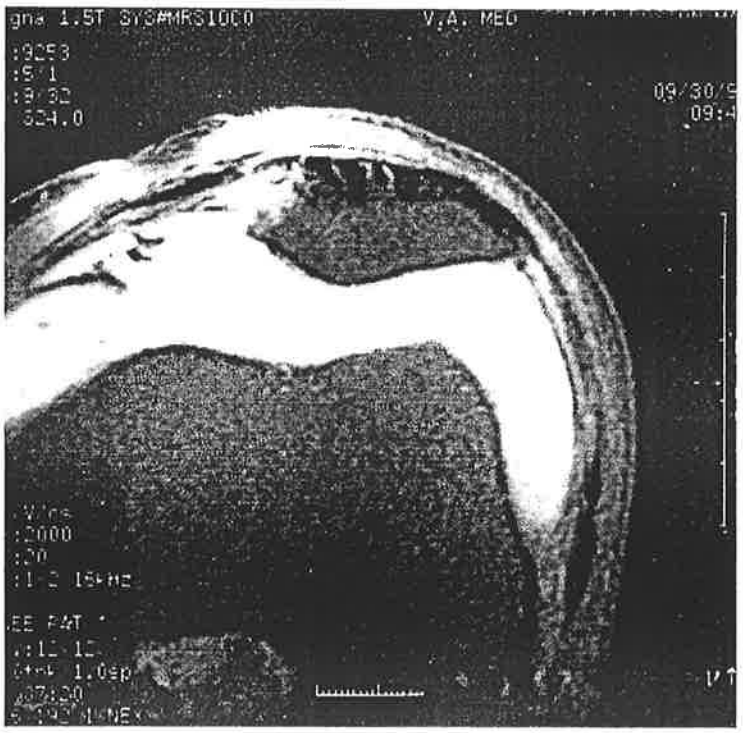

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Figure 1. Axial T2 weighted MR images of (A) small effusion (grade 1), (B) moderate effusion (grade 2), and (C) large effusion (grade 3).

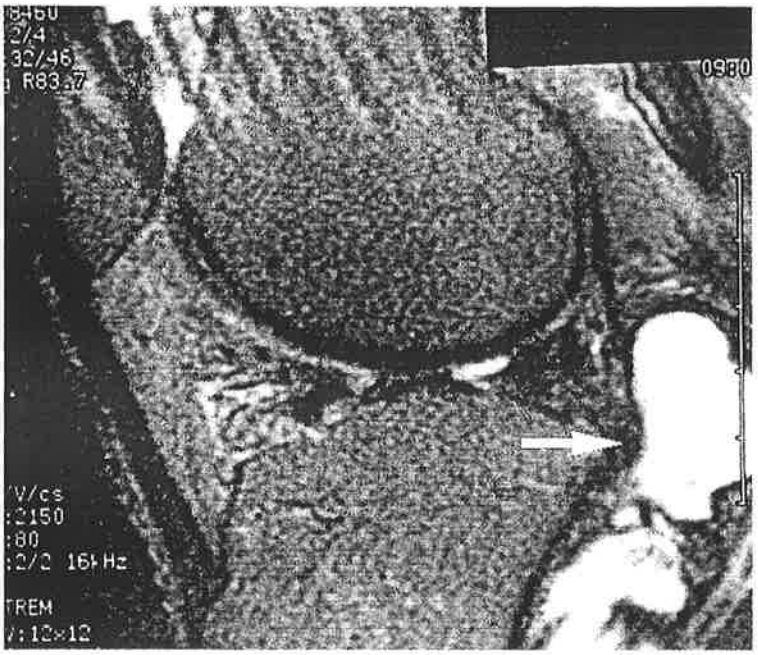

Figure 2. Sagittal T2 weighted MR images of popliteal cyst (grade 3, arrow).

Table 2. Prevalence of effusions and soft tissue lesions.

	Knee Pain XROA Group 1, n = 381	No Knee Pain Combined Group 2+3, n = 77	XROA Group 2, n = 52	No XROA Group 3, n = 25
Effusions, %				
Small (grade 1)	37.1	62.3	64.7	55.6
Moderate (grade 2)	36.0	13.2	13.7	11.1
Large (grade 3)	18.6	1.4	1.9	0
Popliteal cyst, grade ≥ 1, %	33.0	20.8	28.0	9.1

Popliteal cysts were seen in 20.8% of those without knee pain and 33.0% of those with knee pain (Table 2). Popliteal cysts were more common among those with radiographic OA. Popliteal cysts communicate with the knee joint, and we found an association between the presence of effusion and presence of popliteal cyst. In those with moderate or larger effusion, 43.2% had a popliteal cyst compared to 22.7% in those with small or absent effusion ($p < 0.001$, chi-square). Further, there was a weak positive correlation between the size of effusion and the size of the cyst ($r = 0.30$, $p < 0.001$).

Synovial thickening was more prevalent with increasing effusion, from 45.0% in those with no effusion to 80.0% in those with a large (grade 3) effusion ($p = 0.001$, chi-square). In addition, the presence of synovial thickening was more likely with increasing K-L grade, from 24.0% in those with K-L grade 0 to 78.3% in those with grade 3/4 ($p < 0.001$, chi-square).

To test the association of these lesions with knee pain, we compared the prevalence of these findings in Groups 1 and 2 (Knee pain/XROA vs No knee pain/XROA). Moderate and large effusions (grade 2/3) were significantly more common among those with Knee pain/XROA compared to No knee pain/XROA ($p < 0.005$, chi-square). Popliteal cysts were no more common among those with Knee pain/XROA compared to those with No knee pain/XROA. This was also true of larger popliteal cysts (grade > 2).

To further assess the relationship between effusions/popliteal cysts, lesions, and pain, we restricted the sample to those with K-L grade ≤ 2, as none of the No knee pain/XROA subjects had radiographic grades > 2 (Table 3). (Subjects with Knee pain/OA, who had K-L grade 0 due to normal PA views, were defined as having radiographic OA due to definite osteophytes in the patellofemoral joint.) There remained a significant difference between the Knee pain/XROA and No knee pain/XROA subjects in the prevalence of either moderate or greater and large effusions alone ($p < 0.001$, $p = 0.02$, respectively). However, there was no difference between the groups in the prevalence of popliteal cysts.

We evaluated the association of effusion with knee pain by attempting to determine whether pain was specifically associated with synovial thickening or effusion. As effusions and synovial thickening are closely associated, we looked at the prevalence of synovial thickening among persons without clinically important knee effusions. Among those with small (grade 1) or no knee (grade 0) effusion, we found that those with knee pain had a prevalence of synovial thickening of 73.6% compared to 21.4% of those without knee pain ($p < 0.001$, chi-square).

Table 3. Prevalence of effusions and cyst by symptoms and K-L grade.

	Knee Pain/ XROA K-L grade ≥ 3 Group 1, n = 107	Knee Pain/ XROA K-L grade ≤ 2 Group 1, n = 267	No Knee Pain/ XROA K-L grade ≤ 2 Group 2, n = 52
Moderate effusion or greater (grade 2 or 3), %	79.6	44.8**	15.4**
Large effusion (grade 3), %	32.7	13.2*	1.9*
Popliteal cyst, %	53.2	23.4	28.0
Synovial thickening, %	100	73.8	52.9

All those in No knee pain/XROA (Group 2) have K/L grade ≤ 2. A random sample of knees in each group were read for synovial thickening. Total for Knee pain/XROA is different from Table 2 due to 7 missing K/L grades. ** $p < 0.001$, * $p = 0.02$, comparing Knee pain/XROA with K/L grade ≤ 2 and No knee pain/XROA.

Next, we restricted our analyses to those with Knee pain and XROA (Group 1) to test whether any lesion was associated with knee pain severity as assessed by VAS pain score. After adjustment for radiographic severity, there was no difference in VAS pain scores in those with different grades of effusions. Nor, in a similar analysis, was there an association of presence of popliteal cyst with pain severity. However, there was a significant difference in VAS pain scores in those with synovial thickening compared to those without synovial thickening, after adjustment for radiographic severity, size of effusion, age, sex, and BMI. The mean pain score in those with synovial thickening after adjustment for radiographic severity and size of effusion was 47.2 mm (standard error 6.0), compared to 28.2 mm (SE 2.8) in those without synovial thickening ($p = 0.006$).

DISCUSSION

Our study shows that effusions and popliteal cysts observed on MRI are common in older individuals, with 13.0% of asymptomatic people having at least a moderate effusion and 20.8% having evidence of a popliteal cyst. We also found that the presence of moderate and large effusions with capsular distention and synovial thickening were significantly more common among those with knee pain, compared to those without knee pain, suggesting that these lesions may contribute to the pain associated with knee OA.

Although cartilage has no neural elements, studies have shown that intracapsular elements contribute to pain. Creamer, *et al* randomized 20 OA knees to local anesthetic or placebo injection[15]; in 6/10 knees injected with local anesthet-

ic, there was a reduction in pain after 1 hour compared to 2/10 knees injected with placebo, suggesting an intracapsular cause of pain in a substantial percentage of subjects. In addition, other workers have injected OA knees with small doses of morphine, with prolonged pain relief compared with placebo[16]. Our study also suggests that intracapsular elements contribute to knee pain in OA, as we observed an increased prevalence of moderate or larger effusions with associated capsular distention and of synovial thickening in those with knee pain compared to those without pain. These results suggest that there may be 2 independent intracapsular contributors to pain: capsular distention and synovitis. Finally, among those with knee pain, synovial thickening was associated with the degree of pain after adjustment for both radiographic severity and size of effusion.

The cross sectional nature of our study precludes us from making any assumptions about the causation of effusion and synovial thickening on the pain of knee OA. Further longitudinal studies will be helpful in this regard. However, we have found a clear association between effusion and synovial thickening and pain in knee OA. In addition, although we observed intraobserver and interobserver agreements for MRI reading that were substantial beyond chance[17], these levels were still not optimal. It highlights the inherent difficulty of reading MRI scans due to the necessity of reading features across multiple cuts, giving kappa values lower than for reading radiographs. Previous knee MRI studies have generally not reported intra and interobserver reliability[4,6,7]; however, one study of knee MRI reading resulted in kappa levels substantially lower than ours, generally between 0.0 and 0.4 for interobserver agreement[18]. These difficulties are likely to give rise to some misclassification; however, it is likely to bias the results toward the null. In addition, there is the potential for misclassification of early symptomatic OA in the No knee pain/no XROA group, as radiographs are not sensitive enough to detect changes of early OA and the screening question asks about pain over the past 4 weeks. This is also likely to bias results toward the null. In addition, there is the possibility that our sample may not be representative of OA in the general community, particularly for men, in which most of the sample subjects were from the VA system, with likely higher rates of disability and comorbidity than the general elderly US population.

Although we did not use gadolinium in this study to allow us to distinguish synovial inflammation, we were able to find evidence of synovial thickening in and around the infrapatellar fat pad, using a similar MRI evaluation as Fernandez-Madrid and colleagues[6]. In knee OA they found that synovial thickening in this area, detected on noncontrast MR imaging, represented chronic mild synovitis when biopsied[6]. In knees with radiographic OA, they found degrees of synovial thickening at each K-L grade similar to ours[7]. In addition, they showed a nonsignificant increase in synovial thickening in those with symptomatic knee OA, compared to asymptomatic knees[7]. However, the numbers in each group were smaller than ours, and there was no evaluation of the severity of pain.

There are few studies of the prevalence of knee effusions in normal populations. A community study in Sudbury, Massachusetts, showed an effusion in one or both knees in 22.3% of men and 17.3% of women aged 45 years and older[19]. Effusions were measured by clinical examination using the "bulge" sign. There were no significant differences in knee effusions between those who had evidence of arthritis (OA or rheumatoid arthritis) on hand radiographs and those who did not, although no knee radiographs were obtained. We found that 13.0% of subjects over 40 years without knee symptoms had at least a moderate effusion on MRI, which is lower than the Sudbury population; however, that they did not differentiate between those with and without knee symptoms may explain this difference.

MRI studies have shown the prevalence of popliteal cysts is between 5% and 19%; however, these studies used subjects referred for MR imaging for knee symptoms and included few, if any, older subjects[20,21]. Our study revealed a high prevalence of popliteal cysts (20.8%) among asymptomatic older people. The subjects with popliteal cysts on MRI were not examined to determine whether the cysts were clinically detectable. However, of the 16 popliteal cysts identified in this group, only 5 were of moderate or large size, suggesting that most would not be clinically detectable. Another MRI study found that popliteal cysts were most common among those with knee effusions and degenerative joint disease[20].

We observed that small and moderate effusions and popliteal cysts are common among middle aged and elderly subjects using MR imaging. Popliteal cysts occurred with similar prevalence among those with radiographic knee OA regardless of symptoms, and do not appear to be associated with pain. Moderate or larger effusions and synovial thickening were significantly more common in those with knee pain and evidence of radiographic OA than in those with a comparable grade of radiographic severity without pain, suggesting that these lesions may contribute to knee pain in OA. Our finding that synovial thickening was related to the severity of knee pain suggests that it may contribute importantly to the cardinal feature of OA — pain.

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Chapter 3

Hill CL, Gale DR, Chaisson CE, Skinner K, Kazis L, Gale ME, Felson DT. Peri-articular lesions detected on magnetic resonance imaging: Prevalence in knees with and without symptoms. Arthritis and Rheumatism;2003;48:2836-44.

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Work previously mentioned by Creamer and colleagues (1996) demonstrated that, in 40% of osteoarthritis knees injected with local anaesthetic, no pain relief was experienced, suggesting that in a significant proportion of individuals with knee OA pain may arise from outside the joint. Certain periarticular lesions were known to occur with knee OA, although the prevalence was unknown. The best described of these were popliteal cysts and anserine bursitis (Janzen 1994).

Whilst reading the BOKS knee MRIs for effusions, popliteal cysts and synovial thickening, the presence of periarticular lesions was evident. Thus, these MRI images provided an opportunity to describe in this well-defined cohort, the prevalence of these lesions and their association with knee symptoms. The conception and design of this substudy was by myself, with support from Dr Gale and Professor Felson. I performed all the MRI reading, with aid from Dr D Gale. I undertook the analysis and interpretation of data and preparation of manuscript, with support from Professor Felson and other co-authors (see Appendix).

Our results demonstrated that peripatellar lesions (prepatellar or superficial infrapatellar) occurred with similar frequency amongst participants with radiographic knee OA with or without knee symptoms (9.8% vs 15.7%, respectively). However, other periarticular lesions (semimembranosus–tibial collateral ligament bursitis, anserine bursitis, iliotibial band syndrome, tibiofibular cyst) were seen more frequently amongst those with both radiographic OA and knee pain (14.9%), compared to 3.9% in those with radiographic OA but no knee pain (p=0.004). Neither peripatellar or other periarticular lesions were seen in participants who had neither pain or radiographic OA.

Amongst those with knee pain, the prevalence of other periarticular lesions was significantly greater amongst those with large effusion, compared to those with no effusion (23.4% v 6.9% respectively, p=0.046). However, effusion alone could not explain the association between the presence of other periarticular lesions and knee

pain. Using logistic regression, the odds ratio for having a periarticular lesion in patients with knee pain compared with those without knee pain was 4.0 (95% confidence interval 0.9–17.6; p=0.05, after controlling for effusion). There was no association between knee pain severity and presence of other periarticular lesions.

No consistent association was observed between the location of self-reported knee pain or elicited tenderness and periarticular lesions, however, the subset was small and the number of lesions detected was too low in each subgroup for consistent findings.

This study demonstrated that periarticular lesions are common in people with symptomatic knee OA and need consideration as alternative sources of pain.

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Periarticular Lesions Detected on Magnetic Resonance Imaging

Prevalence in Knees With and Without Symptoms

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Objective. **To evaluate, using magnetic resonance imaging (MRI), the prevalence of periarticular lesions in older persons with or without knee pain, and to assess the association of these lesions with knee pain.**

Methods. **Subjects ages 45 years and older, with or without knee pain, were recruited from Veterans Affairs medical centers and from the community. Weight-bearing posteroanterior, skyline, and lateral radiographs were obtained in all subjects. Subjects were divided into 3 groups: those with radiographic OA (ROA) and knee pain (n = 376), those with ROA and no knee pain (n = 51), and those with neither ROA nor knee pain (n = 24). A single knee (the more symptomatic one in subjects with knee pain) was imaged with a 1.5T scanner using T1- and T2-weighted and proton-density spin-echo imaging sequences. MRIs were read for the presence of periarticular lesions, which were categorized (according to their general location) as being either peripatellar (prepatellar, superficial infrapatellar, deep infrapatellar) or "other periarticular lesions" (semimembranosus–tibial collateral ligament bursitis, anserine bursitis, iliotibial band syndrome, tibiofibular cyst).**

Results. **Patients with knee pain had more severe radiographic disease than did subjects who were asymptomatic. Peripatellar lesions (prepatellar or superficial infrapatellar) were present in 12.1% of the patients with knee pain and ROA, in 20.5% of the patients with ROA and no knee pain, and in 0% of subjects with neither ROA nor knee pain ($P = 0.116$). However, other periarticular lesions were present in 14.9% of patients with both ROA and knee pain, in only 3.9% of patients with ROA but no knee pain, and in 0% of the group with no knee pain and no ROA ($P = 0.004$).**

Conclusion. **Although peripatellar lesions are equally common among subjects with knee pain and those without knee pain, other periarticular lesions (including bursitis and iliotibial band syndrome) are significantly more common among subjects with knee pain and may contribute to pain in these individuals.**

The cause of knee pain in patients with osteoarthritis (OA) remains unclear. Because hyaline cartilage has no innervation (1), the primary pathologic abnormality in OA (i.e., loss of hyaline articular cartilage) could occur without producing pain. Sources of knee pain in OA may include subchondral bone marrow lesions, knee joint effusions, and synovial thickening; recent magnetic resonance imaging (MRI) studies have demonstrated an increase in the prevalence of these lesions in patients with symptomatic knee OA compared with patients with no symptoms (2,3). However, the possibility remains that in patients with knee OA, some of the pain does not emanate from the joint itself but rather from structures near the joint that contain pain fibers.

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Knees with OA are biomechanically altered, and these changes may put stress on ligament and tendon insertion sites in and around the knee joint, creating pain. Therefore, OA knees may be vulnerable to periarticular pathology, which can cause symptoms, including bursitis. Because these periarticular conditions may be treatable (independent of knee OA), it is important to identify whether patients with knee OA are at increased risk for periarticular lesions, and which lesions are likely to be present.

A wide range of periarticular lesions occur around the knee joint (4), including pathologic changes near the patella, enthesopathies, and bursitis. One of them, anserine bursitis, is associated with knee OA, but its frequency and that of other periarticular lesions in subjects with or without knee OA is unknown. MRI provides an ideal noninvasive method of identifying fluid-filled lesions and bursitis and detecting enthesopathy.

The objectives of the current study were 2-fold. First, we attempted to estimate the prevalence of periarticular lesions among persons ages 45 and older in the following groups: 1) patients with radiographic OA (ROA) and frequent knee pain, 2) patients with ROA but no knee pain, and 3) subjects with neither ROA nor knee pain. Our second goal was to examine the association of periarticular lesions with symptom occurrence by comparing the prevalence of these lesions in subjects with knee pain and those without knee pain.

PATIENTS AND METHODS

Participant recruitment. The source of subjects for this study has been described previously (2,3). Briefly, patients with knee pain were recruited from 2 cohorts of subjects receiving care at Veterans Affairs (VA) medical centers and from the community. Subjects without knee pain were recruited from the same VA cohorts. The Human Studies Committee and the Institutional Review Board approved the protocols. Informed consent was obtained from all subjects. The minimum age for entry into the study was 45 years for men and 50 years for women. The entry age for women was older than that for men to lessen the chance of inadvertently obtaining radiographs in a pregnant woman.

All subjects were surveyed about knee symptoms. They were asked the following 2 questions: "Over the past 4 weeks, have you had pain, aching, or stiffness in 1 or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" In a followup interview, individuals answering "yes" to both questions were asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified in the interview, the individual was eligible for recruitment as a participant with knee pain. Of all the subjects with knee pain, a subset of 324 who entered a natural history study, either initially or after inclusion into the study, were examined by a rheumatologist (DTF) who confirmed that, in all cases, patients had clinical knee OA rather than isolated tenderness only at sites of localized bursitis or tendinitis (e.g., quadriceps tendinitis) or referred pain from the hip. Subjects with only isolated periarticular tenderness or evidence of hip OA as a source of knee pain were excluded. The remainder of subjects with knee pain and those without knee pain were not examined. We attempted to roughly match subjects without knee symptoms and those with knee symptoms in terms of age and sex. Subjects without knee pain were recruited from among those who answered "no" to both of the screening questions.

Radiographic evaluation. All subjects underwent fluoroscopically positioned weight-bearing posteroanterior (PA) and weight-bearing skyline radiography according to the protocol described by Buckland-Wright (5) and weight-bearing lateral radiography according to the Framingham OA Study protocol (5). One radiologist (DRG) read the radiographs for the presence of definite osteophytes and other features, using an atlas.

If a definite osteophyte was present in a symptomatic knee (including the patella) on any of the 3 views, the knee was characterized as having ROA. This definition of knee OA meets the criteria of the American College of Rheumatology (6). Symptomatic individuals without a definite radiographic osteophyte were excluded from this study because of small numbers ($n = 5$). Radiographic severity was measured according to the Kellgren/Lawrence (K/L) scale (range 0–4) (7) on PA view only (for which reproducibility has previously been reported) (8). Thus, some of the subjects characterized as having ROA had patellofemoral disease, and the K/L grade assigned to them could be <2.

MRI evaluation. Each subject underwent MRI of a single knee. In patients with knee pain, this was usually the more symptomatic knee and was always a knee in which the patient reported current symptoms. If end-stage radiographic disease was present in 1 knee and both knees were symptomatic, the subject's less radiographically affected knee was studied. In subjects without knee symptoms, the dominant knee was selected for imaging. All studies were performed on a General Electric Signa 1.5T MRI system (GE Medical Systems, Milwaukee, WI) using a phased-array knee coil. An anchoring device for the ankle and knee was used to ensure uniformity of positioning between subjects. The imaging protocol included sagittal spin-echo proton-density and T2-weighted images (repetition time [TR] 2,200 msec, time to echo [TE] 20/80 msec) with a slice thickness of 3 mm, a 1-mm interslice gap, 1 excitation, a field of view (FOV) of 11–12 cm, and a matrix of 256 × 192 pixels; and coronal and axial spin-echo fat-saturated proton-density and T2-weighted images (TR 2,200 msec, TE 20/80 msec) with a slice thickness of 3 mm, a 1-mm interslice gap, 1 excitation, an FOV of 11–12 cm, and a matrix of 256 × 128 pixels.

Two readers (CLH and DRG) developed a semiquantitative scale to evaluate periarticular lesions, which were categorized (based on clinical considerations) as either

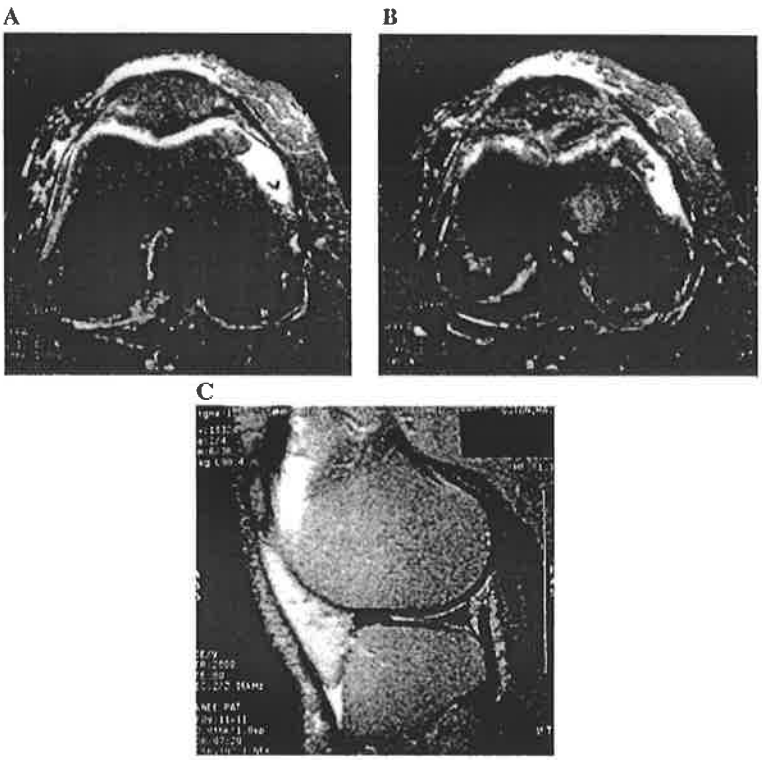

Figure 1. **A** and **B**, Axial T2-weighted magnetic resonance (MR) images of **A**, prepatellar bursitis (grade 3) and **B**, superficial infrapatellar bursitis (grade 3). **C**, Deep infrapatellar fluid (grade 1) on sagittal T2-weighted MR image.

peripatellar lesions or "other periarticular lesions." Peripatellar lesions were graded on a 0–3 scale (0 = normal, 1 = small degree of signal increase within bursa, 2 = moderate signal increase within bursa, and 3 = encapsulated fluid within bursa, on axial and sagittal T2-weighted images) and included prepatellar bursitis, superficial infrapatellar bursitis, and deep infrapatellar bursitis (Figure 1). Other periarticular lesions (distinct from peripatellar lesions) of interest included semimembranosus–tibial collateral ligament (semimembranosus-TCL) bursitis, anserine bursitis, iliotibial band syndrome, and tibiofibular cyst (synovial cyst arising from superior tibiofibular joint) on T2-weighted images using axial, sagittal, and coronal views (Figure 2). One reader (CLH) read all radiographs for the presence of patellar and periarticular lesions, with a random subset reread for intraobserver reproducibility (the weighted kappa value for patellar/periarticular lesions was 0.67). Although we also report here on popliteal cysts, they are intraarticular rather than periarticular lesions and have been the focus of a previous report (2). MRI studies of subjects from each of the 3 study groups were ordered randomly, and the reader was blinded to the participants' group status.

Subject evaluation. The height and weight (using a balance-beam scale) of each participant were measured on the day of the MRI scan. Subjects were asked to evaluate the severity of their knee pain using a knee-specific 100-mm visual analog scale (VAS).

Definition of study groups. For the purposes of this study, we defined 3 study groups. Subjects who responded positively to the screening question about knee symptoms and who had a radiograph demonstrating a definite osteophyte were assigned to group 1 (knee pain/ROA). Subjects who did not report knee symptoms but had a definite osteophyte on radiography were assigned to group 2 (no knee pain/ROA). Last, subjects who did not report knee symptoms and had no definite osteophyte on their knee radiograph were assigned to group 3 (no knee pain/no ROA).

Clinical examination. A drawing, dividing the knee into 12 areas with grid lines, was devised so that each grid area approximated an anatomic area in the knee and also corre-

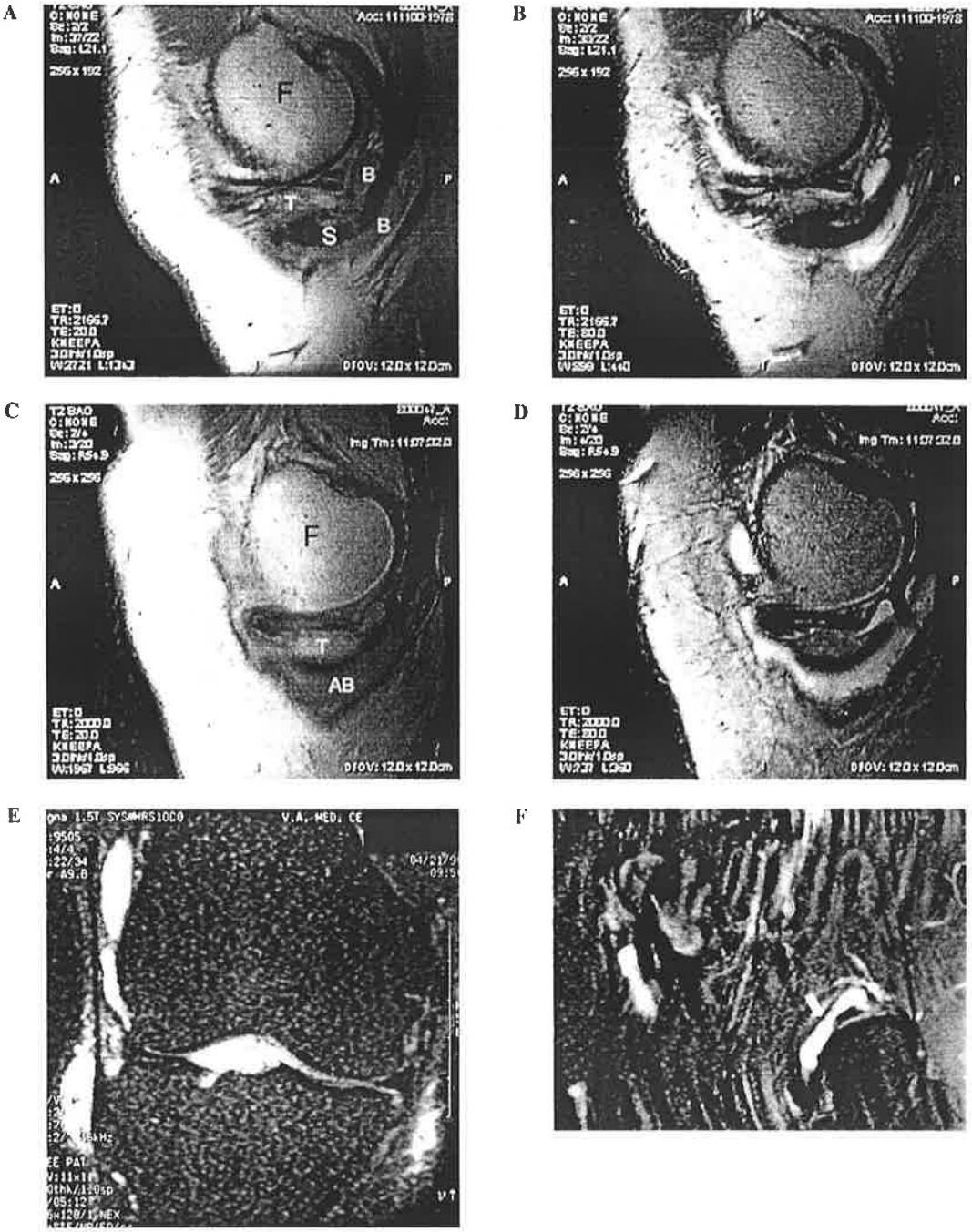

Figure 2. Magnetic resonance (MR) images of proton density (**A**) and T2-weighted (**B**) sagittal images of semimembranosus–tibial collateral ligament bursitis, proton density (**C**) and T2-weighted (**D**) sagittal images of anserine bursitis, T2-weighted image of iliotibial band syndrome (**E**), and T2-weighted image of tibiofibular cyst (**F**) (**arrow**). **AB** = anserine bursa; **B** = bursitis; **F** = femur; **T** = tibia.

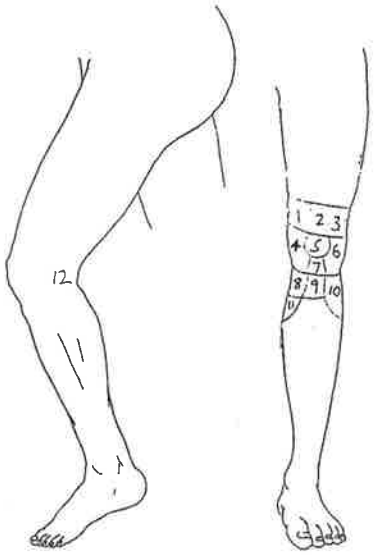

Figure 3. Drawing of the knee, used for documenting knee pain and tenderness.

sponded to areas scored for lesions on the MR images (Figure 3). A subset of 59 patients from group 1 (knee pain/ROA) were asked to demonstrate on their own knees the location of pain in each knee, and this was marked on the drawing. The subjects were then examined by a rheumatologist (CLH) who was unaware of MRI findings. Prior to study commencement, 2 rheumatologists (CLH and DTF) performed several examinations jointly, in order to devise the protocol and ensure standardization of the knee examination.

Before each knee examination, the examiner used a dolorimeter to calibrate finger pressure to 3 kg of force on 5 occasions. Then, an additional 5 blinded repetitions were performed. If blinded repetitions were >0.5 kg from the 3-kg baseline measurement on more than 2 occasions, calibration was repeated. The examiner then exerted finger pressure over each of the 11 anterior areas and 1 posterior area. After each palpation, subjects were asked to indicate to the examiner whether the area was tender or nontender. To maximize accuracy, palpation was repeated in areas that the subject had indicated were painful. Areas were characterized as being tender only when the subject described them as tender on both occasions. The location of tenderness was noted on the same knee diagram.

Based on the locations of tenderness on the knee diagram, we evaluated correlations of the locations with respective pathology as follows: medial tenderness (areas 4, 8, and 11) was correlated with the presence of anserine bursitis and semimembranosus-TCL bursitis; anterior tenderness (areas 5, 7, and 9) was correlated with the presence of patellar lesions (prepatellar bursitis, superficial and deep infrapatellar bursitis); lateral tenderness (areas 3, 6, and 10) was correlated with the presence of iliotibial band syndrome and tibiofibular cyst (areas 6 and 10 only); and posterior tenderness (area 12) was correlated with presence of popliteal cysts.

Statistical analysis. Only 1 knee per subject was studied by MRI; thus, analyses are knee- and subject-specific. Differences between proportions were assessed using the chi-square test, or by Fisher's exact test if expected values were <5. Differences in continuous measures between the 3 groups were examined using analysis of variance (ANOVA). The *P* values reported are 2-sided.

To determine whether peripatellar or periarticular lesions were associated with pain severity in subjects with knee symptoms, we performed linear regression analyses in group 1 (knee pain/ROA) only, using pain reported on a 100-mm VAS as the dependent variable, and results of testing for radiographic severity (K/L grade) and effusion or the number of periarticular lesions as independent variables. Also, to determine whether the association between knee pain and the presence of peripatellar or periarticular lesions was confounded by the presence of effusion that may cause pain, we performed a logistic regression analysis, using the presence of knee pain as the dependent variable and effusion and the presence of periarticular lesions as independent variables. Results of these analyses in men and women are combined because of the small numbers of lesions, and because there were no sex-specific findings.

RESULTS

Three hundred seventy-six subjects with knee pain/ROA (67.6% of whom were male), 51 with no knee pain/ROA (56.9% male), and 24 with no knee pain/no ROA (70.8% male) were recruited. The age of subjects in the 3 study groups was similar (Table 1). Patients in group 1 (knee pain/ROA) tended to have a higher body mass index than did those in the other groups (Table 1) ($P = 0.004$ by ANOVA). Patients in group 1 had a median K/L score of 2, whereas subjects with no symptoms (groups 2 and 3) had a median score of 0, although there was considerable overlap in radiographic severity between the groups with ROA (groups 1 and 2).

The prevalence of MRI findings in patients with knee pain and in subjects without knee pain is shown in Table 2. Prepatellar and superficial infrapatellar bursitis were present in patients with ROA (both those with knee pain and those without knee pain) but were absent in the group with no knee pain and no ROA (Table 2). Small amounts of fluid in the deep infrapatellar bursa were seen commonly in all groups, but evidence of deep infrapatellar bursitis was seen in only 3 subjects (all in the knee pain/ROA group). Peripatellar lesions (either prepatellar or superficial infrapatellar bursitis, or both) were present in 12.1% of the patients with knee pain and ROA, in 20.5% of the patients with ROA and no knee pain, and in 0% of the subjects with neither ROA nor knee pain ($P = 0.116$).

Table 1. Characteristics of subjects in study groups, stratified by sex*

Characteristic	Knee pain/ROA, group 1 (n = 376)		No knee pain/ROA, group 2 (n = 51)		No knee pain/no ROA, group 3 (n = 24)	
	Male	Female	Male	Female	Male	Female
No.	254	122	29	22	17	7
Age, mean years	68.3	65.0	66.8	66.1	63.4	65.3
Body mass index, mean	30.9	32.4	28.5	29.5	28.4	29.8
K/L grade, median (range)†	2 (0–4)	2 (0–4)	0 (0–2)	0 (0–2)	0 (0–1)	0 (0–1)
Pain score, median (range)‡	47 (0–100)	40 (0–100)	0 (0–5)	2 (0–5)	0 (0)	0 (0–5)

* ROA = radiographic osteoarthritis; K/L = Kellgren/Lawrence.
† Seventy patients with knee pain/ROA who had a K/L grade of 0 due to normal posteroanterior views on radiography were defined as having ROA because of the presence of definite osteophytes in the patellofemoral joint.
‡ Measured on a 100-mm visual analog scale.

Other periarticular lesions outside the knee joint capsule (including semimembranosus-TCL bursitis, anserine bursitis, iliotibial band syndrome, and tibiofibular cyst) were significantly more common among subjects with knee pain/ROA than in individuals with no knee pain (Table 2) ($P = 0.004$ by chi-square analysis). Although 14.9% of patients in group 1 (knee pain/ROA) had such lesions, none were present in the group with no knee pain and no ROA. Only 3.9% of subjects in group 2 (no knee pain/ROA) had these lesions (consisting entirely of semimembranosus-TCL and anserine bursitis). Of the subjects with knee pain, 1.9% had ≥2 of these periarticular lesions. Among subjects with knee pain and ROA, there was no difference between men and women in the prevalence of either peripatellar lesions or other periarticular lesions. Popliteal cysts were common among subjects with ROA, irrespective of the presence of symptoms (2).

To further assess the relationship between periarticular lesions and pain, we restricted the analysis to include only subjects with a K/L grade of ≤2, because none of the subjects in group 2 (no knee pain/ROA) had a K/L grade of >2 (Table 3). (Subjects with knee pain and ROA who had a K/L grade of 0 due to normal findings on PA views were defined as having ROA due to the presence of definite osteophytes in the patellofemoral joint.) The prevalence of peripatellar lesions was not significantly different between groups ($P = 0.26$). Among patients with ROA, there was a difference in the prevalence of other periarticular lesions between those with knee pain and those without knee pain ($P = 0.057$).

Table 2. Prevalence of periarticular soft tissue lesions in study groups*

	Knee pain/ ROA, group 1 (n = 376)	No knee pain/ ROA, group 2 (n = 51)	No knee pain/ no ROA, group 3 (n = 24)	Groups 2 + 3 combined (n = 75)
Peripatellar lesion				
Prepatellar bursitis, K/L grade 2/3	3.1	8.1	0	5.9
Superficial infrapatellar bursitis, K/L grade 2/3	10.6	18.0	0	13.2
Deep infrapatellar fluid, K/L grade ≥1	51.6	53.2	63.2	56.1
Other periarticular lesion†	14.9‡	3.9	0	2.7
Semimembranosus-TCL bursitis	4.4	2.2	0	1.6
Anserine bursitis	4.3	2.5	0	1.7
Iliotibial band syndrome	5.4	0	0	0
Tibiofibular cyst	3.7	0	0	0
Popliteal cysts§	33.0	28.0	9.1	20.8

* Values are the percentage of subjects. ROA = radiographic osteoarthritis; K/L = Kellgren/Lawrence; TCL = tibial collateral ligament.
† Seven patients had >1 other periarticular lesion.
‡ $P = 0.004$ versus groups 2 and 3 combined.
§ Data derived from ref. 2.

Table 3. Prevalence of periarticular lesions, according to K/L grade and symptoms*

	Knee pain/ROA, group 1		
	K/L grade ≥3 (n = 106)	K/L grade ≤2 (n = 263)	No knee pain, ROA, group 2 (n = 51)
Prepatellar and superficial infrapatellar bursitis	7.5	10.3	15.7
Other periarticular lesions	23.6	13.3	3.9†

* Values are the percentage of subjects. All patients in group 2 had Kellgren/Lawrence (K/L) grades ≤2. K/L grades were missing for 7 subjects in group 1. ROA = radiographic osteoarthritis.
† $P = 0.057$ versus patients in group 1 with K/L grade ≤2.

Next, we restricted our analyses to include only patients with knee pain and ROA, in order to test whether any of these structural lesions was associated with severity of knee pain as assessed by pain scores on a 100-mm VAS. After adjustment for radiographic severity and the presence of knee joint effusion, there were no differences in VAS pain scores among patients in whom the presence of other periarticular lesions was documented.

Among patients with knee pain, an association was found between the presence of effusion and the presence of other periarticular lesions. The prevalence of other periarticular lesions was 6.9% among subjects with no effusion and 23.4% among those with large effusion ($P = 0.046$). An association between the presence of knee effusion and patellar lesions was not observed ($P = 0.25$). However, effusion alone could not explain the association between the presence of other periarticular lesions and knee pain. By logistic regression, the odds ratio for having a periarticular lesion in patients with knee pain compared with those without knee pain was 4.0 (95% confidence interval 0.9–17.6; $P = 0.05$), after controlling for effusion.

The prevalence of periarticular lesions in the subset of 59 subjects with knee pain/ROA who were examined clinically is shown in Table 4. Among subjects with infrapatellar lesions, the prevalence of positive findings on physical examination was lower than the prevalence of self-reported pain in the relevant areas. No patients in this subgroup had prepatellar or anserine bursitis, so we were unable to determine the correlation between physical examination and MRI findings. One subject had MRI evidence of a large semimembranosus-TCL bursitis, with positive findings on clinical examination of the medial aspect of the knee. Although only 1 of the 3 subjects with iliotibial band syndrome had positive findings on physical examination, each of these 3 patients had low-grade disease (grade 1) on MRI. Two subjects had tibiofibular cysts but no positive findings on physical examination. Popliteal cysts were essentially asymptomatic, with only 2 of the 19 subjects with popliteal cysts having positive findings on clinical examination.

DISCUSSION

Our study shows that periarticular lesions, specifically iliotibial band syndrome, semimembranosus-TCL, anserine bursitis, and tibiofibular cyst, are common in

Table 4. Prevalence of periarticular lesions in 59 patients with positive findings on MRI who underwent physical examination*

	All patients with positive MRI findings	Subgroup with positive clinical findings in location of MRI lesion	Subgroup with self-reported pain in location of MRI lesion
Prepatellar bursitis, K/L grade 2/3	0	–	–
Superficial infrapatellar bursitis, K/L grade 2/3	5	1 (20)	2 (40)
Deep infrapatellar bursitis	25	7 (28)	14 (56)
Anserine bursitis	0	–	–
Semimembranosus-TCL bursitis	1	1 (100)	0 (0)
Iliotibial band syndrome	3	1 (33.3)	0 (0)
Tibiofibular cyst	2	0 (0)	1 (50)
Popliteal cyst	19	2 (10.5)	2 (10.5)

* Values are the number (%) of patients. MRI = magnetic resonance imaging; K/L = Kellgren/Lawrence; TCL = tibial collateral ligament.

patients with chronic knee pain and are substantially more prevalent in this group than in individuals without knee pain. This finding suggests that such periarticular lesions may cause knee pain, even in individuals whose pain is thought to emanate from the joint. Thus, some of the chronic pain associated with OA of the knee may be attributable to a treatable soft tissue disorder. In contrast, patellar lesions involving both prepatellar and superficial and deep infrapatellar bursae demonstrated on MRI are common in older individuals with asymptomatic radiographic knee OA, with equal prevalence among those with symptomatic knee OA.

The wide range of other periarticular lesions observed in patients with knee pain and the absence of such lesions among subjects without knee pain suggest that periarticular lesions may contribute to knee pain. The prevalence of each of the periarticular lesions that we studied was low. Although these lesions are well recognized to cause pain, apart from anserine bursitis, none is well documented to occur in patients with knee OA (9–11). Iliotibial band syndrome has been shown to cause lateral knee pain in athletes (12). In addition, it is possible that tibiofibular cysts could cause lateral knee pain, either directly or via peroneal nerve compression (13). Semimembranosus-TCL bursitis has been observed in middle-aged individuals with medial knee pain, and this entity may be mistaken for anserine bursitis (9). We have demonstrated that at least some of these lesions would have contributed to pain in individual subjects, reinforcing the notion that the source of pain in knee OA may be multifactorial.

In patients with symptomatic knee OA, periarticular lesions may produce no more pain than that produced by other causes (e.g., bone marrow lesions, effusion), which explains our failure to detect an association between these lesions and the severity of knee pain. Given that 1 of these periarticular lesions was present in almost 1 of every 6 symptomatic subjects, such lesions must be considered as another potential source of pain in knee OA. It is conceivable that, in some patients, pain emanates from both the joint and periarticular lesions. In addition, it is possible that iliotibial band syndrome, which has been described predominantly in athletes, may be a consequence of gait changes induced by knee OA and may occur together with symptomatic knee OA. Its presence may reflect the fact that persons with knee pain have an altered gait.

Unlike pain in knee OA from other sources, pain from periarticular sources may be amenable to treatment, such as a physical therapy in patients with iliotibial band syndrome or local corticosteroid injections in patients with anserine bursitis. In other rheumatic diseases such as rheumatoid arthritis (RA) and polymyalgia rheumatica, periarticular lesions identified by careful imaging studies appear to be the source of pain in some cases. For example, in elderly-onset RA, biceps tendinitis and subdeltoid bursitis are common (14) and are likely to contribute to shoulder pain. Therefore, careful physical examination of the patient who experiences a flare in knee OA may alert the clinician to the presence of one of these lesions, which could be confirmed with appropriate radiographic examination. Prepatellar and superficial infrapatellar bursitis were equally prevalent among patients with ROA and knee pain and those with ROA but no knee pain and are therefore unlikely to contribute significantly to knee pain in OA.

Among subjects in this study, we frequently observed a small amount of fluid in the deep infrapatellar bursa and suggest, as have other investigators (4), that this is likely to be a physiologic phenomenon. Interestingly, among the subjects in whom deep infrapatellar fluid was found, more than half reported anterior knee pain. However, patients with greater amounts of deep infrapatellar fluid were also more likely to have a knee effusion, and we have demonstrated that effusion is associated with knee pain.

In the subset of 59 subjects who underwent clinical examination, the lesions identified on MRI were not consistently sites of tenderness. We are not sure how to interpret this finding, especially because of the small number of subjects who had MRI lesions associated with symptoms (the so-called "other periarticular lesions"); for example, none of these subjects had anserine bursitis). Of the 2 subjects with tibiofibular cysts, neither had positive findings on clinical examination. This is not surprising, because the tibiofibular joint is a deep structure, and, according to the limited number of case reports on this subject, most symptoms arising from tibiofibular cysts are attributable to compression of the common peroneal nerve (13). Surprisingly, only 1 of the 3 subjects in whom iliotibial band syndrome was diagnosed on MRI had lateral tenderness; however, no specific maneuvers to elicit iliotibial band tenderness were performed, and in all 3 cases the lesion was low-grade. Among subjects with infrapatellar lesions, most did not have localized tenderness in the extensor compartment. This may suggest that our inability to detect a relationship between peripatellar lesions on MRI and knee pain is attributable to the fact that such lesions on MR images are common and nondiagnostic, and are not indicative of clinical pathology.

Chapter 4

Hill CL, Seo GS, Gale D, Totterman S, Gale ME, Felson DT. Cruciate ligament integrity in osteoarthritis of the knee. Arthritis and Rheumatism;2005;52:794-799. *Impact factor: 7.421*

An association exists between anterior cruciate ligament (ACL) rupture and subsequent development and progression of knee OA (Lohmander 2004), for which anteroposterior laxity may be a contributory factor (Wada 1996, Brage 1994). Anteroposterior laxity increases the external adduction moment, which is known to increase medial knee OA and pain (Schnitzer 1993). In addition, recent work by Davies-Tuck (2008a) has demonstrated an association between peak external knee adduction moment and meniscal damage in both OA and non-OA knees.

MRI is highly sensitive (96%) and specific (98%) in detecting acute ACL rupture when compared with arthroscopy (Lee 1988, Ha 1998), and can be used to study the prevalence of cruciate ligament in established knee OA. The conception and design of this substudy was by Professor Felson and myself with assistance from Dr Gale, Dr Seo and Dr Totterman. MRI reading was undertaken by Drs Seo, Gale and Totterman. I undertook the analysis and interpretation of data and preparation of manuscript, with support from Professor Felson and other co-authors (see Appendix).

A report, in abstract form, from the Health ABC study of 245 elderly (70-79 years) subjects with unilateral or bilateral knee OA described the occurrence of any ligament tear (included both cruciate and collateral ligaments) detected by MRI was 29% of men and 30% of women (Guermazi 2002). Two earlier smaller MRI studies of symptomatic subjects with knee OA found complete ACL rupture in 35% (N=20) and 28% (N=50), respectively (Chan 1991, Link 2003). Neither study included asymptomatic controls.

Therefore, our larger cohort with comparison groups of participants without knee pain with or without radiographic OA allowed more accurate data with regards to prevalence of cruciate ligament rupture and its association with symptoms and recall of significant prior injury. The BOKS study demonstrated that complete ACL rupture was present in 23% of participants with symptomatic knee OA, 4.2% of participants with radiographic knee OA and no knee pain and 0% of those with no radiographic knee OA or knee pain. ACL rupture was associated with more severe radiographic

knee OA, but not with more severe pain. Amongst those with knee pain and radiographic knee OA, about half (47.9%) of those with complete ACL rupture recalled a significant knee injury (defined as a knee injury requiring use of crutches or a cane) compared to 26% of those with an intact ACL. Complete PCL rupture was rare (<1%).

So amongst those with established symptomatic knee OA, ACL rupture was common and was associated with more severe radiographic disease. The absence of recall of a significant prior knee injury in half of the participants with complete ACL rupture suggested that degenerative rupture may occur in older people without major trauma.

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Cruciate Ligament Integrity in Osteoarthritis of the Knee

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Objective. **To evaluate, using magnetic resonance imaging (MRI), the prevalence of anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL) rupture in knees with symptomatic osteoarthritis (OA) compared with those without OA, and the relationship to pain and recalled injury.**

Methods. **MRI and plain radiography of the knee were performed in a group of 360 subjects with painful knee OA (cases; 66.7% male, mean age 67.1 years) and 73 without knee pain (controls; 57.5% male, mean age 66.1 years). MRIs were read for the presence or absence of complete or partial ACL or PCL tear. Subjects with knee pain were asked to quantify severity of pain on a visual analog scale and to report whether they could recall a significant knee injury (requiring use of a cane or crutches). We compared the prevalence of ACL and PCL rupture in those with and those without knee pain and also evaluated whether, in cases, there was any association with recalled knee injury.**

Results. **The proportion of cases who had complete ACL rupture was 22.8%, compared with 2.7% of controls ($P = 0.0004$). PCL rupture was rare both in cases (0.6%) and in controls (0%). Cases with ACL rupture had more severe radiologic OA ($P < 0.0001$) and were more likely to have medial joint space narrowing ($P < 0.0001$) than cases with intact ACLs, but did not have higher pain scores. Among cases, only 47.9% of those with complete ACL tears reported a previous knee injury, compared with 25.9% of those without complete ACL tears ($P = 0.003$).**

Conclusion. **ACL rupture is more common among those with symptomatic knee OA compared with those without knee OA. Fewer than half of subjects with ACL rupture recall a knee injury, suggesting that this risk factor for knee OA is underrecognized.**

Rupture of the anterior cruciate ligament (ACL) is known to lead to premature osteoarthritis (OA) of the knee (1–5). However, the prevalence of ACL and posterior cruciate ligament (PCL) rupture among those with established knee OA and its relationship with pain in those with knee OA or with recalled injury are unknown. ACL ruptures often can be repaired, but if a person is unaware of the injury at its occurrence, an opportunity for preventing later disease may be lost.

ACL tears have the biomechanical effect of increasing anteroposterior laxity by allowing the tibia to sublux anteriorly on the femur. Therefore, the absence of an ACL increases the external adduction moment, which should augment medial loading, increasing the risk of medial knee OA. Adduction moment has also been linked to pain in knee OA (6). If effects on laxity and medial loading are substantial, ACL tears could be an ongoing source of pain in OA, and this might warrant surgical intervention even in patients with established disease.

The overall goal of the present study was to evaluate the associations of ACL and PCL tears in subjects with and those without symptomatic knee OA. We investigated several specific questions about ACL and PCL tears: 1) what their prevalence is in middle-aged and elderly persons with and without symptomatic knee OA; 2) whether they are preceded by a recalled knee injury; 3) whether they are associated with particular structural features of knee OA including severity

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and medial compartment involvement; and 4) whether they are associated with pain severity in persons with symptomatic knee OA.

PATIENTS AND METHODS

Participant recruitment. The study protocol was approved by the Boston University Medical Center and Veterans Affairs Boston Healthcare System Institutional Review Boards. The minimum age for enrollment in the study was 45 years for men and 50 years for women. Enrollment age for women was older to lessen the chance of inadvertently subjecting a pregnant woman to radiography. The source of subjects for this study has been detailed in other publications (7–9). Briefly, subjects with knee pain were drawn from 2 cohorts receiving care at Veterans Administration Medical Centers and from the community. Those without knee pain were drawn from the same Veterans Administration cohorts.

All subjects were asked 2 questions: "Over the past 4 weeks, have you had pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" In a followup interview, those answering positively to both questions were asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified in the interview, then the individual was eligible for recruitment as a subject with knee pain. All subjects who had knee pain either initially or after inclusion in the study were examined by a rheumatologist who confirmed that, in all cases, there was tenderness in or around the knee.

We recruited subjects without knee pain from among those who answered in the negative to both of the above screening questions. We attempted to roughly match those without knee symptoms by age and sex to those with knee symptoms.

Radiographic evaluation. Fluoroscopically positioned weight-bearing posteroanterior (PA) and skyline radiographs (Buckland-Wright protocol) (10) and weight-bearing lateral radiographs (Framingham Study protocol) (11) were obtained in all subjects (7). Radiographs were read for the presence of definite osteophytes and other features by 1 radiologist, using the Osteoarthritis Research Society International atlas (12). If a definite osteophyte was present in a symptomatic knee on any of the 3 views (which included the patella), the subject was characterized as having radiographic OA. This definition meets American College of Rheumatology criteria for knee OA (13). Symptomatic individuals without a definite radiographic osteophyte were excluded from this study because of small numbers (n = 4). Radiographic severity was measured by Kellgren/Lawrence (K/L) grade on the PA view only (for which reproducibility has previously been reported) (14). Thus, some of the subjects characterized as having radiographic OA had patellofemoral disease, and the K/L grade could be <2. Knees with a K/L grade ≥2 and medial joint space narrowing of ≥1 (0–3 scale) on the PA view were characterized as having medial knee OA; knees with a comparable K/L grade and lateral narrowing were characterized as having lateral knee OA (12).

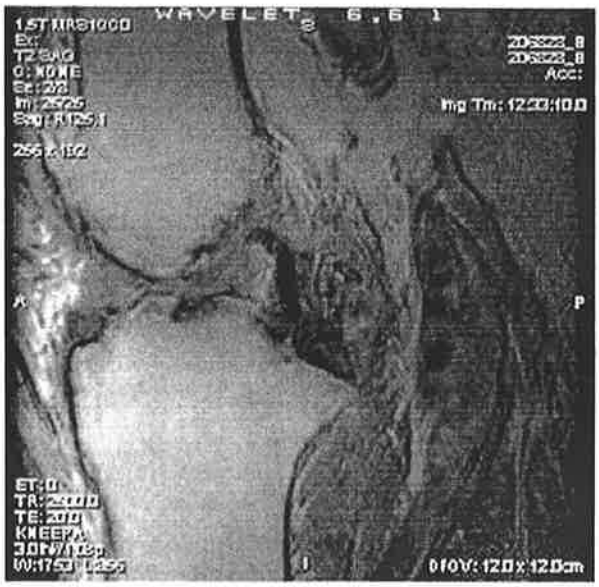

Figure 1. Sagittal proton-density magnetic resonance image of complete anterior cruciate ligament rupture in the vicinity of the posterior cruciate ligament.

Magnetic resonance imaging (MRI) evaluation. Each subject underwent MRI of a single knee. In the subjects with knee symptoms, this was usually the more symptomatic knee and was always a knee in which there were current symptoms (if end-stage radiographic disease was present in 1 knee and both were symptomatic, the subject's less radiographically affected knee was studied). For subjects without knee symptoms, the dominant knee was selected for imaging. All studies were performed with a GE Signa 1.5T MR machine (General Electric Medical Systems, Milwaukee, WI) using a phased-array knee coil which was made locally and specifically for the study. An anchoring device surrounding the leg was made from hard foam to limit rotation and ensure uniform position between subjects. The imaging protocol included sagittal spin-echo proton-density T2-weighted images (repetition time [TR] 2,200 msec, echo time [TE] 20/80 msec, slice thickness 3 mm, interslice gap 1 mm, number of excitations [NEX] 1, field of view [FOV] 11–12 cm, matrix 256 × 192 pixels) and coronal spin-echo fat-saturated proton-density T2-weighted images (TR 2,200 msec, TE 20/80 msec, slice thickness 3 mm, interslice gap 1 mm, NEX 1, FOV 11–12 cm, matrix 256 × 128 pixels).

Two readers read all films for the presence or absence of ACL or PCL tear, with consensus. A complete tear was defined as complete interruption of the cruciate ligament or lack of visualization of an intact cruciate ligament on both the sagittal and coronal images (Figure 1). A random subset of images (n = 31) was read by a third reader for interobserver reproducibility (κ for complete ACL tear = 0.74 [95% confidence interval 0.51–0.98]). MRIs of subjects were ordered

Among cases, there was no significant difference in the prevalence of ACL rupture between men (24.7%) and women (18.9%) ($P = 0.23$). Among cases with complete ACL tears and those without ACL tears, there was no significant difference in age (68.4 years and 66.4 years, respectively; $P = 0.50$) or BMI (31.7 kg/m^2 and 31.0 kg/m^2, respectively; $P = 1.00$). Cases with complete ACL tear had more severe radiographic OA, based on the K/L grade ($P < 0.0001$) (Table 3). Those with complete ACL tear more frequently had evidence of medial joint space narrowing on radiographs (82.1%) compared with those with intact ACLs (47.8%) ($P < 0.0001$). This was not the case for lateral joint space narrowing, for which there was no significant difference between those with and those without complete ACL tear (16.4% and 11.3%, respectively; $P = 0.28$).

Cases with complete ACL tear did not have more pain on VAS than those with intact ACLs, after adjustment for K/L grade and BMI (complete ACL tear 44.3 mm, intact ACL 44.1 mm; $P = 0.95$). Among cases with complete ACL tear, only 47.9% recalled a significant knee injury, requiring use of crutches or cane, in the knee examined. This compared with 25.9% of cases with intact ACLs ($P = 0.003$ by chi-square analysis). There was no difference between men and women in their ability to recall a significant knee injury, irrespective of ACL integrity.

DISCUSSION

Our study demonstrates that complete ACL rupture is common among older people with symptomatic knee OA, and rare among those without knee symptoms. Subjects with complete ACL tears had more severe radiographic OA and, in accordance with the increase in knee adduction moment that occurs with ACL tears, knees with ACL tears tended to have medial knee OA more often than knees without ACL tears. Presence of complete PCL rupture was rare in subjects with and those without knee pain.

Two small MRI studies of cruciate ligament integrity in knee OA have been published previously (16,17). Neither included asymptomatic controls. In 1 study of 20 patients with knee OA, 7 (35%) had complete and 3 (15%) had partial ACL tears, with 1 further patient having a complete PCL tear (16). In another study of 50 patients with knee OA, 14 (28%) had complete ACL tears, all with K/L grade ≥3 (17). Results of both of these studies are consistent with the findings in a larger number of subjects in the current study.

Due to the cross-sectional nature of this study, we could not ascertain when the ACL ruptures occurred. In previous studies, OA has developed in 20–88% of knees following an ACL injury (4), suggesting that ACL rupture probably occurred prior to development of knee OA in most of our subjects. Although more subjects with complete ACL tears recalled a significant knee injury than those with intact ACLs, this still only accounted for just under half of the ACL-deficient subjects. Not only does the severity of knee OA increase with time following an ACL injury, but OA changes appear sooner when patients are older at the time of injury (5). The interval between ACL injury and significant knee symptoms due to OA may be as long as 30 years (18), providing one explanation for the low recall of significant injury in our study.

Previous studies have shown that MRI has >94% sensitivity and 95–100% specificity for detecting acute ACL rupture, when compared with arthroscopic findings (19,20). However, it is likely that the diagnostic performance of MRI for chronic ACL tears may be lower due to their differing appearance from acute ACL tears (21,22). We included angulation of the cruciate ligament or presence of a high-signal-intensity mass as well as discontinuity of the cruciate ligament or lack of visualization, to enhance our detection of chronic ACL tears, as recommended by previous authors (21,22). MRI is highly accurate in detecting PCL rupture (23,24). The gold standard of arthroscopy in detecting cruciate ligament pathology was not within the scope of this study, given the large numbers of subjects and the absence of clinical indication for such an invasive procedure. However, given the lower sensitivity of MRI in detecting chronic ACL tears, our findings with regard to the prevalence of these tears in OA are likely to be conservative.

While our study was cross-sectional and our ability to make longitudinal inferences is therefore limited, our data suggest that ACL tears lead to advanced medial knee OA. This is consistent with the results of studies of male athletes and others which document the increased occurrence of medial tibiofemoral knee OA after ACL tears, and of gait studies which have demonstrated elevated external adduction moments after ACL tears (1–3,25). Previous studies have shown that subjects with meniscal damage in addition to ACL rupture are more likely to develop knee OA than are those with isolated ACL rupture (4,26). However, in our cohort, among cases, meniscal tears were present in 97.3% of those with complete ACL tears (all but 1 subject)

compared with 90.1% of those with intact ACLs (P = 0.16). This high prevalence makes it impossible to determine the combined versus the individual effects of ACL tears and meniscal tears on OA outcomes. Indeed, many of these meniscal tears probably occurred months to years after the original ACL injury (27,28). We have also previously reported that in this sample, meniscal tears have no association with OA pain severity (29).

Because there is little potential for spontaneous recovery of the ACL following complete rupture (18) and OA frequently develops in these individuals, surgical intervention would appear logical to maintain knee joint stability. Despite this, studies have suggested that surgery may actually hasten the development of OA (4). Most of these studies predate the development of contemporary, less invasive surgical techniques, and there are few studies on long-term outcomes of arthroscopic ACL reconstruction. A recent study of 53 patients with chronic ACL rupture and symptoms of "giving way" who underwent arthroscopic ACL reconstruction showed early degenerative changes at 7 years (26); however, no control group was included. Arthroscopic reconstruction of early ACL rupture has recently been shown to lessen episodes of rotational instability compared with knees that remain ACL deficient, leading to speculation that reconstruction may reduce future degenerative damage (25). Surgeons make decisions about ACL reconstructive surgery on the basis of postinjury symptoms (usually related to laxity). However, in patients with complete ACL rupture who have already developed some degenerative changes, the role of ACL reconstruction to reduce progression of knee OA has not been addressed.

In conclusion, complete ACL rupture was common in this population of middle-aged and elderly people with symptomatic knee OA, affecting almost one-quarter of the group. Most subjects with knee OA and complete ACL rupture could not recall a significant knee injury. Those with ACL rupture had more medial compartment OA but did not have more severe pain than those without ACL tears. This potentially remediable condition is underrecognized in knee OA.

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Chapter 5

Hill CL, Hunter DJ, Niu J, Clancy M, Guermazi A, Genant H, Gale D, Grainger A, Conaghan P, Felson DT. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Annals of the Rheumatic Diseases 2007;66:1599-603.

Impact factor: 6.956

Research Highlight: Change in MRI-detected synovitis is correlated with change in pain score in knee OA. Nature Clinical Practice Rheumatology 2008;3:117-8.

Our previous cross-sectional data demonstrated an association between synovial thickening and pain in knee OA (Hill 2001). There was some previous evidence for the role of synovitis in changes in pain in knee OA. A study of intra-articular installation of steroid (Ostergaard 1996) was associated with reduced pain in knee OA and another recent study of intra-articular anakinra (interleukin-1 receptor antagonist) in 7 patients with knee OA resulted in improvement in pain which paralleled improvements in MRI synovial scores (Loeuille 2005b).

The aim was of this study was to examine the association between longitudinal changes in MRI-detected synovitis and changes in knee pain, and also to study the possible relationship between baseline and longitudinal changes in synovitis and cartilage loss in patients with symptomatic knee OA. The conception and design of this substudy was by myself and Professor Felson. I performed the synovitis MRI reading, with aid from Dr D Hunter. Analysis was performed by Ms Niu under direction of Professor Felson and myself. I undertook the interpretation of the data and preparation of manuscript, with support from Professor Felson and other co-authors (see Appendix).

Because of criticism of the use of non-gadolinium-enhanced scoring of synovitis in our previous study (Hill 2001), further validation of the non–gadolinium synovitis scoring was performed by co-investigators (Andrew Grainger and Philip Conaghan) at University of Leeds by evaluating non-gadolinium enhanced and gadolinium enhanced MR images of the infrapatellar fat pad of subjects with knee OA. Of the 20 knees studied, 13 demonstrated identical contrast and non–contrast enhanced synovitis scores, 6 knees showed underestimation of synovitis on the non-contrast images and only 1 knee showed over-reading on the non-contrast image. This data validated our scoring system using non-contrast enhanced MRIs.

EXTENDED REPORT

Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis

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See end of article for authors' affiliations

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Objective: To examine the relationship between longitudinal fluctuations in synovitis with change in pain and cartilage in knee osteoarthritis.

Methods: Study subjects were patients 45 years of age and older with symptomatic knee osteoarthritis from the Boston Osteoarthritis of the Knee Study. Baseline and follow-up assessments at 15 and 30 months included knee magnetic resonance imaging (MRI), BMI and pain assessment (VAS) over the last week. Synovitis was scored at 3 locations (infrapatellar fat pad, suprapatellar and intercondylar regions) using a semiquantitative scale (0–3) at all 3 time points on MRI. Scores at each site were added to give a summary synovitis score (0–9).

Results: We assessed 270 subjects whose mean (SD) age was 66.7 (9.2) years, BMI 31.5 (5.7) kg/m^2; 42% were female. There was no correlation of baseline synovitis with baseline pain score ($r=0.09$, $p=0.17$). The change in summary synovitis score was correlated with the change in pain ($r=0.21$, $p=0.0003$). An increase of one unit in summary synovitis score resulted in a 3.15-mm increase in VAS pain score (0–100 scale). Effusion change was not associated with pain change. Of the 3 locations for synovitis, changes in the infrapatellar fat pad were most strongly related to pain change. Despite cartilage loss occurring in over 50% of knees, synovitis was not associated with cartilage loss in either tibiofemoral or patellofemoral compartment.

Conclusions: Change in synovitis was correlated with change in knee pain, but not loss of cartilage. Treatment of pain in knee osteoarthritis (OA) needs to consider treatment of synovitis.

The cause of pain in knee osteoarthritis remains elusive as the primary site of pathology in OA, cartilage, has no pain fibres.[1] Many other structures around the knee such as the periosteum, subchondral bone, the fat pad, capsule and, inconsistently, the synovium have been shown to contain nociceptive fibres.[1] In addition, inflammation itself appears to play a role in increasing input from peripheral nociceptors.[2] Biopsies of patients with both early and late knee OA have shown low-grade chronic synovitis with production of pro-inflammatory cytokines.[3 4]

Magnetic resonance imaging (MRI) allows evaluation of multiple structures within the knee, including synovium, cartilage, menisci, bone marrow lesions and effusion. In cross-sectional studies of MRI in knee osteoarthritis (OA), bone-marrow lesions, periarticular lesions, knee effusions and synovitis have been shown to be more often present in persons with knee pain than in persons with a comparable amount of radiographic knee osteoarthritis but without pain.[5–8] Fernandez-Madrid *et al* demonstrated that synovial thickening seen on non-contrast enhanced MRI in the infrapatellar region of knees with OA showed low-grade synovial inflammation on biopsy. This feature was present in 73% of knees with early OA.[9]

We have previously shown that this synovial thickening is present in persons with knee pain and OA much more often than in persons with OA but without pain.[7] Among those with pain, the presence of MRI synovial thickening identified those with more severe pain. While this evidence suggests that synovial thickening may affect pain, these data are cross-sectional, making it impossible to evaluate the temporal relation of pain with synovial thickening. More persuasive evidence would emanate from a longitudinal study in which fluctuations in synovial thickening could be tied to fluctuations in the severity of knee pain. Herein, we provide such evidence. Our aims were to study the association between baseline and longitudinal changes in MRI-detected synovitis and changes in knee pain, and also to study the association between baseline and longitudinal changes in synovitis and cartilage loss in patients with symptomatic knee OA.

PATIENTS AND METHODS

Study population

Patients were recruited to participate in a natural history study of symptomatic knee OA, the Boston Osteoarthritis of the Knee Study. The recruitment for this study has been described in detail elsewhere.[10] Briefly, patients were recruited from two prospective studies, one in men and one in women, of quality of life among veterans; from clinics at Boston Medical Center in Boston, Massachusetts; and from advertisements in local newspapers. Potential participants were asked two questions: "Do you have pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" For patients who answered yes to both questions, we conducted a follow-up interview in which we asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified, then the individual was eligible for recruitment. A series of knee radiographs (PA, lateral and skyline) were obtained for each patient to determine whether radiographic OA was present. If patients had a definite osteophyte on any view in the symptomatic knee, they were eligible for the study. Because they had frequent knee symptoms and radiographic OA, all patients met American College of Rheumatology criteria for symptomatic knee OA.[11]

Abbreviations: MRI, magnetic resonance imaging; OA, osteoarthritis; VAS, visual analogue scale; WORMS, whole-organ magnetic resonance imaging score

The study included a baseline and follow-up examinations at 15 and 30 months. At baseline, patients who did not have contraindications to MRIs had an MRI of the more symptomatic knee. MRIs of the same knee were also performed at follow-up visits. At each visit, pain in the imaged knee over the past week was assessed using a visual analogue scale (VAS, 0–100), and subjects were weighed with shoes off on a balance-beam scale. The Institutional Review Boards of Boston University Medical Center and the Veterans Administration Boston Health Care System approved the study.

MRI measurements

All MRIs were performed with a Signa 1.5T system (General Electric, Milwaukee, WI) using a phased-array knee coil. A positioning device was used to ensure uniformity among patients. Coronal, sagittal and axial images were obtained. Fat-suppressed spin-echo proton density and T2-weighted images (repetition time, 2200 ms; echo time, 20/80 ms) with a slice thickness of 3 mm, a 1-mm interslice gap, one excitation, a field of view of 11–12 cm, and a matrix of 256×128 pixels were obtained.

Cartilage morphology was assessed by a musculoskeletal radiologist (AG) using a semiquantitative, multi-feature scoring method (whole-organ magnetic resonance imaging score, WORMS) for whole-organ evaluation of the knee that is applicable to conventional MRI techniques.[12] Intraclass correlation coefficients of agreement among the readers for cartilage readings ranged from 0.72 to 0.97.

Tibiofemoral cartilage on MRI was scored on all 5 plates (central and posterior femur; anterior, central and posterior tibia) in each of the medial and lateral tibiofemoral joints. The anterior femur was not included in this analysis, as this is part of the patellofemoral joint. Patellofemoral cartilage was scored on 4 plates (medial and lateral patella, and medial and lateral anterior femur). These were read using the fat-suppressed T2-weighted FSE images on a 7-point scale: 0 = normal thickness and signal; 1 = normal thickness but increased signal on T2-weighted images; 2 = partial-thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial-thickness (Grade 2) defects intermixed with areas of normal thickness, or a Grade 2 defect wider than 1 cm but <75% of the region; 4 = diffuse (≥75% of the region) partial-thickness loss; 5 = multiple areas of full-thickness loss wider than 1 cm but <75% of the region; 6 = diffuse (≥75% of the region) full-thickness loss.

In WORMS, grade 1 does not represent a morphological abnormality but rather represents a change in signal in cartilage of otherwise normal morphology. Grades 2 and 3 represent similar types of abnormality of the cartilage, focal defects without overall thinning. Scores of 1 and 2 were exceedingly unusual. Therefore, to create a consistent and logical scale for evaluation of cartilage morphological change, we collapsed the WORMS cartilage score to a 0–4 scale, where the original WORMS scores of 0 and 1 were collapsed to 0, the original scores of 2 and 3 were collapsed to 1, and the original scores of 4, 5 and 6 were considered 2, 3 and 4, respectively, in the new scale.[13] The intraobserver agreement for reading of cartilage morphology ranged from 0.65 to 0.78 (kappa). We defined a lesion as occurring in either the medial or lateral tibiofemoral compartment if it was present in the femur or tibia of that compartment. While we conducted analyses using this collapsed WORMS cartilage scale, analyses using the original scale yielded the same results.

On the baseline and follow-up MRIs, effusion was scored 0–3 based on volume. Bone-marrow lesions were scored only on the baseline MRIs using the WORMS scale also in which lesions are scored according to their size (0–3) within quadrants of the femur and tibia.

Synovial reading

Synovial thickening on MRI using sagittal T2-weighted and proton-density sequences was scored separately at 3 locations (infrapatellar fat pad, suprapatellar and intercondylar regions) using a semiquantitative scale (0–3) at all 3 time points (fig 1). Given the confirmation that these MRI findings connote inflammation in the synovium, we shall label these findings as synovitis.

One reader (CLH) read synovitis on MRI's. For each subject, MRIs were blinded to subject's identity and read paired and in sequential order. The intraobserver agreement (kappa) for

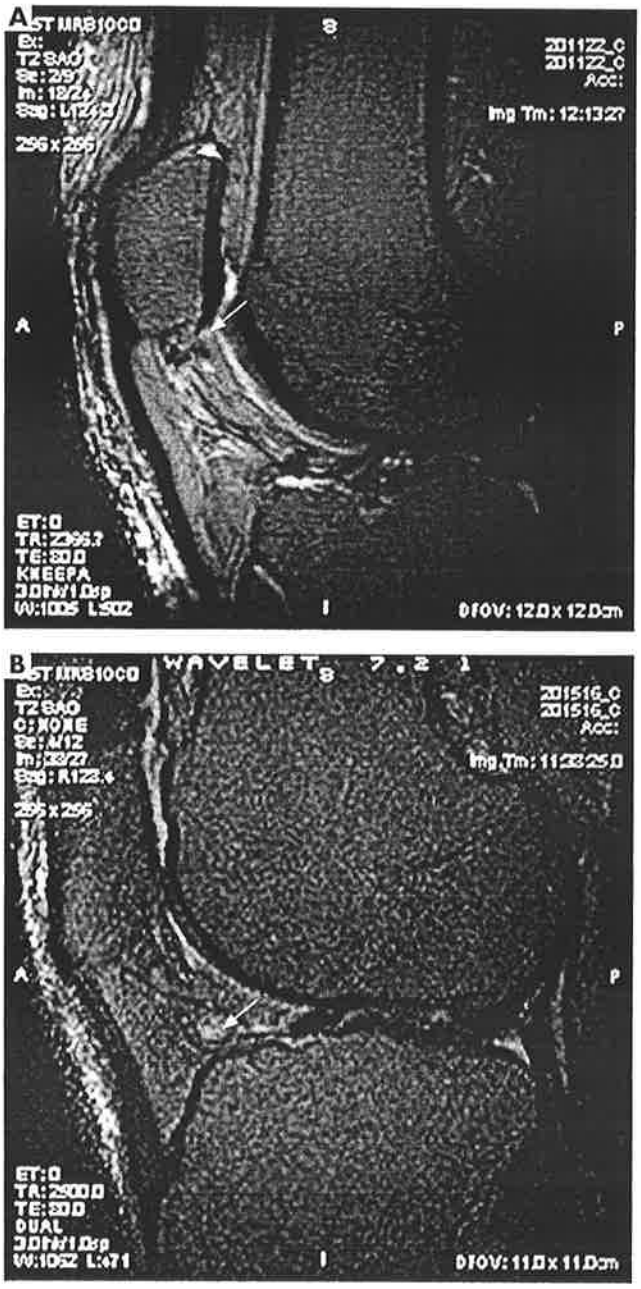

Figure 1 (A) T2-weighted MR image, sagittal view, with soft tissue density and surrounding synovitis in intercondylar region. (B) T2-weighted MR image, sagittal view, with synovitis (grade 2) in infrapatellar region.

infrapatellar fat pad synovitis score was 0.63, intercondylar 0.49 and suprapatellar 0.20.

Validation of non-gadolinium synovitis scoring

To validate non-gadolinium scoring, 20 subjects with knee OA at University of Leeds underwent MRI using a sagittal T2 weighted fat suppressed sequence and a gadolinium enhanced T1 weighted fat-suppressed sequence. A trained reader scored the infrapatellar fat pad for synovial thickening on a 0–3 scale using just the T2 sequence without reference to other sequences (as above). The same reader then scored the infrapatellar synovitis using the same scoring system using just the postgadolinium sagittal sequence again without reference to other sequences. The films were blinded and presented to the reader in random order for the 2 reads, which took place 1 week apart. Of the 20 knees, 13 showed contrast (gadolinium) enhanced and non-contrast enhanced scores that were identical (ranging from 0 to 3). As expected, in 6 knees, the non-gadolinium images underestimated the amount of synovial thickening seen on the contrast enhanced image. Only one knee showed an over-reading of synovial thickening on the non-contrast image (score of 2 vs 1).

Analysis

Synovitis scores at each location were added to give a summary synovitis score at each time point (0–9). Changes in synovitis score were calculated at each time point. In addition, an analysis was carried out for synovitis scores at each individual site.

To examine whether differences in VAS pain score can be explained by differences in synovitis both cross-sectionally and longitudinally, we applied the generalised estimating equation to test this hypothesis with the following statistical model:

$$Y_{it} = \beta_0 + \beta_1 X_{i0} + \beta_2 (X_{it} - X_{i0}),$$

where Y_{it} is the pain score assessed at baseline, at 15 months and at 30 months. X_{i0} is the synovitis assessed at baseline, and X_{it} is the corresponding measure of synovitis assessed at time t, that is, baseline, 15 months and 30 months, respectively. The coefficient β_1 measures the cross-sectional association of the synovitis at baseline and VAS pain score, and β_2 measures the effect of changes in synovitis on changes of VAS pain score.

The interpretation of the estimate from the model is the expected change in pain over time (from baseline to follow-up including both 15 and 30 months) per unit change in synovitis score in the corresponding follow-up period for a given subject.

To examine whether cartilage loss can be explained by baseline synovitis, we used cartilage loss in each compartment (medial tibiofemoral, lateral tibiofemoral, and patellofemoral) in 30-month follow-up for analyses unless unavailable, in which case cartilage loss in 15 months was used. Cartilage loss took whole number values from 0 (no loss) to 4 (maximum loss) and was analysed as ordered categories using the proportional odds logistic regression model. A generalised estimating equations correction was applied to the regression model to account for the association in the cartilage loss outcome between regions within a joint. For change in pain and cartilage loss, analyses were adjusted for baseline cartilage scores, age, sex, BMI, effusion score (0–3) and bone-marrow lesion score (using WORMS), and change in both bone-marrow lesion score and effusion score. For cartilage loss, we adjusted additionally for baseline WORMS based meniscal score.

A similar method was used to examine whether cartilage loss can be explained by synovitis change. The change in synovitis in a 30-month follow-up was used for analyses unless unavailable, in which case the change of synovitis in 15 month follow-up was used.

RESULTS

We assessed 270 subjects (158 male, 112 female) with at least one follow-up MRI. Two hundred and thirty-three subjects were followed for 30 months, and 37 subjects were followed for 15 months. Demographic details are recorded in table 1. The mean age of the subjects was 66.7 years, BMI 31.5 kg/m^2 and VAS pain score 44.2 mm. Most knees had evidence of synovitis at one of the 3 sites at baseline, and about 40% had a change in knee synovitis over time (table 1). The presence of synovitis at baseline was significantly correlated with the baseline Kellgren–Lawrence radiological grade. The Spearman correlation was 0.44, 0.32, 0.27 and 0.39 for the Kellgren–Lawrence grade and summary synovitis, synovitis in infrapatellar fat pad, intercondylar and suprapatellar regions, respectively.

There was no correlation of baseline synovitis with baseline pain score (Pearson correlation coefficient r = 0.09, p = 0.17); an increase in synovitis score at baseline was correlated with a slightly higher baseline VAS pain score (adjusted estimate per increase in one unit of synovitis 0.72, 95% CI; −1.15, 2.59). However, there was a correlation of change of pain with change of synovitis score (r = 0.21, p = 0.0003; adjusted estimate of 3.15 VAS score change (on 0–100 scale) per unit change in

Table 1 Characteristics of subjects

Total	270 subjects
Gender	158 (58.5%) males, 112 females
Age (mean)	66.7 (9.2) years
BMI (mean)	31.5 (5.7) kg/m^2
Kellgren–Lawrence grade* (median, range)	3 (0 to 4)
Baseline pain† (mean, SD) (0–100)	44.2 (25.2) mm
Change in pain (mean, SD) from baseline to follow-up	−1.9 (25.5) mm
Baseline synovitis score 0–9	
Baseline infrapatellar fat pad score, 0/1/2/3 (%)	21.5/40.0/33.9/4.6
Baseline intercondylar notch score, 0/1/2/3 (%)	31.5/52.3/15.0/1.2
Baseline suprapatellar notch score, 0/1/2/3 (%)	24.5/41.2/22.2/12.1
Change in synovitis score	
Change in infrapatellar fat pad score, decrease/no change/increase (%)	15.2/63.1/21.7
Change in intercondylar notch score, decrease/no change/increase (%)	14.3/66.8/18.9
Change in suprapatellar notch score, decrease/no change/increase (%)	20.4/59.2/20.4
Baseline cartilage score in 14 plates (mean, SD)	16.1 (9.2)
Baseline summary bone-marrow lesion (mean, SD)	3.2 (3.1)
Baseline effusion score (mean, SD)	0.9 (0.8)

*Subjects with "Knee pain/OA", who had Kellgren–Lawrence grade 0 due to normal PA views, were defined as having radiographic OA due to definite osteophytes in patello-femoral joint; †pain was measured on a 100-mm visual analogue scale.

receptor 6 (CCR6) is the main surface molecule expressed by T_H17 cells. CCL20, the known ligand for CCR6, attracts T_H17 cells into synovial tissue, where the cells initiate the first stages of inflammation.

Once the process is underway, synoviocytes are activated to produce several proinflammatory cytokines. In turn, these cytokines lead to increased CCL20 production, which then attracts more T_H17 cells in a vicious, positive-feedback loop. In the mouse model, treatment with a monoclonal antibody specific for CCR6 was associated with a significantly longer time to disease onset, and the animals developed less-severe arthritis than those in control groups. This finding suggests disruption to the inflammatory cycle.

The authors conclude that CCR6 expression contributes to T_H17 cell function in autoimmune disease, especially in autoimmune arthritis, and its blockade could provide a potential therapeutic strategy in RA.

Original article Hirota K *et al.* (2007) Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J Exp Med* **204:** 2803–2812

Serum RANKL levels predict response to TNF antagonists in patients with RA

The molecular process underlying rheumatoid arthritis (RA) involves three key components of the TNF signaling pathway. Of particular importance is the balance between RANKL (the ligand for a membrane-bound osteoclast receptor [RANK] that initiates osteoclastic bone resorption), RANK (receptor activator for nuclear factor-κB) and osteoprotegerin. Osteoprotegerin is a key inhibitor of bone resorption that acts as a soluble, nonsignaling decoy receptor for RANKL.

González-Alvaro *et al.* investigated whether the serum levels of RANKL and osteoprotegerin measured at baseline in RA patients could predict the degree of response to the TNF antagonists adalimumab or infliximab. A total of 75 patients, mostly female with chronic, refractory RA, were studied during treatment and for 7 months after treatment.

Baseline disease activity in most patients was deemed severe, and osteoprotegerin levels correlated with physicians' assessments of disease severity. When serum RANKL levels and the ratio of RANKL to osteoprotegerin at baseline were compared with the response to treatment, the authors noted that patients who achieved the highest remission levels at 3 months and 7 months after treatment had significantly lower RANKL levels and lower RANKL-to-osteoprotegerin ratios. Osteoprotegerin levels fell substantially after treatment, but no correlation was noted between osteoprotegerin at baseline and therapeutic response levels.

The authors conclude that RA patients with low serum levels of RANKL and low RANKL-to-osteoprotegerin ratios are most likely to have an optimal response to treatment with TNF antagonists.

Original article González-Alvaro I *et al.* (2007) Baseline serum RANKL levels may serve to predict remission in rheumatoid arthritis patients treated with TNF antagonists. *Ann Rheum Dis* **662:** 1675–1678

Change in MRI-detected synovitis is correlated with change in pain score in knee OA

The cause of pain in patients with knee osteoarthritis (OA) is unclear, although cross-sectional studies suggest that bone marrow and periarticular lesions, knee effusion and synovial thickening are observed more frequently in patients who report pain than in those with similar radiographic damage but no pain. Hill and colleagues aimed to evaluate the temporal relationship between pain and MRI-detected synovitis in knee OA.

The study included 270 patients (mean age 66.7 years, 58% male) who met American College of Rheumatology criteria for symptomatic knee OA. Synovial thickening was scored at three separate sites (infrapatellar fat pad, suprapatellar and intercondylar regions) using MRI of the most symptomatic knee at baseline, with the sum of all three scores combined (overall scale 0–9); the same knee was evaluated again after 15 months and 30 months. At the same time points, pain experienced in the imaged knee over the previous week was assessed using a visual analog scale (VAS; scale 0–100).

Synovitis score and pain score were not correlated at baseline; however, change in synovitis score positively correlated with

change in pain score ($r=0.21$, $P=0.0003$), with a VAS increase of 3.15 mm per unit of synovitis score (95% CI 1.04–5.26, $P=0.003$). Changes in synovitis score at the infrapattellar fat pad and intercondylar region were also significantly correlated with increased pain scores.

The authors conclude that the relationship shown between changes in MRI-detected synovial thickening and pain suggests that treatments targeting synovitis might help to reduce pain in patients with knee OA.

Original article Hill CL *et al.* (2007) Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. *Ann Rheum Dis* **66:** 1599–1603

Patients with hand OA have increased BMD levels at axial sites

A few studies have reported increased BMD in patients with osteoarthritis (OA), but the findings for hand OA (HOA) have been inconclusive. Haugen *et al.*, therefore, compared BMD levels and frequency of osteoporosis at the total hip, femoral neck and lumbar spine in patients with HOA, rheumatoid arthritis (RA) and in controls; furthermore, the relationship between BMD and disease characteristics in patients with HOA was investigated.

The study, conducted in Oslo, Norway, included women (aged 50–70 years) with HOA ($n=190$) and RA ($n=194$), and population controls ($n=122$). Participants' BMD was measured by the same dual-energy X-ray absorptiometry equipment, and self-reported questionnaires, clinical joint examination and interview were used to obtain demographic and clinical variables.

BMD levels (adjusted for height, weight and age) were increased in patients with HOA compared with those in controls or in patients with RA, but BMD levels did not correlate with either symptom duration or health status in patients with HOA. Frequency of osteoporosis was lower in patients with HOA than those with RA, but was not significantly different between patients with HOA and controls. Lastly, adjusted BMD levels were similar for patients with HOA only and those with additional knee OA.

The findings provide evidence that increased BMD precedes the development of OA, although the authors concede that lack of adjustment for confounders such as smoking might have contributed to the increased BMD in the cohort of patients with HOA.

Original article Haugen IK *et al.* (2007) Bone mineral density in patients with hand osteoarthritis compared to population controls and patients with rheumatoid arthritis. *Ann Rheum Dis* **66:** 1594–1598

C5a receptor blocker fails to show clinical benefit in patients with RA

In rheumatoid arthritis (RA), the synovial compartment is infiltrated by a variety of immune cells. One factor that seems to be involved is C5a, a protein involved in chemotaxis. Theoretically, blocking C5a receptor (C5aR) activity could form a therapeutic strategy for RA. The recently developed cyclic peptide AcF-[OpdChaWR] (PMX53) competes effectively with C5aR without causing agonist effects. Preliminary results in rats suggest that PMX53 reduces the symptoms of experimental arthritis, and Vergunst *et al.* have investigated its potential as a therapeutic agent for RA in a proof-of-concept trial.

A total of 21 RA patients participated in a double-blind, placebo-controlled, phase Ib clinical trial. Orally administered PMX53 was assessed for safety, and its ability to reduce synovial inflammation was determined. The mean serum concentration of PMX53 achieved—40.8 nmol/h/l—has been shown *in vitro* to block C5aR-mediated cell activation. When synovial tissue obtained after 28 days of treatment was compared with that obtained at baseline, however, no changes in cell infiltration or key biomarkers were detected. The treatment group showed no clinical improvement, or even a trend towards it, and there was no correlation between the serum level of PMX53 and clinical response in individual patients.

Despite reaching serum levels high enough for C5aR-blocking activity, treatment of human patients with PMX53 did not reduce synovial inflammation. The authors conclude that C5aR blockade by PMX53 does not reduce synovial inflammation in human patients with RA.

Original article Vergunst CE *et al.* (2007) Blocking the receptor for C5a in patients with rheumatoid arthritis does not reduce synovial inflammation. *Rheumatology* **46:** 1773–1778

Chapter 6

Felson DT, Chaisson CE, Hill CL, Totterman SMS, Gale ME, Skinner KM, Kazis L, Gale DR. The association of bone marrow lesions with pain in knee osteoarthritis. Annals of Internal Medicine 2001;134:541-9. *Impact factor: 15.5*

Felson DT, McLaughlin S, Goggins J, La Valley MP, Gale ME, Totterman S, Li W, Hill CL, Gale DR. Bone marrow edema and its relation to progression of knee osteoarthritis. Annals of Internal Medicine 2003;139: 330-336. *Impact factor: 15.5*

Bony sclerosis on plain radiographs in knee OA has long been recognized. However, the importance of subchondral bone in pain and progression in knee OA was recognized by Dieppe and colleagues (1993) in which late-phase tracer uptake on bone scan in subchondral bone in knee OA was found to be associated with knee pain and radiographic progression.

Bone marrow oedema lesions are unique MRI-determined abnormalities which produce high signal lesions with ill-defined margins in the medullary space extending to the subcortical bone on fat-suppressed T-2 weighted MR images. These have also been commonly observed in other inflammatory arthritis, enthesitis, osteomyelitis and following joint trauma (Conaghan 2006a). In knee OA, corresponding histological examination of MRI bone marrow lesions has demonstrated predominately bone marrow necrosis, fibrosis and microtrabecular remodeling (Bergman 1994, Zanetti 2000). These lesions have also been shown to correlate with positive scintigraphy described above by Dieppe (McAlindon 1991).

Prior to the current study, there had been few studies evaluating the prevalence and associations of bone marrow lesions in knee OA. Lotke (2000) studied 41 patients with early painful knee OA and found that the largest bone marrow edema lesions were most likely to be associated with persistence of pain.

The data included in these two papers for which I am a co-author is an extension to the previous work outlined above. The conception and design of these substudies was by Professor Felson. I performed MRI reading of effusion, with aid from Dr D Gale. Professor Felson undertook the analysis and interpretation of data and preparation of the manuscript, with the support of myself and other co-authors (see Appendix).

The analysis of bone marrow lesions in the BOKS study demonstrated that these lesions were much more common in those with knee pain (77.5%) compared to those without knee pain (30%, $p<0.001$). Large bone marrow lesions were present almost exclusively amongst those with knee pain (35.9% vs 2%, $p<0.001$). These associations remained after adjustment for age, sex, radiographic grade and presence of effusion. However, bone marrow lesions were not associated with pain severity.

Given the association of bone scan findings in knee OA with radiographic progression (Dieppe 1993) and a more recent study demonstrating that limb malalignment is a potent risk factor for structural progression in knee OA (Sharma 2001), studying the relationship of bone marrow lesions to disease progression and limb malalignment was timely and feasible with the collection of longitudinal radiographic (including limb alignment), clinical and MRI data.

Bone marrow lesions were associated with radiographic progression in the same compartment over a 15 month period, after adjustment for age, sex and BMI. This increased risk was partially attenuated when limb alignment was taken into consideration.

Recognition of bone marrow oedema and malalignment as important risk factors for progression of knee OA has implications for the design of clinical trials in OA by allowing effective identification patients at high risk for progression by screening for bone marrow lesions on MRI.

Annals of Internal Medicine | ARTICLE

The Association of Bone Marrow Lesions with Pain in Knee Osteoarthritis

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Background: The cause of pain in osteoarthritis is unknown. Bone has pain fibers, and marrow lesions, which are thought to represent edema, have been noted in osteoarthritis.

Objective: To determine whether bone marrow lesions on magnetic resonance imaging (MRI) are associated with pain in knee osteoarthritis.

Design: Cross-sectional observational study.

Setting: Veterans Affairs Medical Center.

Patients: 401 persons (mean age, 66.8 years) with knee osteoarthritis on radiography who were drawn from clinics in the Veterans Administration health care system and from the community. Of these persons, 351 had knee pain and 50 had no knee pain.

Measurements: Knee radiography and MRI of one knee were performed in all participants. Those with knee pain quantified the severity of their pain. On MRI, coronal T_2-weighted fat-saturated images were used to score the size of bone marrow lesions, and each knee was characterized as having any lesion or any large lesion. The prevalence of lesions and large lesions in persons with and without knee pain was compared; in participants with knee pain, the presence of lesions was correlated with severity of pain.

Results: Bone marrow lesions were found in 272 of 351 (77.5%) persons with painful knees compared with 15 of 50 (30%) persons with no knee pain ($P < 0.001$). Large lesions were present almost exclusively in persons with knee pain (35.9% vs. 2%; $P < 0.001$). After adjustment for severity of radiographic disease, effusion, age, and sex, lesions and large lesions remained associated with the occurrence of knee pain. Among persons with knee pain, bone marrow lesions were not associated with pain severity.

Conclusions: Bone marrow lesions on MRI are strongly associated with the presence of pain in knee osteoarthritis.

Ann Intern Med. 2001;134:541-549. www.annals.org

For author affiliations, current addresses, and contributions, see end of text.

See editorial comment on pp 591-593.

Knee osteoarthritis affects 11% to 15% of the U.S. population 65 years of age or older (1) and is a leading cause of disability in the elderly. The major source of disability and care seeking for patients with osteoarthritis is pain in the knee (2).

The cause of knee pain in patients with osteoarthritis is unclear. Osteoarthritis has been considered a disease whose characteristic pathologic feature is loss of hyaline articular cartilage, but that tissue contains no pain fibers. Pain fibers are present in several other structures, however, that are often affected by pathologic processes in knee osteoarthritis, including the joint capsule, ligaments in and around the knee joint, the outer third of the meniscus, and possibly the synovium (although for this last tissue, evidence is conflicting [3, 4]). In addition, bone in the periosteum and bone marrow is richly innervated with nociceptive fibers and represents a potential source of pain in patients with knee osteoarthritis.

In athletes and younger adults who do not have osteoarthritis, traumatic knee injuries produce high-signal lesions in the medullary space extending to subcortical bone according to T_2-weighted magnetic resonance imaging (MRI). These lesions are thought to represent contusions within the bone marrow and have been correlated with the occurrence of pain in athletes (5). Bone marrow lesions that are similar in appearance to those contusions have been noted (6) in patients with knee osteoarthritis, but their association with the occurrence of pain in this disease is unknown.

The treatment of pain in osteoarthritis has been frustrating, in part because the target of therapy is unclear. Creamer and colleagues (7) injected intra-articular anesthetic into joints and found that only 6 of 10 persons with painful osteoarthritis had pain relief. This suggests that in some patients, pain originates from extra-articular, noncapsular sources, one of the most likely of which is bone. If pain in some patients does emanate from bone, this finding would have important therapeutic implications and suggests that for these patients, anti-inflammatory treatments targeted at synovitis or intra-articular drainage to relieve capsular distention would be ineffective.

We sought to evaluate whether persons with knee pain and osteoarthritis were more often affected by bone

marrow lesions than similarly aged persons without knee pain, many of whom also had radiographic knee osteoarthritis. We tested whether pain in the knee was associated with the presence of bone marrow lesions after adjustment for the severity of radiographic osteoarthritis. In addition, among persons with symptomatic knee osteoarthritis, we evaluated whether the severity of their pain was associated with the presence of these lesions.

METHODS

Patient Selection

The minimum age for entry into the study was 45 years for men and 50 years for women. The entry age for women was chosen to lessen the chance of inadvertently obtaining radiographs in pregnant women. Male participants were drawn from the Veterans Health Study (VHS), a prospective observational study of health outcomes in 2425 veterans (8). Participants in the VHS were recruited from all men receiving ambulatory care between August 1993 and March 1996 at four Veterans Administration system facilities in the Boston area. Veterans who indicated that they could not read, were identified as unable to answer questions by an accompanying proxy, were disoriented, or did not complete the screening questionnaire were ineligible.

A random sample of eligible respondents was contacted by telephone and recruited for the VHS. Of the 4137 patients who were telephoned, 2425 (59%) participated in the VHS. Participant age ranged from 22 to 91 years (mean, 62.4 years). The VHS was designed to be representative of users of ambulatory care in the Veterans Administration system. Compared with all utilizers of the Veterans Administration health care system, the sample underrepresented patients with less education or limitations in literacy or cognitive functioning. Patients in the VHS had lower functional status scores on the physical and mental health components of the Short Form-36 survey (a measure of health status) and had more comorbid conditions (8) than do men 45 years of age or older in the general U.S. population. Male participants were also drawn separately from Veteran Affairs clinics and from the community.

Female participants were drawn from clinics at Boston Medical Center and the Veterans Affairs Medical Center; from advertisements in local newspapers; and from a study of women veterans, the Veterans Administration Women's Health Project ($n = 719$), that was designed to describe the health status of female veterans using ambulatory health care services. The human studies committee and the institutional review board approved protocols. Informed consent was obtained from all participants.

All participants were surveyed about knee symptoms. They were asked two questions: "Do you have pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" For persons interested in participating in our study of knee pain and osteoarthritis, we conducted a follow-up interview in which those who answered "yes" to both questions were asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified in the interview, the person was eligible for recruitment as a participant with knee pain (which we characterize here as knee symptoms).

Figure 1 is a flow diagram of the source of participants. Of our male participants, 151 came from the Veterans Health Study, 76 came from Veterans Administration ambulatory clinics, and 8 came from the community. Of our female participants, 18 came from the Veterans Administration Women's Health Project, 9 came from ambulatory clinics, and 89 came from the community.

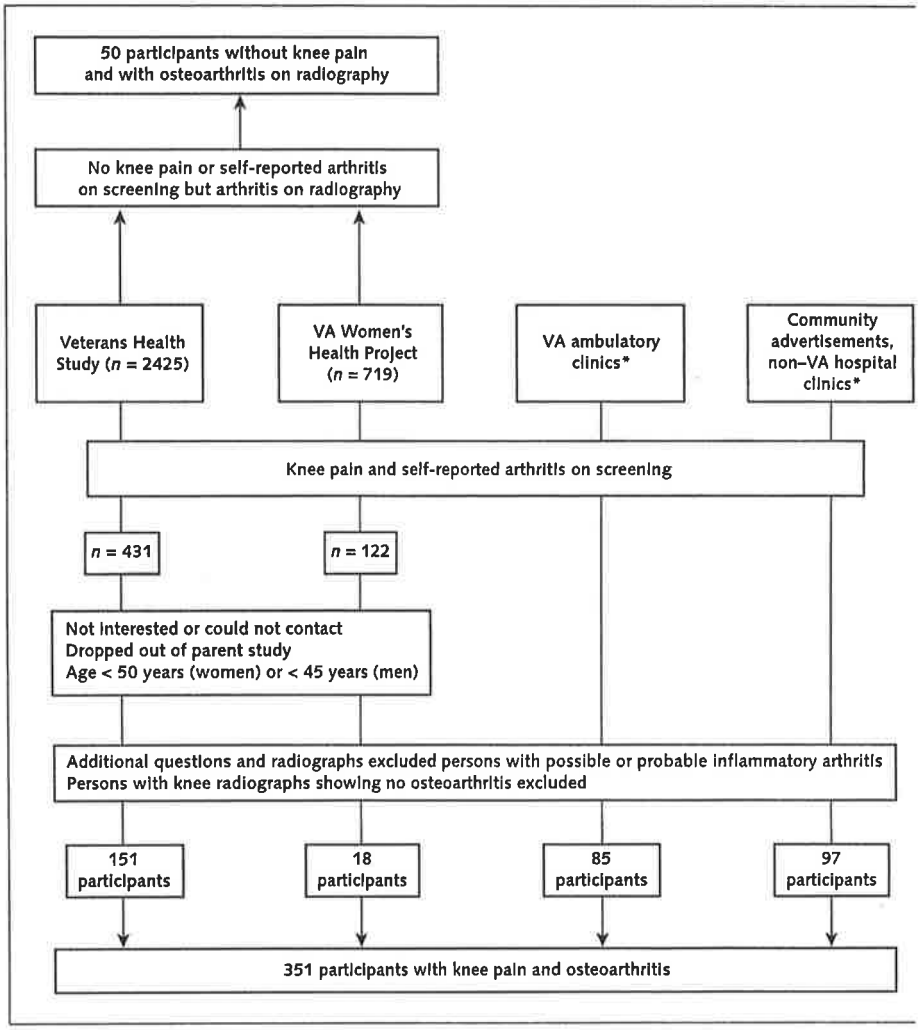
We recruited participants from the VHS and the Veterans Administration Women's Health Project without knee pain from among those who answered "no" to both of the above screening questions (**Figure 1**).

We also asked participants to evaluate the severity of pain in each knee, which they scored by using a 100-mm visual analogue scale (generating a score of 0 [no pain] to 100 [most severe pain possible]). Participants also filled out the WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) questionnaire (9), a validated instrument that assesses knee pain and disability during various activities; we analyzed their WOMAC pain subscale score.

Radiographic Evaluation

All participants underwent weight-bearing posteroanterior radiography by using the protocol of Buckland-Wright (10 and weight-bearing skyline (9) and weight-bearing lateral radiography (11). For the posteroanterior view, the knee was positioned and radio-

Figure 1. **Sources of study participants.**



VA = Veterans Administration.

graphed under fluoroscopy so that the anterior and posterior medial tibial plateaus were superimposed; this was done to optimize measurement of joint space. Radiographs were read for the presence of definite osteophytes and other features by one radiologist using an atlas.

If a definite osteophyte was present in a knee (including the patella) on any one of the three views, the knee was characterized as having osteoarthritis regardless of whether the participant experienced symptoms. This definition of radiographic disease has been recommended by other investigators (22). On the basis of responses to the screening questions, we defined a knee as symptomatic if the participant stated that he or she had pain or aching in that knee on most days. This definition of symptomatic osteoarthritis meets American College of Rheumatology criteria (12). We identified too few symptomatic persons without a radiographic osteophyte to include them as a separate study group ($n = 4$) and therefore excluded them; we also excluded 16 participants without knee pain whose radiographs showed no osteophytes.

Kellgren and Lawrence grades have been developed for the anteroposterior (posteroanterior) view. We therefore assigned Kellgren and Lawrence grades (0 to 4) on

this view only. In addition, we read posteroanterior, skyline, and lateral radiographic views and scored them for individual radiographic features—osteophytes (scale of 0 to 3), joint space narrowing (scale of 0 to 3), cysts (scale of 0 to 1), and sclerosis (scale of 0 to 3)—by using the Framingham Osteoarthritis Study atlas (13). The reproducibility of readings of these features and of the Kellgren and Lawrence scale is reported elsewhere (14).

Magnetic Resonance Imaging

Each person with knee pain underwent MRI of the more symptomatic knee. For persons without knee pain, the dominant knee was selected for imaging. All studies were performed on a General Electric Signa 1.5-Tesla MRI system (GE Medical Systems, Milwaukee, Wisconsin) using a phased-array knee coil. A positioning device for the ankle and knee was used to ensure uniformity between patients. Coronal, sagittal, and axial images were obtained in each participant. Coronal spin-echo fat-saturated proton-density and T_2-weighted fat-saturated images (repetition time, 2200 ms; echo time, 20/80 ms) with a slice thickness of 3 mm, a 1-mm interslice gap, 1 excitation, a field of view of 11 to 12 cm, and a matrix of 256 × 128 pixels were obtained.

To evaluate bone marrow lesions on MRI, we used coronal spin-echo T_2-weighted fat-saturated images. Each femur and tibia was divided into medial, central, and lateral quadrants, resulting in six potential sites of lesions in each knee. We defined bone marrow lesions as discrete areas of increased signal adjacent to the subcortical bone in either the femur or the tibia, and we scored each bone marrow lesion from 0 to 3 on the basis of lesion size (**Figure 2**). Lesions with a score of at least 1 were considered definite bone marrow lesions, and lesions with a score of at least 2 were considered large bone marrow lesions.

We mixed MRIs of participants with and without knee pain and blinded the reader to the participants' knee pain status. Overall, intraobserver agreement for bone marrow score was a weighted κ value of 0.66 (95% CI, 0.59 to 0.72), which indicates substantial agreement beyond chance (15). We also scored knee MRIs for effusions on a scale of 0 to 4 on the basis of effusion size (16).

Statistical Analysis

We studied one knee per participant, and our unit of analysis was the knee. Preliminary analyses revealed that when we added lesion scores from all quadrants, the summed score clustered in the lower end of the range, with none exceeding 9; 75% of the knees had scores of 2 or less. To simplify analyses and because we hypothesized that single bone marrow lesions, especially large ones, would be associated with knee pain, we decided to evaluate knees as not having or having bone marrow lesions (any score ≥ 1) and to evaluate knees with and without large bone marrow lesions (any score ≥ 2). We compared the prevalence of bone marrow lesions and large bone marrow lesions in persons with symptomatic knee osteoarthritis with those in persons without pain by using chi-square or the Fisher exact test where appropriate.

To evaluate whether pain was associated with the presence of bone marrow lesions, we adjusted for radiographic severity because participants with symptomatic osteoarthritis had greater severity of structural disease than did those without pain. We restricted the group with knee symptoms to persons whose Kellgren and Lawrence grades or scores for individual radiographic features were in the same range as those of participants without knee pain (scores of 1 to 5 for individual radiographic features). The individual radiographic features score sums the scores for presence of all osteophytes, narrowing, cysts, and sclerosis on any of the three views. We used this score to provide more detail on radiographic severity and to incorporate radiographic features seen on views other than the posteroanterior.

Because the literature suggests an association of capsular distention with knee pain and because we found an association of effusion with knee pain in this sample (16), we performed analyses with adjustment for the size of the knee effusion. We performed logistic regression analyses to test the association between bone marrow lesions (an independent variable) and knee pain (a dichotomous dependent variable), after adjustment using forced entry for the following independent variables: radiographic severity (sum of the scores of individual radiographic features), age, sex, and effusion score. We performed identical analyses for bone marrow lesions (yes or no) and large bone marrow lesions (yes or no). In similar analyses incorporating body mass index, results were unchanged.

We next evaluated whether, among persons with symptomatic knee osteoarthritis, those with bone marrow lesions experienced more severe pain than those

without such lesions. For each bone marrow and large bone marrow lesion, we performed two different linear regression analyses. In one analysis, the dependent variable was score on the visual analogue scale for pain in the knee, and in the other, it was the WOMAC subscale score for knee pain. We included the following independent variables by using forced entry: presence or absence of bone marrow lesions, sum of the scores of individual radiographic features, sex, age, and effusion score.

Role of the Funding Sources

This research was supported by Bayer Corp., the Arthritis Foundation, and the National Institutes of Health. None of these agencies had a role in the design, conduct, or reporting of this study.

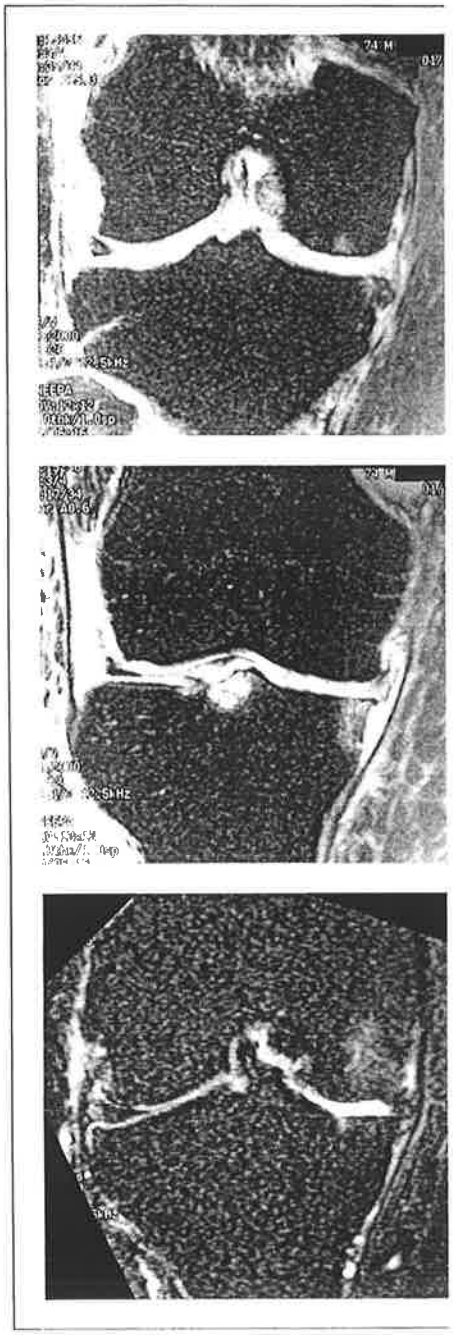
RESULTS

We studied 351 participants who had knee pain and 50 participants who had no knee pain. All participants had evidence of osteoarthritis (at least a small osteophyte) on radiography. The mean age was 66.8 years in participants with knee pain and 66.9 years in those without knee pain (**Table 1**). Participants with knee pain had higher Kellgren and Lawrence grades on the posteroanterior radiograph than did those without knee pain. The range of grades varied considerably, and some participants with knee pain had grades of 0 (because the Kellgren and Lawrence grade was scored on the posteroanterior radiograph only and did not reflect disease in the patellofemoral joint).

Of participants with knee pain, 77.5% had MRI evidence of a bone marrow lesion compared with only 30.0% of participants without knee pain ($P < 0.001$). Even more striking was the difference in the prevalence of large bone marrow lesions between participants with knee pain and those without knee pain (35.9% vs. 2.0%; $P < 0.001$) (**Table 2**).

We speculated that bone marrow lesions may be highly correlated with the severity of radiographic disease, which differed substantially between participants with and those without knee pain. Therefore, we looked within each Kellgren and Lawrence grade at the prevalence of bone marrow lesions, comparing participants with knee pain with those without it. Within each Kellgren and Lawrence grade, the prevalence of bone marrow lesions in painful knees differed substantially from

Figure 2. **Grades of bone marrow lesions.**



Top. Two grade 1 lesions beneath the medial femoral condyle and medial tibial plateau. Both lesions were seen on one adjacent slice. Middle. Grade 2 lesion beneath the medial tibial plateau. This particular lesion was seen on three adjacent slices. Bottom. Grade 3 lesion beneath the medial femoral condyle, seen on four adjacent slices. Small grade 1 lesions (which still sum to a grade 1 lesion on the basis of the total volume of lesions) on the medial tibial plateau are also visible.

Table 1. **Participant Characteristics**

Characteristic	Knee Pain and Osteoarthritis (n = 351)	No Knee Pain and Osteoarthritis (n = 50)	P Value*
Women, %	33	48	0.04
Mean age ± SD (range), *y*	66.8 ± 9.3 (47–91)	66.9 ± 8.5 (47–85)	>0.2
Mean body mass index ± SD (range), kg/m^2	31.6 ± 5.8 (19–60)	28.8 ± 4.7 (18–37)	0.01
Median Kellgren and Lawrence grade of studied knee (range)	2 (0–4)	0 (0–2)	<0.001
Mean sum of individual radiographic features ± SD (range)†	6.1 ± 4.2 (0–21)	1.4 ± 1.5 (0–5)	<0.001

* Chi-square test.
† The individual radiographic feature score of studied knee consisted of total of osteophyte, narrowing, sclerosis, and cyst scores on all views.

that in nonpainful knees. In addition, bone marrow lesions were more frequent in those with higher grades of radiographic disease. Among participants with knee pain, the prevalence of lesions ranged from 48% of knees (30 of 63) with Kellgren and Lawrence grades of 0 to 100% (15 of 15) of those with Kellgren and Lawrence grades of 4.

When we restricted our evaluation to the presence of large bone marrow lesions, we found a substantial prevalence of such lesions among participants with knee pain; this prevalence increased with increasing Kellgren and Lawrence grade. Of participants without knee pain, almost none had large bone lesions; among knees with Kellgren and Lawrence grades of 0 and 1, the difference in prevalence between participants with (16 of 129 [12.4%]) and without knee pain (0 of 38 [0%]) was substantial.

We evaluated whether bone marrow lesions were statistically more prevalent in participants with knee pain than in those without knee pain after adjustment for other factors that may contribute to knee pain. We restricted these analyses to participants who had relatively low Kellgren and Lawrence grades (0 to 2) because no participant with a painless knee had a Kellgren and Lawrence grade greater than 2. Thus, 221 participants with knee symptoms were analyzed. Forty-seven participants without knee pain were included in the analysis; three high-quality radiographic views were available for each, which made it possible to generate a score for individual radiographic features. When we adjusted for overall scores of individual radiographic features, effusion score, sex, and age, we found that bone marrow lesions were associated with the presence of knee pain (odds ratio, 3.31 [95% CI, 1.54 to 7.41]). Using the same analytical approach, we focused on large bone marrow lesions and found that large lesions were also strongly associated with the presence of pain (odds ratio, 5.78 [CI, 1.04 to 111.11]). Results were similar when we used Kellgren and Lawrence grade as our measure of radiographic severity instead of score for individual radiographic features.

Table 2. **Bone Marrow Lesions in Participants with and without Knee Pain**

Finding	Knee Pain and Osteoarthritis	No Knee Pain and Osteoarthritis	P Value
	n (%)		
Bone marrow lesion	272 (77.5)	15 (30.0)	<0.001*
Large bone marrow lesion	126 (35.9)	1 (2.0)	<0.001†

* Chi-square test.
† Fisher exact test.

Finally, we tested whether the presence of bone marrow lesions or large bone marrow lesions was associated with a greater severity of knee pain. We analyzed 243 knees with symptomatic osteoarthritis, for which we had information on all model variables. Compared with knees that did not have bone marrow lesions, the presence of lesions was associated with a 7.8-mm higher average pain score (range, 0 to 100 mm) (CI, −1.1 to 16.7 mm; $P = 0.08$), whereas the presence of large lesions (compared with no large lesions) was associated with a 2.6-mm higher average pain score (CI, −4.3 to 9.5 mm; $P > 0.2$). Results were similar when the WOMAC pain score was used.

DISCUSSION

Our results show that bone marrow lesions in knees are associated with the most important symptom of osteoarthritis: pain. Bone marrow lesions were much more prevalent in participants with knee pain than in those without it. This association could not readily be explained by such confounders as severity of radiographic

disease and presence of effusions, another potential cause of pain. Thus, our results suggest that bone marrow lesions contribute to the occurrence of pain in persons with knee osteoarthritis. In participants with knee pain, we found no association between presence of these lesions and severity of pain.

Several caveats are in order. First, our results are cross-sectional, and any relation between bone marrow lesions and pain should be corroborated in a longitudinal study. Second, our comparisons of persons with and without knee pain were restricted to persons with relatively mild radiographic severity, because no one in the group without knee pain had severe radiographic disease. The lack of pain-free participants with more severe radiographic osteoarthritis precluded us from estimating the specificity of bone marrow lesions for absence of knee pain. Our results may therefore not be generalizable to persons with more severe radiographic disease.

Our separate analyses of bone marrow lesions (any lesion $\geq$ grade 1) and large lesions (any lesion $\geq$ grade 2) are not independent of one another. If a Bonferroni correction because of nonindependence were performed, each comparison of participants with pain and those without pain would remain statistically significant at a P value less than 0.001.

Our failure to find an association of bone marrow lesions with severity of pain in persons with knee pain suggests that such pain stems from many causes. Other potential causes of knee pain include capsular distention from large effusions and synovitis. Any given cause (for example, bone marrow lesions) may not produce worse knee pain than any other one (for example, capsular distention).

The involvement of bone in the pathologic process of osteoarthritis has been neglected. Recent evidence suggests that juxtaarticular lesions on bone scintigraphy, similar to the bone marrow lesions that we observed, identify persons with osteoarthritis who are at high risk for progression (17). Thickening of the superficial subchondral plate may be separable from deeper pathology, which the bone marrow lesions we describe may represent.

Histologically, these bone marrow lesions generally reflect pathologic evidence of increased water, blood, or other fluid inside bone, such as might occur with localized edema or contusions. Information on other painful regional musculoskeletal disorders supports our contention that bone marrow lesions are associated with pain. In addition to the example of athletes with bone contusions (5), in a recent report of 37 patients with hip osteonecrosis, a striking association was observed between bone marrow edema lesions on MRI and pain (18). Bone marrow edema lesions occurred in 50% (7 of 14) of persons with pain but in only 4% (1 of 23) without pain. Furthermore, resolution of pain coincided with the disappearance of marrow edema. Similar findings on MRI typify a syndrome called "transient painful osteoporosis" (19). Patients with this syndrome present with a painful joint and have similar bone marrow lesions on MRI, but radiography is usually normal. Since osteoporosis has not been documented in these patients, some investigators (19) have suggested that the syndrome be renamed "the transient marrow edema syndrome."

In work that may be related to ours, Arnoldi and colleagues (19) reported that patients with knee and hip osteoarthritis often have intraosseous hypertension due to poor venous drainage from the marrow. Such patients had positive technetium phosphate bone scans, a finding that correlates highly with bone marrow lesions on MRI (20). The researchers suggested that this intraosseous hypertension caused joint pain and reported that fenestration of the bony cortex and osteotomy both reduced this hypertension.

The reproducibility of our bone marrow lesion readings was substantial ($\kappa = 0.66$) although not high. We believe that scoring MRIs is inherently more difficult and likely to produce lower levels of reader agreement than scoring radiographs, because readers must score the size of lesions spread over multiple image slices. Other investigators have reported κ values for reliability in reading knee MRIs that were substantially lower than ours, generally 0 to 0.4 (21). Even though we provided guidelines to accomplish this task, it remained challenging. In addition, our method of testing reliability was to standardize the reader according to the atlas, ask them to read the sample of films (which took more than 1 year), and test the reliability on a random sample of the films they had read, some of which were read 1 year before. This results in an observer agreement value that is realistic but tends to be lower than values obtained when reliability is measured in one session or two sessions close in time.

In conclusion, persons with knee pain and osteoarthritis more often have lesions on MRI suggestive

of bone marrow edema than do persons with a similar degree of radiographic osteoarthritis but without knee pain. In persons with knee pain, these lesions were not associated with severity of pain. Our results suggest that bone marrow lesions may contribute to the central disabling feature of osteoarthritis: pain.

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"Do you understand me, child?"

"Of course," she said. "Why shouldn't I?"

"It surprises you that I say the blood circulates through the body, no doubt?"

"That could only surprise a physician," she said. "Any farmer knows it."

"How do you mean?"

"If you bleed a pig, you cut the main vein in its neck. The pig bleeds to death and produces soft white meat. How else could all the blood come out of one slit unless it was all connected? And it moves of its own accord, almost as though it is being pumped, so must go round and round. That is all obvious, isn't it?"

I blinked, and stared at her. It had taken practitioners of the medical art the better part of two thousand years to make this astounding discovery, and there was this girl saying she knew it all along. A few days ago, I would have been furious at her impudence. Now I merely wondered what else she—and the country folk she mentioned—might know if only people troubled to ask them.

Iain Pears
An Instance of the Fingerpost
New York: Riverhead Books; 2000:87

Submitted by:
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Submissions from readers are welcomed. If the quotation is published, the sender's name will be acknowledged. Please include a complete citation (along with page number on which the quotation was found), as done for any reference.–*The Editor*

Bone Marrow Edema and Its Relation to Progression of Knee Osteoarthritis

David T. Felson, MD, MPH; Sara McLaughlin, MPH; Joyce Goggins, MPH; Michael P. LaValley, PhD; M. Elon Gale, MD; Saara Totterman, MD; Wei Li, MBA; Catherine Hill, MD, MSc; and Daniel Gale, MD

Background: While factors affecting the course of knee osteoarthritis are mostly unknown, lesions on bone scan and mechanical malalignment increase risk for radiographic deterioration. Bone marrow edema lesions on magnetic resonance imaging correspond to bone scan lesions.

Objective: To determine whether edema lesions in the subarticular bone in patients with knee osteoarthritis identify knees at high risk for radiographic progression and whether these lesions are associated with limb malalignment.

Design: Natural history study.

Setting: A Veterans Administration hospital in Boston, Massachusetts.

Patients: Persons 45 years of age and older with symptomatic knee osteoarthritis.

Measurements: Baseline assessments included magnetic resonance imaging of the knee and fluoroscopically positioned radiography. During follow-up at 15 and 30 months, patients underwent repeated radiography; at 15 months, long-limb films were obtained to assess mechanical alignment. Progression was defined as an increase over follow-up in medial or lateral joint space narrowing, based on a semi-quantitative grading. Generalized estimating equations were used to evaluate the relation of medial bone marrow edema lesions to medial progression and lateral lesions to lateral progression, before and after adjustment for limb alignment.

Results: Of 256 patients, 223 (87.1%) participated in at least one follow-up examination. Medial bone marrow lesions were seen mostly in patients with varus limbs, and lateral lesions were seen mostly in those with valgus limbs. Twenty-seven of 75 knees with medial lesions (36.0%) showed medial progression versus 12 of 148 knees without lesions (8.1%) (odds ratio for progression, 6.5 [95% CI, 3.0 to 14.0]). Approximately 69% of knees that progressed medially had medial lesions, and lateral lesions conferred a marked risk for lateral progression. These increased risks were attenuated by 37% to 53% after adjustment for limb alignment.

Conclusion: Bone marrow edema is a potent risk factor for structural deterioration in knee osteoarthritis, and its relation to progression is explained in part by its association with limb alignment.

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For author affiliations, see end of text.

Osteoarthritis, the most common form of arthritis, is the leading cause of mobility-related disability in elderly persons (1). With the aging of the population, the prevalence of osteoarthritis is increasing. Loss of hyaline articular cartilage is a central pathologic event in osteoarthritis, but the pathogenesis of cartilage loss is poorly understood. Specifically, there is a paucity of information about what factors identify joints at high risk for progression. Identification of such factors might permit better understanding of the disease process.

While cartilage loss is a major pathologic feature of osteoarthritis, abnormal bone has been documented as another important element. Bone scan studies of persons with osteoarthritis have reported late-phase uptake of tracer in subchondral bone, signifying accelerated bone turnover. This increase in tracer has been associated with joint pain (2) and with a markedly increased risk for radiographic progression in osteoarthritis of the knee (3) and hand (4). The study in knees, however, was limited by the use of outdated radiographic techniques (5).

Increased uptake on bone scan has a parallel finding on magnetic resonance imaging (MRI): bone marrow edema (6, 7). Bone marrow edema is indicated by focally increased signal in the marrow on fat-suppressed T2-weighted images. McAlindon and colleagues (7) found that of 12 knees with bone scan lesions, 11 had bone marrow edema lesions in the same location. The question of whether bone marrow edema lesions on MRI affect structural change in the osteoarthritic joint has not been longitudinally evaluated. We previously reported that among persons with radiographic knee osteoarthritis, those with bone marrow edema lesions more often had knee pain than those without (8). In patients without osteoarthritis, these edema lesions have been associated with bone trauma (9, 10).

Like lesions on bone scans, limb malalignment has also been reported as a potent risk factor for structural progression of osteoarthritis. In a recent longitudinal study (11), patients with varus alignment were at high risk for subsequent medial progression of knee osteoarthritis, while limbs with valgus alignment were at commensurately high risk for lateral progression. The accepted mechanism for the effect of malalignment is that increased stress on one side of the joint leads to cartilage loss.

We performed a natural history study of knee osteoarthritis using MRIs and knee radiography. One goal of our study was to examine the effect of bone marrow edema lesions on structural deterioration of the joint, as indicated by joint space loss on radiographs. Previous work (12) documented the correlation between joint space width and articular cartilage thickness, and other studies (11, 13) have used joint space loss as a proxy for cartilage loss. Our objectives were to investigate the relation of bone marrow

Context

Bone marrow edema on magnetic resonance imaging (MRI) correlates with pain in patients with knee osteoarthritis, but its association with progression of joint changes is unknown.

Contribution

Among 223 patients with knee osteoarthritis, bone marrow edema on MRI was associated with radiographic progression in the same compartment over the following 15 to 30 months after adjustment for age, sex, body mass index, and limb malalignment (another predictor of progression).

Cautions

While this study shows that bone marrow edema is associated with the progression of knee osteoarthritis, we do not know whether it is causal or an epiphenomenon. These findings do not define a role for MRI in the routine evaluation of knee osteoarthritis.

–The Editors

edema lesions to joint space loss in patients with osteoarthritis, to evaluate whether these lesions were associated with malalignment, and to determine whether some of the relation of marrow lesions to progression could be explained by their association with malalignment. In addition, if bone marrow edema lesions were associated with malalignment, we postulated that they had a local effect and that the contralateral side of the joint was protected.

METHODS

Patients were recruited to participate in a natural history study of symptomatic knee osteoarthritis. All patients in the current study are a subset of patients whose recruitment has been described in detail elsewhere (8). Briefly, patients were recruited from two prospective studies, one in men and one in women, of quality of life among veterans; from clinics at Boston Medical Center in Boston, Massachusetts; and from advertisements in local newspapers. Potential participants were asked two questions: "Do you have pain, aching, or stiffness in one or both knees on most days?" and "Has a doctor ever told you that you have knee arthritis?" For patients who answered yes to both questions, we conducted a follow-up interview in which we asked about other types of arthritis that could cause knee symptoms. If no other forms of arthritis were identified, then the individual was eligible for recruitment. A series of knee radiographs were obtained for each patient to determine whether radiographic osteoarthritis was present. If patients had a definite osteophyte on any view in the symptomatic knee, they were eligible for the study. Because they had frequent knee symptoms and radiographic osteoarthritis, all patients met American College of Rheumatology criteria for symptomatic knee osteoarthritis (14).

For the natural history study, we enrolled patients who were interested in participating and who could walk with or without a cane. Of 351 patients from the cross-sectional study (8), 324 met these criteria. Of these, 193 men and 19 women received care from the Veterans Administration Health Care System and were recruited from the outpatient clinics there. Eight men and 104 women were recruited from the community.

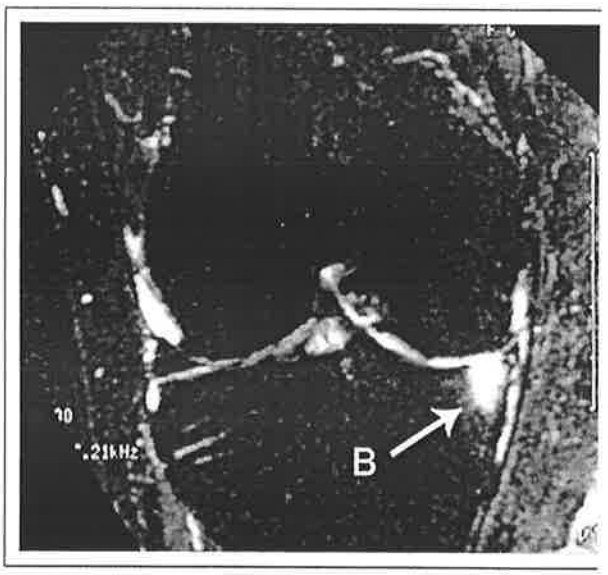
The study included a baseline examination and follow-up examinations at 15 and 30 months. At baseline, patients who did not have contraindications to MRIs had MRI of the more symptomatic knee. At all examinations, patients had knee radiography and answered questionnaires about the severity of knee symptoms, including the Western Ontario McMaster Osteoarthritis (WOMAC) questionnaire. Patients were also weighed, with shoes off, on a balance-beam scale, and height was assessed. At the first follow-up visit, long-limb films were obtained with a 14 × 51 cassette, using methods described elsewhere (15). Our study focuses on baseline MRI findings as predictors of change in radiographs over follow-up. The institutional review boards of Boston University Medical Center and the Veterans Administration Boston Health Care System approved the baseline and follow-up examinations.

Assessments

Magnetic Resonance Imaging

All studies were performed with a Signa 1.5T MRI system (General Electric Corp., Milwaukee, Wisconsin) using a phased-array knee coil. A positioning device was used to ensure uniformity among patients. Coronal, sagittal, and axial images were obtained. Coronal spin-echo fat-saturated proton density and T2-weighted fat-saturated

Figure 1. **Bone marrow edema lesion (*B*) on magnetic resonance imaging.**



This lesion was scored as grade 2 in size on a scale of 0 to 3.

images (repetition time, 2200 milliseconds; echo time, 20/80 milliseconds) with a slice thickness of 3 mm, a 1-mm interslice gap, one excitation, a field of view of 11 to 12 cm, and a matrix of 256 × 128 pixels were obtained.

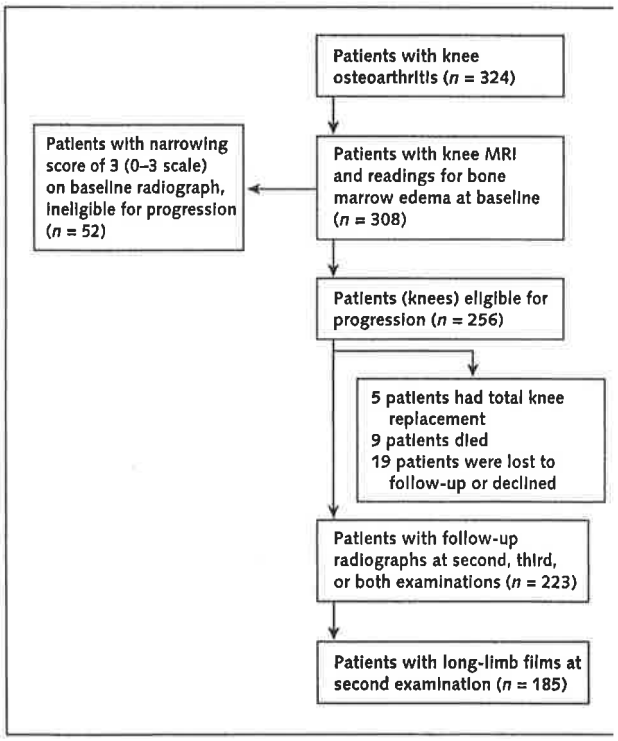
To evaluate bone marrow lesions, we used the coronal T2-weighted fat-saturated images. As previously reported (8), each femur and tibia were divided into medial, central, and lateral quadrants, resulting in six potential sites of lesions for each knee. We defined lesions as areas of increased signal adjacent to the subcortical bone; a single radiologist, blinded to patient characteristics and radiographs, graded lesions from 0 to 3 on the basis of their size. Because previous work (8) demonstrated that lesions of grade 2 or greater were more strongly associated with the presence of knee pain (grade 1 lesions were common in those with and without knee pain), we focused on lesions that were grade 2 or larger. Such lesions encompassed at least one quarter of the width of the compartment on two or more slices (**Figure 1**). For intraobserver agreement for reading of these lesions, the κ value was 0.66 ($P < 0.001$). We defined a lesion as occurring in either the medial or lateral compartment if it was present in the femur or tibia of that compartment.

Radiography

Patients underwent weight-bearing posteroanterior radiography using the protocol of Buckland-Wright (16). Using fluoroscopic positioning, we aligned the beam relative to knee center, and the knee was flexed so that the anterior and posterior lips of the medial tibial plateau were superimposed. Feet were rotated until the tibial spines were centered in the notch, and outlines of foot rotation were then made on foot maps so that the foot rotation would be the same for subsequent films. Fluoroscopic positioning has been shown to more accurately assess joint space compared with nonfluoroscopic acquisition and to improve reproducibility of joint space assessment. Other films obtained at baseline included weight-bearing skyline (17) and weight-bearing semi-flexed lateral films; the latter were obtained according to the Framingham Study protocol.

For evaluation of progression, we focused on the width of the joint space in medial and lateral compartments, since that has been found to correlate with cartilage thickness (12). Films were read by using the Osteoarthritis Research Society International Atlas (18), in which each medial and lateral tibiofemoral joint space is graded from 0 (normal) to 3 (bone on bone). We defined progression of joint space narrowing in a knee compartment as progression by at least one grade. A reader unfamiliar with the MRI findings read all films. All films were read unblinded to sequence; however, films for a subsample of patients were also read blinded to sequence to test the reproducibility of progression measurement and to evaluate possible bias in characterizing progression. Unlike previous cross-sectional studies, in which agreement was most relevant for one point in time, we were interested primarily in studying change on radiographs and therefore tested agreement in evaluating progression between films that were blinded to sequence and those that were unblinded. For intraobserver agreement for reading progression, the κ value was 0.81 ($P < 0.001$), and disagreements between blinded and unblinded readings were in no particular direction, that is, there was no greater tendency for unblinded readings to be read as showing progression.

Figure 2. **Flow of patients through the study.**



MRI = magnetic resonance imaging.

Other Measures

Mechanical alignment, assessed at the first follow-up examination, was measured in degrees on a continuous scale, with values less than 0 representing valgus alignment, values of 0 representing neutral alignment, and values greater than 0 representing varus alignment. For interobserver agreement for reading alignment, the intraclass correlation coefficient was 0.97 ($P < 0.001$).

Statistical Analysis

Patients who were eligible for the current study underwent MRI at baseline in which the knee imaged did not have grade 3 joint space narrowing at baseline. We compared those who had at least one radiograph on follow-up examination with those who had none by using the chi-square test for dichotomous variables, the *t*-test for contin-

Table 1. **Characteristics of Patients Who Participated in Follow-up Compared with Those Who Were Not Followed***

Characteristic	Followed (n = 223)	Not Followed (n = 33)	P Value
Age, *y*	66.2 ± 9.4	67.8 ± 9.6	>0.2
Women, %	41.7	15.2	0.003
BMI, kg/m^2	31.1 ± 5.8	31.0 ± 6.0	>0.2
Weight, *kg*	191.5 ± 38.3	200.3 ± 40.7	>0.2
WOMAC pain score (range, 0–20)	6.9 ± 3.6	9.1 ± 4.7	0.02
WOMAC disability score (range, 0–68)	23.4 ± 11.2	30.2 ± 16.4	0.03
Mechanical alignment, *degrees*	2.8 ± 5.0†	NA	
Medial bone marrow edema lesions, %	33.6	45.5	0.18
Lateral bone marrow edema lesions, %	17.9	15.2	>0.2
Kellgren–Lawrence grade, %			
0	5.8	9.1	>0.2
1	19.3	15.2	
2	20.2	30.3	
3	44.4	39.4	
4	10.3	6.1	
Follow-up at first follow-up examination only, *n (%)*	25 (11.2)	NA	
Follow-up at study end, *n (%)*	198 (88.8)	NA	

* Values presented with plus/minus signs are means ± SD. BMI = body mass index; NA = not available; WOMAC = Western Ontario McMaster Osteoarthritis questionnaire.
† A positive value indicates that the mean is in a varus direction.

uous variables, and the Wilcoxon rank-sum test for ordinal variables (19).

To test the relation of bone marrow lesions to mechanical alignment, we grouped the limbs according to quartile of mechanical alignment and tested for an association by performing two logistic regression analyses with medial and lateral lesions, respectively, as dependent variables and alignment as the independent variable. To evaluate the relation between bone marrow edema lesions and compartment-specific progression, we first laid out simple tables testing whether knees with lesions had higher rates of progression than knees without lesions at the first or second follow-up examinations. We tested ipsilateral (for example, medial lesions leading to medial progression) and contralateral (for example, medial lesions leading to lateral progression) effects. Because repeated radiographic assessments were performed during follow-up, and because we wanted to control for confounders such as age, sex, and body mass index, we ultimately performed logistic regression analyses in which the referent dependent variable was no radiographic progression. To adjust for correlated data over time in individual patients, we used generalized estimating equations (20).

One of the goals of our study was to evaluate whether an association with alignment explained the effect of bone marrow edema lesions. To evaluate this, we used the same logistic regression analyses described earlier to test whether the relation of marrow edema with progression was attenuated after alignment was added as an independent variable, comparing the odds ratio associating bone marrow edema lesions with progression before and after adjustment for alignment. We defined a significant attenuation of the relation as at least a 10% decrease in the odds ratio (21). Results were unchanged in additional analyses in which we adjusted for the severity of pain in the knee (using a visual analogue scale pain measure). All P values reported are two-sided.

Role of the Funding Sources

The funding sources had no role in the collection, analysis, or interpretation of the data or in the decision to submit the manuscript for publication.

RESULTS

Two hundred fifty-six patients, each with one knee studied, met our inclusion criteria (**Figure 2**). Of these, 223 (87.1%) had at least one follow-up examination with a radiographic assessment. **Table 1** compares the baseline characteristics in those followed versus those lost to follow-up. Those lost to follow-up did not differ substantially from the other participants in age, weight, or prevalence of bone marrow lesions but were more likely to be men and to have higher WOMAC pain and disability scores at baseline. Of the 33 patients characterized as lost to follow-up, 5 came to the follow-up examinations but had undergone

Table 2. **Relation of Bone Marrow Edema Lesions to Mechanical Alignment***

Alignment	Knees with Medial Lesions, %	Knees with Lateral Lesions, %
Quartile 1 (alignment ≤ 0 degrees, most valgus)†	16.4	29.5
Quartile 2 (alignment 1–3 degrees)	18.8	16.7
Quartile 3 (alignment 4–6 degrees)	40.0	6.7
Quartile 4 (alignment ≥ 7 degrees, most varus)	74.3‡	8.6§

* Based on 189 knees.
† Alignment ≤ 0 degrees includes neutral alignment and all limbs that were valgus; alignments for quartiles 2–4 are all varus limbs.
‡ $P < 0.001$ for trend.
§ $P = 0.002$ for trend.

Table 3. **Bone Marrow Edema Lesions and Their Relation to Ipsilateral Radiographic Progression**

Variable	Knees with Progression on Side of Lesion, *n/n (%)*	Adjusted Odds Ratio for All Patients in the Longitudinal Analysis (95% CI)*
Medial progression		
Medial lesion	27/75 (36.0)	6.5 (3.0–14.0)
No medial lesion	12/148 (8.1)	1
Lateral progression		
Lateral lesion	10/40 (25.0)	6.1 (2.2–16.5)
No lateral lesion	10/183 (5.5)	1

* Adjusted for age, sex, and body mass index. Odds ratios (95% CI) for these variables were as follows for medial progression and lateral progression, respectively: age (per year), 1.0 (0.9–1.0) and 1.1 (1.0–1.1); sex (women), 0.8 (0.4–1.8) and 3.1 (1.1–8.8); body mass index (per unit), 1.1 (1.0–1.1) and 1.0 (0.9–1.1).

total replacements of their study knees. Four additional patients had had their study knees replaced by the second follow-up visit; however, because radiographic follow-up was obtained at the first follow-up visit, these patients were included as having been followed.

We found a striking association between bone marrow edema lesions and mechanical alignment (**Table 2**). Limbs with varus alignment, especially if marked (≥7 degrees), had a remarkably high prevalence of medial lesions compared with limbs that were neutral or valgus (74.3% vs. 16.4%; $P < 0.001$ for relation between alignment and medial lesions). Conversely, limbs that were neutral or valgus had a much higher prevalence of lateral lesions than limbs that were in the most varus group (29.5% vs. 8.6%; $P = 0.002$ for alignment and lateral lesions). When we subdivided the 45 valgus limbs at the median for valgus angulation (3 degrees), we found that the most valgus limbs had a higher prevalence of lateral lesions (40.9%) than less valgus limbs (26.1%).

Of 223 knees followed, 39 showed evidence of medial progression. Of 75 knees with medial lesions, 27 (36.0%) showed medial progression compared with 12 of 148 knees (8.1%) without medial lesions (**Table 3**), a 6.5-fold increase in the odds of progression. Of the knees with medial progression, 27 (69.2%) had medial bone marrow lesions at baseline.

We found a similar strong association between lateral lesions and lateral progression (**Table 3**). Of 40 knees with lateral lesions, 10 (25.0%) showed lateral progression compared with 10 of 183 without lateral lesions (5.5%). Of knees with lateral progression, half (10 of 20) had lateral bone marrow lesions at baseline. The odds of lateral progression were increased approximately sixfold among knees with lateral lesions.

While medial lesions increased the risk for medial progression, they decreased the risk for lateral progression (**Table 4**). Specifically, only 3 of 75 knees with medial lesions (4.0%) showed lateral progression compared with 17 of 148 knees without these lesions (11.5%). Lateral lesions had a modest protective effect on medial progression; 5 of 40 knees with lateral lesions showed such progression (12.5%) versus 34 of 183 knees without lateral lesions (18.6%). When we examined only patients who had alignment evaluations, this association with progression increased to an odds ratio of 8.9, which was attenuated by 37% (from 8.9 to 5.6) after adjustment for alignment (**Table 5**). For the association of lateral bone marrow edema with progression, the association was attenuated 53% by adjustment for alignment and became statistically nonsignificant. When we analyzed lesions by the bone involved, we found similar effects. For example, medial lesions, whether in the tibia or femur, increased the risk for medial progression. Also, when we looked at knees with lesions in only medial or lateral locations, not in both, we found similar results.

Discussion

Results of this longitudinal study to examine the effects of bone marrow edema on the course of knee osteoarthritis suggest that these lesions powerfully predict risk for local structural deterioration. Risk for medial progression was increased more than sixfold in patients with medial lesions, and patients with lateral lesions were at a commensurate high risk for lateral progression. That medial lesions protected against lateral progression suggests a uniquely local effect.

Another important finding was that bone marrow lesions are strongly related to frontal plane malalignment. Varus limbs in our study had an extraordinarily high prevalence of medial bone marrow lesions, whereas lateral lesions occurred preferentially in valgus limbs. Indeed, much of the relationship of bone marrow edema lesions to radiographic progression was explained by their association with malalignment. While malalignment and bone marrow lesions are closely correlated, each adds prognostic information in the presence of the other. For example, according to **Table 5**, in the presence of bone marrow edema, every 3-degree departure from neutral alignment increases the odds of progression on the same side as the malalignment

Table 4. **Bone Marrow Edema Lesions and Their Relation to Contralateral Radiographic Progression**

Variable	Knees with Progression on Opposite Side of Lesion for All Patients in the Longitudinal Analysis, *n/n (%)*	Adjusted Odds Ratio (95% CI)*
Lateral progression		
Medial lesion	3/75 (4.0)	0.3 (0.1–1.0)
No medial lesion	17/148 (11.5)	1
Medial progression		
Lateral lesion	5/40 (12.5)	0.7 (0.2–1.8)
No lateral lesion	34/183 (18.6)	1

* Adjusted for age, sex, and body mass index. Odds ratios (95% CI) for these variables were as follows for lateral and medial progression, respectively: age (per year), 1.1 (1.0–1.1) and 1.0 (0.9–1.0); sex (women), 3.1 (1.1–8.7) and 0.7 (0.4–1.6); body mass index (per unit), 1.0 (0.9–1.1) and 1.1 (1.0–1.1).

by 50% to 100%. Disease progression in patients with bone marrow lesions may be the consequence of the lesions themselves, or malalignment may produce both the traumatic bone lesions and the wearing away of local cartilage evidenced by joint space loss.

Even after adjustment for malalignment, there was a substantial residual association of bone marrow edema lesions with radiographic progression. Alignment as assessed on long-limb radiographs represents alignment during standing, or so-called static alignment. Dynamic alignment or alignment during walking as measured in a gait laboratory can differ from static alignment (22, 23). Knees with medial lesions in which static alignment was neutral could have dynamic malalignment. If that were true, it would suggest that frontal plane malalignment statically or dynamically accounts for the preponderance of structural progression in knee osteoarthritis.

On histopathologic examination, bone marrow edema lesions show surprisingly little edema (24, 25) but show abnormal bone with excessive fibrosis, small areas of osteonecrosis, and extensive bony remodeling with reversal lines. Such remodeling often occurs after fatigue fractures in bone, although microfractures themselves have not been reported. The picture is most consistent with ongoing bone trauma, which would help explain the association of malalignment with these lesions and would be consistent with histologic findings in states in which bone marrow edema occurs with microfractures.

Although bone marrow edema was a powerful predictor of disease progression in our study, that does not mean that MRIs should be ordered to evaluate these lesions in patients with knee osteoarthritis. Currently, there are no treatments for bone marrow edema. Furthermore, it is not clear whether these lesions directly cause structural damage or are a consequence of malalignment. It remains to be determined whether adding MRIs to identify bone marrow edema, long-limb radiographs to check alignment, or both to the evaluation of knee osteoarthritis adds sufficient predictive information to merit their clinical use.

Limitations of our study include chronologic assessment of alignment in the middle of the study rather than at the beginning. We found the same relations among malalignment, marrow edema, and progression (although fewer patients progressed) when we restricted analyses to knees from the middle to the end of the study. Also, our study was based in the Veterans Health Care System and therefore included mostly men, while most persons with knee osteoarthritis are women. Last, we found that the contralateral side of the joint was protected from progression. However, since we evaluated progression by radiography, we could have missed contralateral cartilage loss that might have been more sensitively detected by MRI.

Further studies evaluating the longitudinal course of bone marrow edema lesions are needed. Better understanding of the interrelation of cartilage and the bone immediately under it is also necessary. Our findings have major implications for the design of clinical studies, including trials in osteoarthritis. They suggest that patients at high risk for progression could be efficiently identified by screening for bone marrow edema on MRI. Indeed, 69.2% of knees that eventually developed medial progression in our study had large medial lesions at baseline. Our definition of bone marrow edema lesions excluded smaller lesions. However, when such lesions were included, we found that 81% of knees with medial progression had had medial lesions. Until now, it has been extraordinarily difficult to detect structural deterioration, and this has prevented the development of preventive therapies. In fact, in longitudinal radiograph-based studies of knee osteoarthritis (26, 27), most patients did not show progression, especially if followed for less than 5 years. Bone marrow edema could be used to select patients at truly high risk for structural progression. Trials restricted to such patients would provide a sample that includes many persons likely to experience progression and would facilitate the development of preventive treatments.

In summary, in patients with knee osteoarthritis, bone marrow edema lesions in bone underneath cartilage markedly increase risk for structural progression in the knee, especially in the compartment affected by the bone marrow lesion. Bone marrow edema lesions are strongly related to malalignment toward the side of the lesion. Our findings provide fundamental insights into the process of structural deterioration in knee osteoarthritis.

Table 5. **Bone Marrow Edema Lesions and Their Relation to Progression before and after Adjustment for Mechanical Alignment***

Variable	Adjusted Odds Ratio (95% CI)†	Adjusted Odds Ratio† Including Alignment (95% CI)‡
Medial lesion	8.9 (3.6–21.8)	5.6 (2.1–14.8)
No medial lesion	1 (referent)	1
Lateral lesion	5.9 (1.9–18.1)	2.8 (0.8–10.1)
No lateral lesion	1 (referent)	1

* Analyses restricted to 183 knees with limb alignment measurement and longitudinal follow-up.

† Adjusted for age, sex, and body mass index. Odds ratios (95% CI) for these variables were as follows for medial progression before and after adjustment for alignment, respectively: age (per year), 1.0 (0.9–1.0) and 1.0 (0.9–1.0); sex (women), 1.0 (0.4–2.4) and 1.2 (0.5–2.9); body mass index (per unit), 1.1 (1.0–1.2) and 1.1 (1.0–1.2); alignment (per degree), 1.1 (1.0–1.3). Odds ratios (95% CI) for these variables were as follows for lateral progression before and after adjustment for alignment, respectively: age (per year), 1.0 (0.9–1.0) and 1.1 (1.0–1.1); sex (women), 4.2 (1.3–14.1) and 3.0 (0.8–11.1); body mass index (per unit), 0.9 (0.8–1.1) and 1.0 (0.9–1.1); alignment (per degree), 0.8 (0.7–0.9).

‡ Alignment was treated as a continuous measure in these analyses.

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Current Author Addresses: Drs. Felson, LaValley, and Hill and Ms. McLaughlin, Ms. Goggins, and Ms. Li: Boston University School of Medicine, 715 Albany Street, A203, Boston, MA 02118.
Drs. M.E. Gale and D. Gale: Radiology Department, Veterans Affairs Boston Health Care System, 150 Huntington Avenue, Boston, MA 02130.
Dr. Totterman: Department of Radiology, University of Rochester Medical Center, 601 Elmwood Avenue, PO Box 694, Rochester, NY 14624-8648.

Author Contributions: Conception and design: D.T. Felson.
Analysis and interpretation of the data: D.T. Felson, J. Goggins, M.P. LaValley, S. Totterman, W. Li.
Drafting of the article: D.T. Felson.
Critical revision of the article for important intellectual content: M.P. LaValley, C. Hill, D. Gale.
Final approval of the article: D.T. Felson.
Provision of study materials or patients: D.T. Felson, J. Goggins.
Statistical expertise: D.T. Felson, M.P. LaValley.
Obtaining of funding: D.T. Felson.
Administrative, technical, or logistic support: D.T. Felson, J. Goggins, M.P. LaValley, M.E. Gale, W. Li, D. Gale.
Collection and assembly of data: D.T. Felson, S. McLaughlin.

Chapter 7

7.1 Contribution and impact

The work presented in this MD thesis has provided important information about the structural pathology, sources of pain and the natural history of knee OA and has added to 'whole-joint' concept knee OA, as distinct from the 'chondro-centric' emphasis. It has provided an impetus for further investigation of the role of synovitis, effusion, cruciate ligaments and bone marrow lesions in knee OA.

There is a need to look beyond cartilage in the search for the elusive structure-modifying osteoarthritis drug (SMOAD) that researchers and sufferers alike are keen to discover. Until recently, SMOAD development has focused on chondroprotection, however this approach has not been rewarding to date. Despite improvements in knowledge of cartilage metabolism and pathogenic processes, no chondroprotective agents has demonstrated unequivocal efficacy in human trials. Consequently, there is currently no licensed SMOAD on the market in Australia. A recent editorial has suggested that the most logical and promising targets for future SMOAD development are synovial inflammation and inflammatory mediators, inhibitors of cartilage metabolism and inhibitors of subchondral bone remodeling (Pelletier 2007). To move forward in this field, sensitive structural outcome measures and innovative therapies are required. It is also likely that, given the impact of joint malalignment in knee OA, a structure-modifying drug used in combination of physical unloading of the joint will be more effective (Felson 2007b). The work presented in this thesis has contributed to the knowledge of pain sources and structural pathology in knee OA that are potential targets for SMOADs.

Chapters 2, 3 and 5 address the role of inflammation in knee OA by evaluating the presence of effusions, synovitis and periarticular lesions. These studies represented the largest studies at the time looking at the relationship between these MRI features and pain in knee OA. This study demonstrated that moderate or larger effusions were more common in those with knee pain and radiographic knee OA than those without knee pain, suggesting that effusion and capsular distention are sources of pain in knee OA. Subsequent work by Torres (2006) confirmed these findings. In contrast, peripatellar lesions and popliteal cysts commonly identified on knee MRI in people with radiographic knee OA were found to occur with similar frequency amongst those with or without knee symptoms, suggesting that these lesions do not contribute - significantly to pain. However, other periarticular lesions (e.g. anserine bursitis) were

7.2 Place of magnetic resonance imaging in the assessment of knee osteoarthritis

Over recent years, the increased availability of MR scanners has lead to a dramatic increase in the clinical use of knee MRI. Recent administrative data from Norway demonstrated a rapid increase in use of knee MRIs particularly in patients over 50 years, suggesting that OA is one of the primary indications for use of MRI (Espeland 2007). However, the clinical use of MRIs in knee OA has not been established and probably has no current place in routine care of knee OA (Conaghan 2006b). In addition, incidental meniscal findings on MRI are present in up to 23% of the middle-aged and elderly without symptoms or radiographic OA (Englund 2008), making interpretation of MRI in these patients problematic. Whilst it has proven invaluable in the research setting, ethical issues of using knee MRI as an investigational tool related to the detection of unexpected findings also need to be considered. Grainger and colleagues (2008) examined 733 subjects (601 asymptomatic, 132 with knee OA) who underwent a limited knee MRI for cartilage volume measurement and found 2.3% had potentially clinically significant abnormalities requiring further investigation.

There are limitations to utilization of MRI to determine structural pathology and sources of knee pain as outlined in this MD thesis. Imprecision can be introduced into studies through both the MRI scoring methods and methods of pain measurement.

1. MRI Scoring methods.

Semi-quantitative methods were used in the studies included in this MD for all MRI features. Cartilage scoring was measured using the Whole-Organ Magnetic Resonance Imaging Score (WORMS; Peterfy 2004). At present, there are three semi-quantitative whole organ scoring systems (Peterfy 2004, Kornaat 2005, Hunter 2008b), but there is currently no reference standard and there are no data to establish superiority of one scoring system over another (Guermazi 2008). An alternative approach is use of a quantitative measure for such features as synovial volume and cartilage volume. Cartilage volume measurement has not been shown to be superior to semi-quantitative methods of measuring cartilage change in longitudinal studies, and the role of synovial volume measurements in knee OA is under investigation (Pelletier 2008).

2. Methods of pain measurement.

Although, in BOKS standard measures of pain and disability were used (VAS, WOMAC), there are many variables that can influence pain over both the short and long term. Longitudinal studies have demonstrated that most people with knee OA have increased pain over time but this is highly variable. Dieppe and colleagues (2000) in a longitudinal study of knee OA over an 8 year period found the prevalence of those reporting 'severe' pain at baseline was 25%, 17% at 3 years and 27% at 8 years with 80% feeling overall that they had worsened. Over shorter periods, knee OA pain can fluctuate, including diurnal variation (Bellamy 1990, Gooberman-Hill 2007). The LEAP study, which employed weekly phone interviews, found that up to 49% of patients with knee OA experienced fluctuations in pain (Hutchings 2007). There is likely to be factors contributing to changing patterns of pain over time. These influences could include changes in physical activity, co-morbidities, social circumstances and mood as well as changes in the source of pain over time. In addition, it can be postulated that certain structural features are more likely to be associated with certain types of pain, for example, bone marrow lesions with nocturnal pain. This is likely, at least partially, to explain the lack of close correlations of individual structural features with pain. It also highlights the need for precise methods of pain measurement which capture variability of the pain experience in terms of timing and characteristics of the pain.

The work presented here has largely examined individual features separately and predominantly in a cross-sectional way. Utilizing the structural abnormalities that we have demonstrated, other researchers have subsequently explored the role of multiple MRI features of knee OA and their contribution to pain in knee OA. Torres and colleagues (2006) examined 143 subjects with symptomatic knee OA using MRI and found synovitis/effusion (these were graded together), bone marrow lesions, bone attrition and meniscal tears were each associated with increasing pain severity. They also noted a weak correlation between knee pain and cartilage morphology. Zhai and colleagues (2006) examined 500 subjects (50-79 years old, 48% with knee pain) and found that full-thickness and partial thickness medial tibial chondral defects and bone marrow lesions were associated with knee pain. Interestingly they also noted an association with radiographic hip, but not radiographic knee, OA. To account for the presence of other MRI features of knee OA, in the longitudinal studies of the role of synovitis and bone marrow lesions (Chapters 5 and 6), adjustment for other known MRI features of knee pain such as effusion was included in the analysis.

The work presented here and subsequent work has established the utility of MRI for research purposes in knee OA. This modality has rapidly expanded our knowledge of the structural pathology and morphological correlates of pain in knee OA and offers new potential targets for structural modification in OA intervention trials.

7.3 Future directions

There is a need for further work to define the usefulness of MRI to measure outcomes in OA intervention trials. Three areas in which MRI is likely to be helpful in the definition of the efficacy of OA therapeutic interventions to retard progression of disease are:

(1) Identification of those patients at risk of rapid disease progression and therefore with the most to gain from successful interventions. These factors may be related to local, systemic or MR features.

(2) Further definition of subsets of knee OA. Using MRI, we are increasingly recognizing the heterogeneous nature of knee OA. This may allow targeting of specific therapies.

(3) Establishment of precise, validated imaging methods that are sensitive to change. These may include the use of synovitis and bone marrow lesions as structural outcome measures, as well as therapeutic targets. However, more work needs to be undertaken to further refine the MR measurement of these features and their sensitivity to change over time. In addition, newer MRI cartilage techniques including functional MRI with delayed gadolinium-enhanced MRI (dGEMRIC) and T2 mapping to improve cartilage assessment is also likely to play a role.

Further work we are currently undertaking is a randomized clinical trial to investigate the benefits of high dose (anti-inflammatory) fish oil with symptomatic and MRI structural outcomes (NHMRC Project ID 451900. Chief Investigators: Hill, Cleland, Jones, March).

There is likely to be even more rapid progress in the understanding of knee OA with the public availability of the initial Osteoarthritis Initiative data (Osteoarthritis Initiative 2008).This is an ongoing 4-year observational study in approximately 4800 participants with knee OA or at high risk for development of knee OA. The study is using knee MRI and biomarkers to evaluate the development and progression of symptomatic knee OA, and is funded by National Institutes of Health.

Further investigation of the potential role of enthesopathy in OA pathogenesis is underway.

7.4 Conclusion

The work presented in this MD thesis has provided important information about the structural pathology, sources of pain and the natural history of knee OA. It has demonstrated the association of pain with moderate to large knee effusions, periarticular lesions, synovitis and bone marrow lesions in knee OA. In addition, it showed the high prevalence of complete ACL rupture amongst those with symptomatic knee OA and the longitudinal relationships between synovitis and pain; and bone marrow lesions and radiographic progression. These studies have significantly added to the knowledge in this field and opened up avenues for further research in this common and disabling disease.

Appendix A.

Author Contributions:

Boston Osteoarthritis of the Knee Study (BOKS):

Conception and design of: DT Felson, SMS Totterman, L Kazis, DR Gale

Obtaining of funding: DT Felson

Funding for BOKS: NIH AR 20613, Arthritis Foundation Clinical Sciences Grant, Bayer Corporation, Grant SDR 91006.S from the Veterans Administration

Support for candidate: AFA-Heald Scholarship from Arthritis Foundation of Australia

Chapter 2:

Hill CL, Gale DG, Chaisson CE, Skinner K, Kazis L, Gale ME, Felson DT. Knee effusions, popliteal cysts and synovial thickening: Association with knee pain in those with and without osteoarthritis Journal of Rheumatology 2001;28:1330-7.

Substudy conception and design: Hill

Acquisition of MRI data: Hill, Gale D

Study support: Chaisson, Skinner, Kazis, Felson

MRI reading: Hill, with subset read by Gale D

Analysis and interpretation of data: Hill, Gale D, Felson

Statistical analysis: Hill

Manuscript preparation: Hill

Critical revision of manuscript: Hill, Gale D, Chaisson, Kazis, Felson

Chapter 3

Hill CL, Gale DR, Chaisson CE, Skinner K, Kazis L, Gale ME, Felson DT. Peri-articular lesions detected on magnetic resonance imaging: Prevalence in knees with and without symptoms. Arthritis Rheum;2003;48:2836-44.

Substudy conception and design: Hill, with support from Gale DR, Felson

Acquisition of data: Hill, Gale DR, Chaisson, Kazis, Skinner, Gale ME, Felson

MRI reading: Hill, with subset read by Gale DR

Study support: Chaisson, Skinner, Gale ME, Kazis, Felson

Analysis and interpretation of data: Hill, Gale D, Felson

Statistical analysis: Hill

Manuscript preparation: Hill

Critical revision of manuscript: Hill, Gale D, Chaisson, Kazis, Skinner K, Gale ME, Felson

Chapter 4

Hill CL, Seo GS, Gale D, Totterman S, Gale ME, Felson DT. Cruciate ligament integrity in osteoarthritis of the knee. Arthritis Rheum 2005;52:794-799.

Substudy conception and design: Hill, Gale, Totterman, Felson

Acquisition of data: Hill, Seo, Gale D, Totterman, Felson

Study support: Gale ME, Felson

MRI reading: Seo, Gale D, Totterman

Analysis and interpretation of data: Hill, Seo, Gale, Felson

Statistical analysis: Hill

Manuscript preparation: Hill

Critical revision of manuscript: Hill, Gale D, Felson

Chapter 5

Hill CL, Hunter DJ, Niu J, Clancy MM, Guermazi A, Genant H, Gale D, Grainger A, Conaghan P, Felson DT. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis 2007;66:1599-603.

Substudy conception and design: Hill, Felson

Acquisition of data: Hill, Hunter, Gale, Clancy, Felson

MRI reading of synovitis: Hill, with subset read by Hunter

MRI reading (WORMS): Guermazi, Genant, Gale

MRI reading (synovitis validation): Grainger, Conaghan

Analysis and interpretation of data: Hill, Felson, Hunter

Statistical analysis: Niu, Hill

Manuscript preparation: Hill

Critical revision of manuscript: Hill, Felson, Hunter, Conaghan

Chapter 6

Felson DT, Chaisson CE, Hill CL, Totterman SMS, Gale ME, Skinner KM, Kazis L, Gale DR. The association of bone marrow lesions with pain in knee osteoarthritis. Ann Int Med 2001;134:541-9.

Substudy conception and design: Felson, Totterman, Skinner, Kazis, Gale DR, Gale ME.

Acquisition of data: Felson, Chaisson, Hill, Totterman, Gale ME, Skinner, Kazis, Gale DR.

MRI reading of bone marrow lesions: Gale DR, Totterman

MRI reading of effusion: Hill, Gale DR.
Analysis and interpretation of data: Felson, Chaisson, Skinner, Kazis, Gale DR
Manuscript preparation: Felson, Chaisson, Hill, Skinner, Totterman, Kazis
Critical revision of the article for important intellectual content: Hill, Totterman, Skinner, Kazis, Gale D.
Statistical analysis: Felson
Final approval of article: Felson, Hill, Skinner

Felson DT, McLaughlin S, Goggins J, LaValley MP, Gale ME, Totterman S, Li W, Hill CL, Gale DR. Bone marrow edema and its relation to progression of knee osteoarthritis. Ann Int Med 2003;139: 330-336.
Substudy conception and design: Felson
Acquisition of data: Felson, McLaughlin, Goggins, Gale DR
MRI reading of bone marrow lesions: Gale DR, Totterman
MRI reading of effusion: Hill, Gale DR.
Analysis and interpretation of data: Felson, Goggins, LaValley Totterman, Li
Manuscript preparation: Felson, Hill, LaValley, Gale DR
Critical revision of the article for important intellectual content: La Valley, Hill, Gale
Statistical analysis: Felson, LaValley, Li

Appendix B

Correspondence from Professor David Felson

Boston University
School of Medicine

BOSTON MEDICAL CENTER

Clinical Epidemiology
Research and
Training Unit
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September 12, 2007

Professor Richard Russell
Dean of Graduate Studies
Adelaide Graduate Centre
Level 13, 10 Pulteney Street
THE UNIVERSITY OF ADELAIDE
SA 5005

RE: Catherine Hill

Dear Professor Russell:

It is my pleasure to write a letter of clarification regarding Catherine Hill's involvement in a series of studies examining the relation of MRI features to knee pain in osteoarthritis. Catherine took the lead authorship position on some of these papers (those focusing on synovitis) and took a co- author position on others. The work looking at MRI features and their relation to knee pain in 300 veterans with symptomatic knee OA and a smaller number of veteran controls with knee OA, but without pain was done while Catherine was doing her research training here in Boston. Catherine was integrally involved in the planning and investigation for all of these papers and took the lead in studying the relation of synovitis and periarticular lesions with knee pain. As part of that work, she developed scales for the reading of synovitis and then, working with a musculoskeletal radiologist, she read synovitis herself on these MRI's. She did the analysis herself and in every way deserves credit for the importance and impact of these papers.

Catherine also played a major intellectual role in the other papers in this series of papers, specifically the ones on bone marrow lesions seen on MRI. She participated actively in discussions about our findings relating bone marrow lesions to knee pain, providing advice and help about how to structure the analysis and write up the results; her data on synovitis was used to adjust in the analysis for the co-occurrence of this other feature. She was involved actively in writing the manuscript on bone marrow lesions and pain. She played a similar role in the other paper in the Annals of Internal Medicine on bone marrow lesions and its relation to progression of disease. This_later paper was written after Catherine had left Boston, but she was involved long distance in the drafting of the manuscript and critical revisions.

It is fair to say that Catherine played a leading and critical role in this series of papers on MRI findings and their relation to knee pain and osteoarthritis progression including papers on synovitis, on periarticular lesions, on effusions and on bone marrow lesions,. She took the first author's role in those on synovitis and took a back seat to me in those on bone marrow lesions, but that doesn't diminish her intellectual contribution to them all.

Sincerely,

David T Felson, MD, MPH
Professor of Medicine and Epidemiology
Chief, Clinical Epidemiology Unit
Boston University School of Medicine

Appendix C

Curriculum Vitae

Academic qualifications

M.B.,B.S.	University of Adelaide. Graduated 1988. Conferred May 1989.
F.R.A.C.P.	Royal Australian College of Physicians; December 1995 Sub-Specialty:Rheumatology
M.Sc.(Epidemiology)	Boston University; May 2000

Academic record

Undergraduate
The Robert and Lynda Stamp Prize for highest mark in Community Medicine.

Postgraduate Masters (1998-2000)
Admitted to Delta Omega Society (Alpha Beta Chapter) for high achievement in Masters program
Masters Thesis: 'The frequency of specific cancer types in dermatomyositis and polymyositis: Combined population data from three Nordic countries.'

Current Appointments

Staff Specialist, Rheumatology Unit, The Queen Elizabeth Hospital
Clinical Senior Lecturer, University of Adelaide
Medical Advisor, Adelaide Evaluation Group, Dept of Public Health, University of Adelaide

Work experience

1989	Intern, Royal Adelaide Hospital
1990-1992	Basic Physician Training, Flinders Medical Centre
1993-1994	Advanced training in rheumatology, The Queen Elizabeth Hospital
1995	Advanced training in rheumatology, Royal Adelaide Hospital
1996-June 98	Visiting Consultant Rheumatologist, The Queen Elizabeth Hospital
1996-June 98	Research Fellow, Rheumatology Unit, Royal Adelaide Hospital (part time)
Sept 98-July 00	Rheumatology Research Fellow. Boston University Arthritis Center (supervisor David T. Felson)
June-Aug 1999	Physician Examiner, Framingham Heart Study, Massachusetts USA
Nov 2000-	Staff Specialist, Rheumatology Unit, TQEH
Jan-Dec 2002	Maternity leave
Jan 2003-	Staff Specialist, Rheumatology Unit, TQEH
Dec 2006-	Medical Advisor, Adelaide Evaluation Group, Dept of Public Health, University of Adelaide

Teaching

1993-1998	Undergraduate medical students (3rd, 4th, 6th year)
1994-1998	Postgraduate physician trainees
2000-	Undergraduate medical student (2^{nd}, 4-6^{th} year)
2000-	Postgraduate physician trainees

Presentations

1993,1994,1995,1997, 2001, 2002, 2008 Australian Rheumatology Association (SA Branch) Annual Scientific Meeting
1994 Australian Rheumatology Association Annual Scientific Meeting, Melbourne

2. Hill CL, Gill TK, Appleton S, Cleland L, Taylor AW, Adams RJ (2008). The use of fish oil in the community: Results of a population-based study. Rheumatology (Oxford) (Manuscript accepted for publication November 21st 2008)
3. Adams RJ, Stocks N, Wilson DH, Hill CL, Gravier S, Kickbusch I, Beilby J (2008) Health Literacy: A new concept for general practice? Aust Fam Physician (Accepted for publication September 9th 2008)
4. Cole A, Gill T, Shanahan EM, Phillips P, Taylor AW, Hill CL. (2008) The associations of shoulder pain and diabetes in a population-based cohort study J Rheumatol November 15 (Epub ahead of print)
5. Menz H, Gill T, Taylor AW, Hill CL (2008) Predictors of podiatry attendance in a population-based cohort study. J Foot Ankle Res 1:8.
6. Hill CL, Lu TY, Cervelli M, Mathew T. Failure of rasburicase therapy in patient with recurrent acute gout with tophi. International Journal of Rheumatic Diseases (Manuscript accepted for publication, July 26th, 2008)
7. Hill CL, Gill T, Menz H, Taylor AW (2008). The prevalence and associations of foot pain in a population-based cohort study J Foot Ankle Res 1:2.
8. Adams RJ, Appleton S, Hill CL, Wilson DW, Taylor AW, Dal Grande E, Chittleborough C, Gill T, Ruffin R (2008). Independent association of HbA1C and incident cardiovascular disease in people without diabetes. Obesity (Manuscript accepted for publication, May 31st, 2008)
9. Adams RJ, Tucker G, Hugo G, Hill CL, Wilson DH (2008). Projected future trends of hospital service use for selected obesity-related conditions. Obesity Research & Clinical Practice 2:133-141.
10. Lu TY, Hill CL, Pontifex E, Roberts-Thomson (2008). Breast cancer and systemic sclerosis: A clinical description of twenty-one patients in a population-based cohort study Rheumatol Int 28:895-9.
11. Massy-Westropp N, Johnston R, Hill CL. (2008) Postoperative therapy for metacarpophalangeal arthroplasty. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD003522. DOI: 10.1002/14651858.CD003522.pub2. (Available at: www.thecochranelibrary.org)
12. Hill CL, Buchbinder R, Osborne RH (2007). The quality of reporting of RCT at the American College of Rheumatology Annual Scientific Meeting. J Rheumatol 34:2476-80.
13. Hill CL, Hunter DJ, Niu J, Clancy MM, Guermazi A, Genant H, Gale D, Grainger A, Conaghan PG, Felson DT (2007). Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Annals Rheum Dis 66:1599-603.
14. Proudman SM, Keen HI, Stamp LK, Lee ATY, Goldblatt F, Ayres OC, Rischmueller M, James MJ, Hill CL, Caughey GE, Cleland LG (2007). Response-driven combination therapy with conventional DMARDs can achieve high response rates in early rheumatoid arthritis with minimal glucocorticoid and non-steroidal anti-inflammatory drug use. Seminars in Arthritis and Rheumatism 37:99-111.
15. Hill CL, Gill T, Daly A, d'Espaignet E, dal Grande E, Adams RJ, Taylor A (2007). Psychological factors and quality of life in arthritis: a population-based study. Clin Rheumatol; 26:1049-54.
16. Pontifex E, Hill CL, Roberts-Thomson PJ (2007). Risk factors for lung cancer in patients with scleroderma: A nested case-control study Annals Rheum Dis 66:551-3.
17. Lu TY, Pink J, Chin M, Whitten L, Hill CL, Adams RJ, Marchant Y, Gibb C. (2006) A champion-driven pathway towards quality improvement in the medical management of osteoporotic fractures. MJA 185:341-2.
18. Plint AC, Moher D, Morrison A, Schulz K, Altman DG, Hill CL, Gaboury I. (2006) Does the CONSORT checklist improve the quality of reports of randomized controlled trials: A systematic review MJA ;185:263-7.
19. Lu T, Hill CL. (2006) Managing patients taking tumour necrosis factor inhibitors. Australian Prescriber;29:67-70.
20. Keen HI, Pile KD, Hill CL. (2005) The prevalence of under-powered randomized clinical trials in Rheumatology. J Rheumatol;32:2083-8.
21. Bayat N, Keen HI, Hill CL. (2005) Randomized clinical trials of osteoarthritis: a review. APLAR J Rheumatol;8:171-7.

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26. Hill CL, Nguyen A, Roder D, Roberts-Thomson PJ. (2003) Risk of cancer in patients with scleroderma: A population-based cohort study. Annals of the Rheumatic Diseases;62 728-731.
27. Iyngkaran P, Limaye V, Hill C, Henderson D, Pile KD, Rischmueller M. (2003) Rheumatoid vasculitis following influenza vaccination. Rheumatology;42:907-9.
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30. Hill CL, La Valley MP, Felson DT. (2002). Secular changes in the quality of published randomized clinical trials in rheumatology. Arthritis Rheum;46:779-84.
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33. Felson DT, Chaisson CE, Hill CL, Gale DG, Kazis L, Tottermann S. (2001) Bone marrow lesions in knee osteoarthritis Ann Intern Med;134:541-9.
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35. Hill CL, Roberts-Thomson P, Pollard A, Gillis D, Kirkham B. (1996) Clinical associations of anti-lamin autoantibodies. Aust NZ J Med;26:162-166.
36. Hill CL, Romas E, Kirkham BW. (1996) Use of sequential DTPA clearance and high resolution computerised tomography in monitoring interstitial lung disease in dermatomyositis. Br J Rheum;35:164-166.
37. Cleland LG, Hill CL, James M. (1995) Diet and arthritis. In 'Innovative Treatment Approaches for Rheumatoid Arthritis' Bailliere's Clinical Rheumatology;9:771-785.
38. Hill CL, Pile K, Henderson DRF, Kirkham BW (1995). Neurological effects of gold. Br J Rheum;34:989-990.
39. Hill CL, Zeitz C, Kirkham BW. (1995). Dermatomyositis with lung involvement in a patient receiving simvastatin. Aust NZ J Med; 25:745-6.
40. Alderman CP, Hill CL. (1994) Abnormal bone metabolism after long-term anticonvulsant treatment. Ann Pharmacother ;28:47-48.

Book Chapters

Hill CL, Cleland LG. (1996) Prostaglandins in 'Meyler's Side Effects of Drugs' Elsevier Science

Journal Reviewer

Annals of Internal Medicine
Archives of Medical Research
APLAR Journal of Rheumatology
Arthritis & Rheumatism
Arthritis Care & Research
Clinical Trials: Journal of the Society for Clinical Trials
International Journal of Evidence-based Healthcare

Journal of Rheumatology
Lancet Oncology
Obesity Research and Clinical Practice
The Journal of the National Cancer Institute
Reviewer, Australian Medicines Handbook 2008-

Grant Reviewer
Arthritis Australia (2006, 2007, 2008)
NHMRC (2004)

Abstract Reviewer
American College of Rheumatology Annual Scientific Meeting Abstracts (Category: Epidemiology) 2006

Appendix D.

Statement of Medical Achievements

Research

I am a clinical rheumatologist and epidemiologist. I was awarded the AFA/Heald Scholarship in 1998, which enabled me to undertake research work at Boston University Arthritis Center from 1998-2000. I was awarded the degree of MSc in Epidemiology from Boston University in May 2000 and was admitted to Delta Omega Society (Alpha Beta Chapter) for high achievement in Masters program. This comprised 50% coursework exclusively related to epidemiology and biostatistics and 50% research thesis. The substantive work of the thesis was published in the *Lancet* (Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A, Evans SR, Felson DT. Frequency of specific cancer types in dermatomyositis and polymyositis: Combined population data from three Nordic countries. Lancet 2001; 357:96-100). The research work was performed under the supervision of Professor David Felson and Dr Yuqing Zhang. Whilst in Boston, I also undertook studies on the quality and methodology of rheumatology randomized clinical trials and was an investigator on the Boston Osteoarthritis of the Knee Study (BOKS), a longitudinal study of knee OA progression using MRI. This interest has continued since returning and I have continued to publish in these areas. Since returning from Boston in 2000, I have had 2 periods of maternity leave (May-Nov 2000 and Jan-Dec 2001) and have worked part time (0.6FTE) since 2000 to allow time to care for young children. Despite this, I have published 40 papers in major international journals with a total of over 690 citations.

My research interests fall into four major areas:

Knee osteoarthritis

Whilst in Boston, I was an investigator on the Boston Osteoarthritis of the Knee Study (BOKS), a longitudinal cohort study of knee OA progression using MRI and other outcome measures. This community-based cohort study has been fruitful in its contribution to the knowledge of the natural history of knee osteoarthritis. In addition to recruitment of people with symptomatic knee OA, 80 with no symptoms also underwent knee MRI. The focus of my work within this cohort has been investigation of the contributing factors to the pain of knee OA which has been elusive, given that cartilage, the loss of which is the main pathological finding in OA, is aneural. The collaboration with Professor Felson and his group at Boston University has continued since my return to Adelaide, as I have been able to continue reading MRIs and analysis of BOKS data since returning.

This interest has culminated in the award of a 3 year NHMRC-funded project grant to study the effects of fish oil supplementation on symptoms and structural progression in knee osteoarthritis in a multicentre RCT using MRI ($618,625; PI: Catherine Hill, CI Prof Leslie Cleland, A/Prof Lyn March, Prof Graeme Jones).

I have collaborated with Dr Richard Osborne, Prof Stephen Graves, and Prof Rachelle Buchbinder on an Arthritis Australia-funded study of 'Quality of Life and disability of people waiting for joint replacement surgery'.

Relevant publications:

1. Hill CL, Hunter DJ, Niu J, , Clancy MM, Guermazi A, Genant H, Gale D, Grainger A, Conaghan PG, Felson DT. Synovitis detected on magnetic resonance imaging and its relation to pain and cartilage loss in knee osteoarthritis. Ann Rheum Dis 2007;66:1599-603.
2. Osborne RH, Buchbinder R, Hill CL, Ackerman IN, Wengier L. Prioritization for joint replacement: Head to head comparison for the Victorian Hip and Knee Questionnaire and the New Zealand Priority Criteria. Int Med J 2007; 37(Suppl 2):A50.

Australia) dataset, a telephone survey of health and well-being in 7500 individuals in relation to arthritis (ref 2). As part of the Arthritis Subgroup of the North West Adelaide Health Study (other members: AW Taylor, TK Gill, EM Shanahan), I have facilitated the inclusion of data collection on musculoskeletal disease in the NWAHS study (a longitudinal cohort study of 4000 randomly selected individuals in the North-West area of Adelaide). This will provide accurate estimates of musculoskeletal burden in this population-based cohort. The second round of clinical examinations has recently finished and data was chosen for an oral presentation at the 2006 American College of Rheumatology Annual Scientific Meeting in Washington DC.

Relevant publications:

1. Hill CL, Gill TK, Appleton S, Cleland L, Taylor AW, Adams RJ (2008). The use of fish oil in the community: Results of a population-based study. Rheumatology (Oxford) (Manuscript accepted for publication November 21st 2008)
2. Cole A, Gill T, Shanahan EM, Phillips P, Taylor AW, Hill CL. (2008) The associations of shoulder pain and diabetes in a population-based cohort study J Rheumatol November 15 (Epub ahead of print)
3. Menz H, Gill T, Taylor AW, Hill CL (2008) Predictors of podiatry attendance in a population-based cohort study. J Foot Ankle Res 1:8.
4. Hill CL, Gill T, Menz H, Taylor AW (2008). The prevalence and associations of foot pain in a population-based cohort study J Foot Ankle Res 1:2.
5. Hill CL, Gill T, Daly A, d'Espaignet E, dal Grande E, Adams RJ, Taylor A (2007). Psychological factors and quality of life in arthritis: a population-based study. Clin Rheumatol 26:1049-54.
6. Hill CL, Parsons J, Taylor A, Leach G. (1999). Health related quality of life in a population sample with arthritis J Rheumatol;26:2029-35.

Cancer and Connective Tissue Diseases

Since publication of the study of the frequency of specific cancer types in dermatomyositis and polymyositis as my thesis, I have continued research in the area of the associations between connective tissue disease and malignancy, by collaborating with Professor Peter Roberts-Thomson (Flinders Medical Centre) by linking the South Australian Cancer Registry with the South Australian Scleroderma Registry. This fruitful collaboration has produced 3 manuscripts. Current research in this area is continuing in a study of the association between biopsy-proven temporal arteritis and malignancy, using data from RAH, FMC and TQEH with linkage to the SA Cancer Registry. This data was recently presented at the Australian Rheumatology Association (SA Branch) Annual Clinical and Scientific Meeting in November 2008.

Relevant publications:

1. Lu TY, Hill CL, Pontifex E, Roberts-Thomson (2008). Breast cancer and systemic sclerosis: A clinical description of twenty-one patients in a population-based cohort study. Rheumatol Int 28:895-9.
2. Pontifex E, Hill CL, Roberts-Thomson PJ (2007). Risk factors for lung cancer in patients with scleroderma: A nested case-control study. Annals Rheum Dis 66:551-3.
3. Hill CL, Nguyen A, Roder D, Roberts-Thomson PJ. (2003) Risk of cancer in patients with scleroderma: A population-based cohort study. Annals of the Rheumatic Diseases;62 728-731.
4. Buchbinder R, Hill CL. (2002) Malignancy in patients with inflammatory myopathy. Current Rheumatology Reports Oct;4(5):415-26
5. Hill CL, Zhang Y, Sigurgeirsson B, Pukkala E, Mellemkjaer L, Airio A, Evans SR, Felson DT. (2001) Frequency of specific cancer types in dermatomyositis and polymyositis: Combined population data from three Nordic countries. Lancet; 357:96-100.

Other research-related activities

I currently review for a number of international journals (including *Arthritis & Rheumatism, Arthritis Care and Research, Journal of Rheumatology, Annals of Internal Medicine, Archives of Medical Research, Clinical Trials: Journal of the Society for Clinical Trials, Lancet Oncology* and *The Journal of the National Cancer Institute*). I have been a grant reviewer for NHMRC and am currently on the Grant Review Committee for Arthritis Australia. Most recently, I was an abstract reviewer (subsection: epidemiology) for the American College of Rheumatology Annual Scientific Meeting in Washington DC.

Teaching

I am involved with undergraduate and postgraduate teaching at a number of levels. She currently teaches 4th year medical students as part of the Orthopaedic/Rheumatology Program which involves outpatient teaching and tutorials on osteoarthritis and evidence-based rheumatology. This involves critical appraisal of rheumatology randomized clinical trials with teaching of RCT methodology to allow application to appraisal of trials in other specialties. During general medicine ward service, she also teaches 4th year medical students on general medical rotations. I have previously been involved in 4th and 6th year clinical examinations.

Postgraduate teaching includes short case teaching of rheumatology to physician trainees and supervision of advanced trainees in rheumatology in both clinical and research areas. I have supervised 5 advanced trainees in rheumatology with research projects that have culminated in presentations at national or international meetings and publications.

Other Activities

Since 2004, I have been a member of the Australian Drug Evaluation Committee (ADEC) of the Therapeutic Goods Administration (TGA) which advises the Health Minister on registration of new drugs for the Australian market. I am Chair of the TQEH Drug & Therapeutics Committee and a member of the Clinical Trial Subcommittee of TQEH Human Ethics Committee. In late 2006, I joined the Adelaide Evaluation Group of the Department of Public Health, University of Adelaide, as medical advisor which provides evaluation of pharmaceutical products for the Pharmaceutical Benefits Advisory Committee (PBAC). Most recently, I have been a reviewer for the Australian Medicines Handbook.

I am currently President of the SA Branch of Australian Rheumatology Association and on the Australian Rheumatology Association Federal Council. From 2004-5, I was the secretary of the Australian Rheumatology Association (SA Branch). I am a member of the Australian Rheumatology Association Database (ARAD) Committee, which collects surveillance data on the effectiveness and adverse events of TNF-blockers in patients with rheumatic diseases.

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