

TECHNISCHE UNIVERSITÄT MÜNCHEN  
Klinikum rechts der Isar  
Institut für Röntgendiagnostik  
(Direktor: Univ.-Prof. Dr. E. J. Rummeny)

Analysis of the Osteoarthritis Initiative Incidence Cohort:  
Patellar Cartilage T2 and Focal Knee Pathology  
Derived from 3T MRI in Relation to Physical Activity

Hans Liebl

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1. Univ.-Prof. Dr. E. J. Rummeny
2. Assoc. Prof. Dr. T. M. Link,  
University of California, San Francisco / USA

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## Abbreviations:

ACL = anterior cruciate ligament

BME = bone marrow edema like lesions

BMI = body mass index

CV = coefficient of variation

CNR = contrast to noise ratio

DESS = dual-echo in steady state

dGEMRIC = delayed Gadolinium-Enhanced MR Imaging of Cartilage

ECM = extracellular matrix

FLASH = fast low angle shot gradient echo sequence

FOV = field of view

FS = fat suppression

FSE = fast spin-echo

GAG = glycosaminoglycan

gagCEST = glycosaminoglycan chemical exchange dependent saturation transfer

IW = intermediate-weighted

JSW = joint space width

KL = Kellgren-Lawrence grading

KOOS = Knee injury and Osteoarthritis Outcome Score

ME = multi-echo

MRI = magnetic resonance imaging

MTC = Magnetization Transfer Contrast

NIH = National Institutes for Health

NSAIDs = non-steroidal anti inflammatory drugs

NSF = nephrogenic systemic fibrosis

OA = osteoarthritis

OAI = the Osteoarthritis Initiative

PASE = Physical Activity Scale of the Elderly

PG = proteoglycan

QA = quality assurance

SAR = signal absorption rate

SE = spin-echo

SI = signal intensity

SNR = signal to noise ratio

SPGR = spoiled gradient echo sequence

T = Tesla

T1 rho = T1 relaxation time

T2 = T2 relaxation time

T2\* = T2 signal decay based on a gradient echo sequence

TENS = trans cutaneous electric nerve stimulation

UCSF = University of California San Francisco

UTE = ultra short echo time acquisition

WE = water excitation

WOMAC = Western Ontario and McMaster Osteoarthritis

WORMS = Whole-Organ Magnetic resonance imaging Score

## 1 Introduction

*Osteoarthritis* (OA) is a multifactorial degenerative joint disease and a leading cause of disability worldwide. 12.1% of the US population ages 25–74 years have clinically defined OA of some joint with the knee being the site most commonly affected [79]. OA is characterized by typical imaging characteristics on conventional radiographs and *magnetic resonance imaging* (MRI) including osteophytes, joint space narrowing, cartilage defects, meniscal and ligamentous abnormalities, bone marrow edema like lesions as well as subchondral cysts [79, 91]. Multiple risk factors have been linked to OA in epidemiology studies including age, female gender, obesity, sports activities, previous injury, proprioceptive deficits and genetic elements such as calcium crystal deposition disease. A number of studies examined these risk factors in relation to quantitative and qualitative cartilage loss determined with MRI [23, 32, 39, 41, 133]. However, there is a paucity of data analyzing cartilage degeneration in relation to *physical activity* using MRI. Knowledge of the effect physical activity has on the risk for developing OA is limited, as studies investigating its effect on weight-bearing joints have reported conflicting results [19, 149, 152].

To better understand the natural evolution of OA using MRI the National Institutes of Health NIH launched the *Osteoarthritis Initiative (OAI)*, a longitudinal, observational multicenter study enrolling up to 5,000 patients. The study aims to create a public archive of data, biological samples and joint images at four recruitment centres across the United States, focusing primarily on knee OA.

Early biological processes of cartilage degeneration are known to precede clinical symptoms of OA. Among other things, an alteration of proteoglycan (PG) turnover and elevation of cartilage water content [117]. Changes in the cartilage matrix are therefore an early and key finding in the evolution of OA. Magnetic Resonance Imaging (MRI) is currently the best-established and standard non-invasive diagnostic technique to assess the *cartilage matrix*. Since hyaline cartilage does not regenerate and cartilage loss is irreversible, it would be crucial to diagnose degeneration at the earliest time possible or even before significant cartilage loss occurs. MR biomarkers were developed to characterize the cartilage matrix with one of the most frequently used parameters being *T2 relaxation time measurements*. The estimation of T2 values yields information concerning cartilage biochemical composition: it is sensitive to a wide range of water interactions in tissue and

therefore in particular depends on the content, orientation and anisotropy of collagen [137]. A T2 mapping sequence was also acquired as part of the OAI MRI protocol. Considerable efforts have been taken to develop treatment strategies and thus prevent disease progression including altering physical activity, weight control, pain relief techniques, pharmacological therapy as well as surgical interventions [5, 40]. Characterization of the cartilage matrix with T2 relaxation time measurements may potentially help in the prevention of OA progression by identifying individuals at risk for OA that may benefit from treatment, before irreversible structural changes occur. In addition this technique could also be applied to monitor the progression of the degenerative changes or to evaluate the efficacy of treatment efforts.

## 2 Specific Aims

To our knowledge, there is no conclusive data on the impact of physical activity on the onset of OA. Thus the aim our research was (i) to assess the prevalence of cartilage damage, meniscal and ligamentous as well as bone marrow edema like lesions (BME) in middle-aged patients (45 - 55 years) with high and low levels of physical activity and no clinical symptoms of pain. Furthermore our goal was to correlate patellar cartilage T2 with (ii) pathologies found in focal cartilage, menisci and ligaments on 3.0 Tesla (T) MR examinations of the knee, as well as with (iii) physical activity level.

We hoped to find evidence to suggest that vigorously physically active individuals will show a significantly higher number and larger size of abnormalities than sedentary subjects. We also tried to identify whether T2 measurements of the patellar cartilage could be used to differentiate subjects with focal abnormalities from those without joint pathology. In addition, we sought to give proof that new MRI techniques such as T2 relaxation time measurements allow the assessment of degenerative joint disease at earlier stages, before significant amounts of cartilage are lost and when preventive and therapeutic interventions may potentially prove most useful.

## 3 Background

### 3.1 Osteoarthritis

#### 3.1.1 Etiology of Osteoarthritis

Osteoarthritis (OA) was previously thought to be a normal consequence of aging and was often referred to as degenerative joint disease. Today it is accepted that OA results from an interplay of a variety of factors, including joint integrity, mechanical forces, genetics, local inflammation, as well as cellular and biochemical processes. Since mature chondrocytes do not divide and the numbers of progenitor cells is limited, the capabilities of cartilage tissues to regenerate are poor. Once the articular cartilage matrix is disrupted and substance loss occurs, the cartilage integrity is inevitably damaged and consolidation results in scar tissue of different biochemical composition with altered functional properties. Subsequently neighbouring articular surface areas and the other joint compartments have to compensate the changes in loading and mechanical stress distribution, leading to an increased risk for further degeneration and cartilage loss creating a vicious cycle.

Given the irreversible nature of cartilage defects in OA, it is even more crucial to identify modifiable elements that could potentially prove useful for the treatment of the disease. Factors that lead to subsequent chronic overloading of the weight-bearing joints have been identified such as obesity and misalignment. Other risk factors known to increase the risk of OA include acute injury or trauma, such as meniscal tears [23]. In addition, invasive iatrogenic processes such as arthroscopy and surgery may be triggering cartilage degeneration. Aside from chronic overload also chronic unloading seems to disturb cartilage function and may result in pathology related to OA [97, 136]. Summarizing, any major disturbance of the delicate balance between biomechanical forces on the one side and physiological chondrocyte function on the other side may eventually result in OA.

OA initiates with damage to the collagen-proteoglycan matrix and elevation of cartilage water content, before progressive loss of hyaline articular cartilage and clinical symptoms occur [86]. OA does not only affect the articular cartilage, but involves the entire joint, including the subchondral bone, capsule, synovial membrane, synovial fluid, ligaments, and adjacent muscles. The knee is the site most commonly affected with an incidence of about 240 per 100,000 individuals a year,

followed by hand OA (100/100,000 individuals) and hip OA (88/100,000 individuals) [69]. Key to OA research is the identification of potentially modifiable risk factors related to the onset and progression of OA, to allow for early diagnosis and reliable monitoring.

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### 3.1.2 Osteoarthritis and Physical Activity

Joint health depends on a variety of influences including genetic factors such as anatomic joint alignment and cartilage composition, but also lifestyle related factors such as different levels of biomechanical stress and metabolic conditions. Physical activity is one of the OA risk factors most controversially discussed. The effect of different levels of physical activity on OA remains unclear, as some studies suggest a detrimental effect on articular cartilage [20] and have demonstrated a high number of cartilage abnormalities in athletes [63, 93], while others report no associated risks [19]. Contrary to that, some studies have even found beneficial effects of exercise on OA [128]. While it is known that healthy cartilage depends on moderate amounts of loading to develop and function properly, excessive stress may initiate or accelerate cartilage degeneration [55, 129]. Excessive physical activity may also enforce the impact of other known risk factors such as genetic predisposition, misalignment, previous knee surgery or injury. The conflicting findings could therefore be in part explained by the different selection criteria applied for the individual studies, and isolated risk factors chosen.

Aside from its relevance to the development of OA however, physical activity is of tremendous importance at a societal level. Recreational sport is known to be beneficial to the cardiovascular system and elderly persons who engage in running and exercise regularly show lower mortality rates and are less likely to develop disability compared to members of the general population [43]. As our societies age, more and more people live active lifestyles and remain engaged in recreational activities at older ages compared to previous generations. While certain activity levels may be well tolerated by some subjects, other individuals seem to be more prone to develop cartilage damage. Given the fact, that cartilage defects do not regenerate and heal in adults, elevated levels of exercise and physical activity may accelerate the process of cartilage degeneration, once cartilage defects are present. Vignon et al. found, that the risk for knee and hip OA correlates with intensity and duration of exposure to physical activities [153]. More active subjects with rigorous exercise

routines may therefore be more susceptible to joint damage and cartilage degeneration even at younger ages. Up to this day, there is no comprehensive understanding on how to best identify subjects at increased risk for osteoarthritis. As physical activity is one of the few OA related risk factors that is comparably easy to influence in daily life, the investigation of its effect on the development of OA as well as the quantification of individually tolerable exercise levels are of crucial interest. In summary, the interplay of factors is not understood well enough. In particular, there is a paucity of data investigating how different levels of habitual physical activity affect knee articular cartilage in asymptomatic subjects.

## 3.2 Diagnostic Techniques

### 3.2.1 Radiographic Appearance of Osteoarthritis

Radiography has long been accepted as easily available and affordable diagnostic standard for the assessment of osteoarthritis. The method most widely used to monitor progression of knee OA is the sequential assessment of the joint space width (JSW) on plain radiographs.

In addition to joint space width narrowing, X rays of the affected joint can also show other pathologies associated with OA. The Kellgren-Lawrence (KL) Score evaluates signs of OA on plain radiographs based on joint space width narrowing and osseous changes as demonstrated in Figure 1. A KL grade of 1 represents doubtful narrowing of the joint space and possible osteophytic lipping. KL grade 2 requires the presence of definite osteophytes and definite narrowing of the joint space. A KL grade of 3 represents moderate multiple osteophytes, definite narrowing of the joint space, some sclerosis and possible deformity of the bone contour. Finally, a KL grade of 4 presents with large osteophytes, marled narrowing of the joint space, severe sclerosis and definite deformity of the bone contour [65].

However, plain radiography is limited in the depiction of cartilage tissue and may not show early cartilage degeneration, before much cartilage substance loss has taken place. The natural history of OA limits the ability to see the earliest changes associated with degeneration on plain film radiography, such as disruptions of the cartilage matrix. The onset of biochemical changes leading to irreversible cartilage loss and the corresponding radiographic signs may be several years apart. Valuable

time is lost, that would potentially allow for therapeutic interventions or to modify risk factors at the earliest stages. Another limitation of radiography is its two dimensionality, as the angle in which the X rays are taken may affect the precision of this method [28]. Exemplary X ray images illustrating pathology associated with OA are demonstrated in Figure 1.

**Figure 1: Radiographic changes associated with osteoarthritis**



Anteroposterior (Top) and Lateral (Bottom) Radiographs of Knees with KL scores of 1–4. A, Knee with a KL score of 1 with minimal Osteophytes at the Medial Femoral Condyle (Arrowhead in Anteroposterior View) and the Patellar Joint Surface (Arrowhead in Lateral View) and Sharpening of the Medial Tibial Spine (Arrow). B, Knee with a KL score of 2 with small but definite Osteophytes (Arrows) but unimpaired Joint Space (Anteroposterior View). C, Knee with a KL score of 3 with moderately impaired Joint Space (Arrow) and Osteophytes (Arrowheads). D, Knee with a KL score of 4 with substantially impaired Joint Space (Arrow), severe Osteophytes (white Arrowheads), and Sclerosis of Subchondral Bone (black Arrowhead). Figure was obtained from Reference [91].

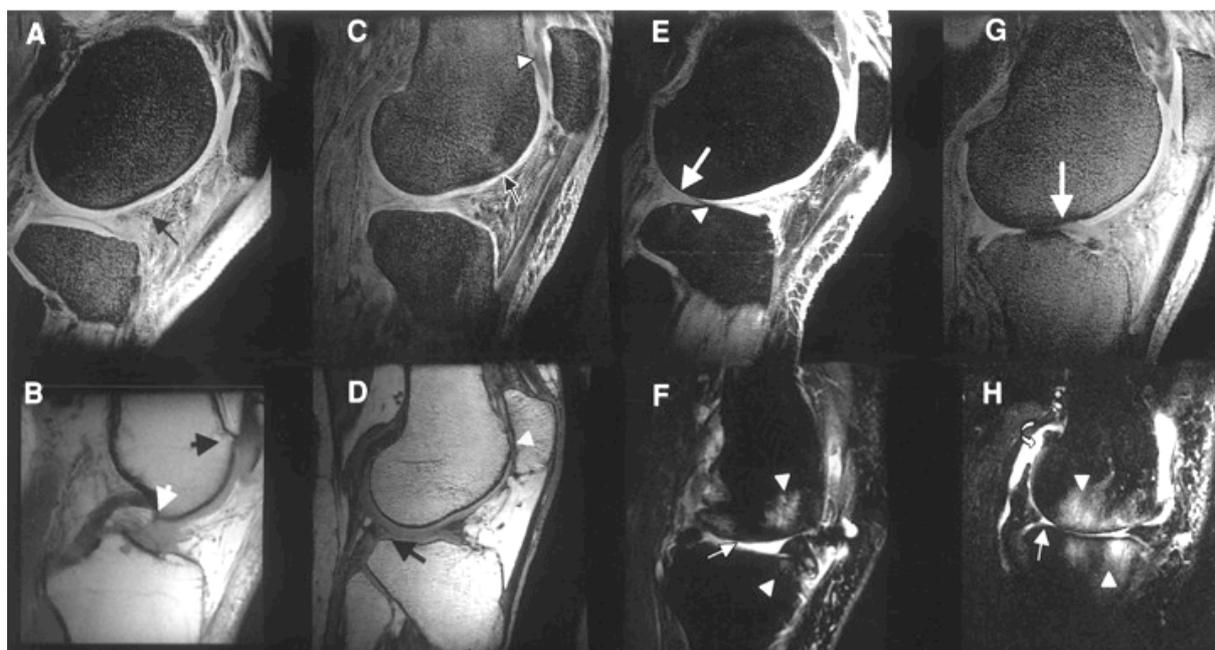
### 3.2.2 Appearance of Osteoarthritis in MRI

Magnetic resonance imaging is a powerful tool for the detection, location and the grading of OA, exceeding by far the limited possibilities as provided by radiography, depicting morphology only. The more widespread clinical use of high field MRI at 3T is particularly advantageous, increasing the signal to noise ratio (SNR), allowing for thinner sections and higher spatial resolutions resulting in better visualization of anatomical structures and pathologies [119]. There has been discussion about the

best-suited sequences for cartilage imaging: gradient echo sequences such as FLASH (fast low angle shot) and SPGR (spoiled gradient echo) and intermediate- and T2-weighted FSE sequences with and without fat saturation have been the preferred sequences [46, 90, 115]. In a clinical setting, however, intermediate-weighted FSE sequences are currently the preferred sequences as demonstrated in multiple studies [25, 116, 162]. Aside from the sequences used, benefits of high-field MRI also heavily depend on suitable coils.

Pathologies most commonly associated with OA are changes in cartilage signal, cartilage thinning and loss, focal lesions at the cartilage surface and overall joint effusion. Furthermore, osseous changes like osteophytes, subchondral cysts and bone marrow edema like lesions may be present alongside with joint space width narrowing. Clinically speaking, joint pain and stiffness resulting in limited function and disability of movement are the most commonly encountered problems. Figure 2 demonstrates degenerative changes as detectable in plain radiography as well as morphological changes typically found on MR images in OA patients. More detailed illustrations of morphological abnormalities associated with knee osteoarthritis are given in the following (please see 3.2.3 *Cartilage Scoring Techniques*).

**Figure 2: Osteoarthritis related Pathology as Demonstrated on MRI**



**Sagittal MR images with representative Findings in knees with KL scores of 1–4. A and B: Knees with a KL score of 1. A: Fat-suppressed spoiled gradient-echo (SPGR) Image depicting Cartilage Thinning (Arrow) of less than 50% at the Femur. B: T1-weighted spin-echo Image showing mild Osteophytes (Arrows) at the Femur. C and D: Knees with a KL score of 2. C: Fat-suppressed SPGR Image showing Cartilage Signal Intensity Alterations at the Femoral Condyle**

(Grade I) and Thinning of less (Grade IIa, Arrow) and more (Grade IIb, Patella) than 50% of the Cartilage. Additional Joint Effusion (Arrowhead) is pointed out. D: T1-weighted spin-echo Image depicting a Tear of the Posterior Horn of the Lateral Meniscus (Arrow) and Cartilage Thinning (Arrowhead) in the Femoropatellar Joint. E and F: Knees with a KL score of 3. E: Fat-suppressed SPGR image showing a Grade IIb Lesion (Arrow) at the Femoral Condyle and a Grade III Lesion (Arrowhead) of the Tibia. F: Fat-suppressed T2-weighted FSE Image showing Bone Marrow Edema (BME) like lesions (Arrowheads) of the Femur and the Tibia as well as Joint Effusion (Arrow). G and H: Knees with a KL score of 4. G: Fat-suppressed SPGR Image depicting Grade III Cartilage Lesions (Arrow) at the Femur and the Tibia. H: Fat-suppressed T2-weighted FSE Image showing severe BME (arrowheads) in the Femur and Tibia as well as Destruction of the Posterior Horn of the Medial Meniscus (Straight Arrow). Joint Effusion (Curved Arrow) extending into a Popliteal Cyst. Figure was obtained from Reference [91].

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### 3.2.3 Cartilage Scoring Techniques

A variety of grading methods and scores exists for the classification of pathologies associated with OA. In the following, different grading methods are outlined, that have been used for the assessment and monitoring of OA in arthroscopy and MRI evaluation.

#### *Outerbridge Classification*

Outerbridge et al. published an arthroscopic scoring system evaluating macroscopic changes of chondromalacia of the patella in 1961. The classification differentiates 4 grades: grade 1 with softening and swelling of the cartilage; grade 2 for fragmentation and fissuring in an area of half an inch in diameter or less; grade 3 for a lesion larger than half an inch in diameter; finally grade 4 if there is a full thickness defect with erosion of cartilage down to the subchondral bone [110].

#### *Noyes and Stabler*

As an alternative to the Outerbridge score Noyes and Stabler proposed a more detailed macroscopic scoring system including the following four additional variables: location, diameter and depth of the lesion, as well as integrity of the cartilage surface. In their classification system the description of the surface appearance was separated from the depth of involvement distinguishing three surface grades: grade 1 with intact articular cartilage surface; grade 2: articular cartilage surface damaged; grade 3: open lesion with exposed bone. Depending on the depth of involvement each grade can be further divided into subtype A or B (grade 2 A: less than one-half thickness / B: greater than one-half thickness; grade 3 A: any surface exposure with normal bone contour / B: cavitation or erosion) [108].

### *Recht (modified Noyes and Stabler)*

The modified Noyes and Stabler MRI classification as published by Recht et al. differentiates 4 grades: grade 1 cartilage lesions are characterized by a focal signal abnormality of the cartilage with or without swelling; grade 2A focal defects involve less than half of the cartilage thickness, whereas grade 2B lesions affect more than 50% of the articular cartilage thickness; grade 3 lesions involve the entire cartilage layer with the exposure of subchondral bone; grade 3A lesions are characterized by a normal bony surface, 3B lesions include an erosion of the bony surface. [121]

### *WORMS (Whole-Organ-MRI-Score)*

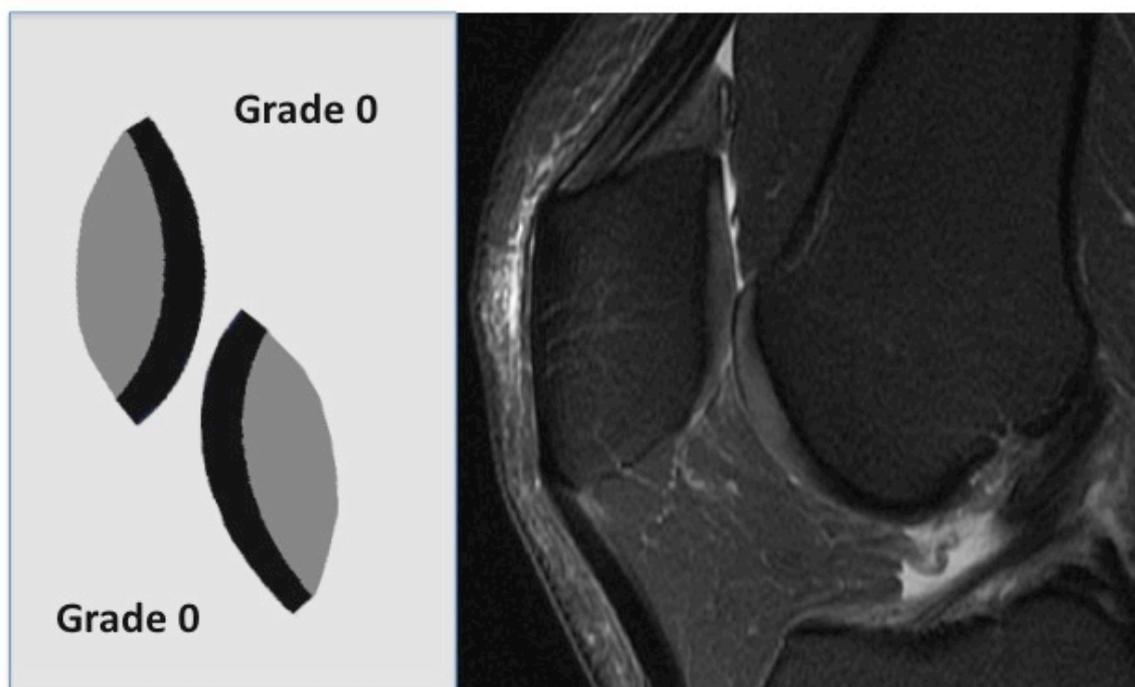
The whole-organ magnetic resonance imaging score (WORMS) differentiates 15 compartments. The cartilage WORMS score assesses both depth and size of the cartilage lesions using an eight-point scale: grade 1 lesions have a normal thickness but abnormal signal on fluid sensitive sequences; grade 2.0 lesions are partial-thickness focal defects, which are smaller than 1 cm in the greatest width; grade 2.5 are full-thickness focal defects smaller than 1 cm in greatest width; grade 3 lesions are defined as multiple areas of partial-thickness (Grade 2.0) defects intermixed with areas of normal thickness, or a Grade 2.0 defect wider than 1 cm but affecting <75% of the region; grade 4 lesions are diffuse partial-thickness lesions affecting more than 75% of the region); grade 5 lesions show multiple areas of full-thickness cartilage loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region and finally grade 6 lesions demonstrate more than 75% of the region full-thickness cartilage loss [112].

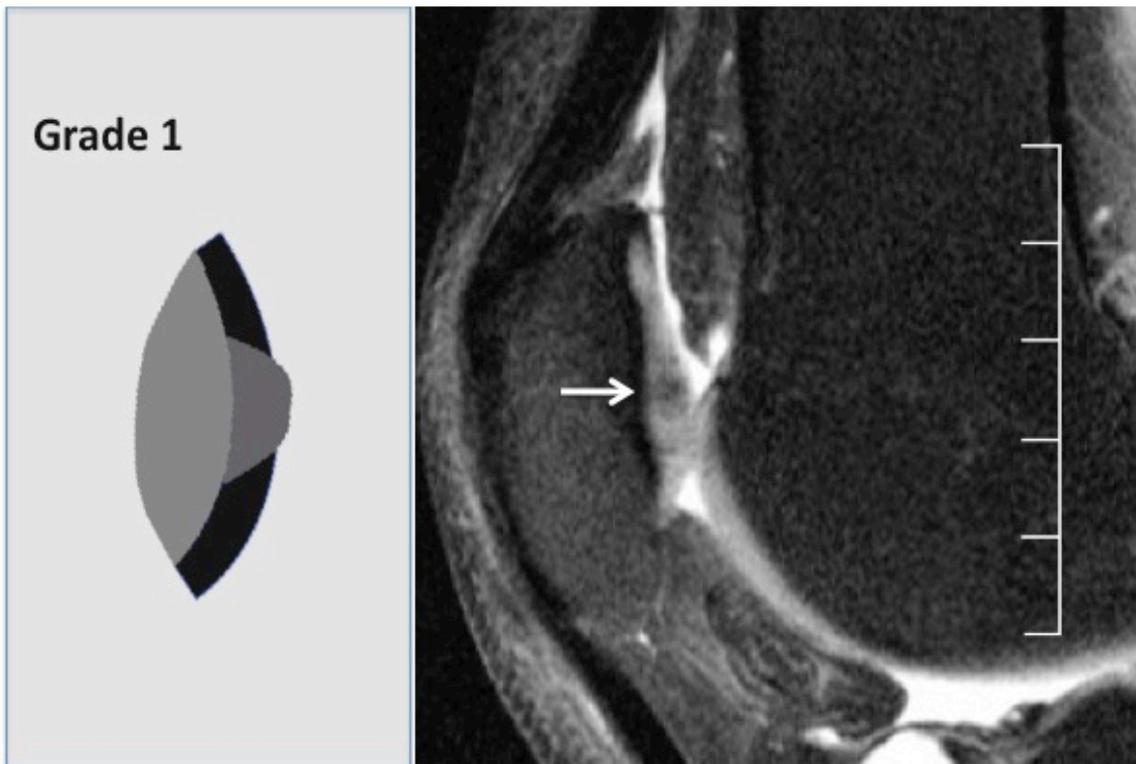
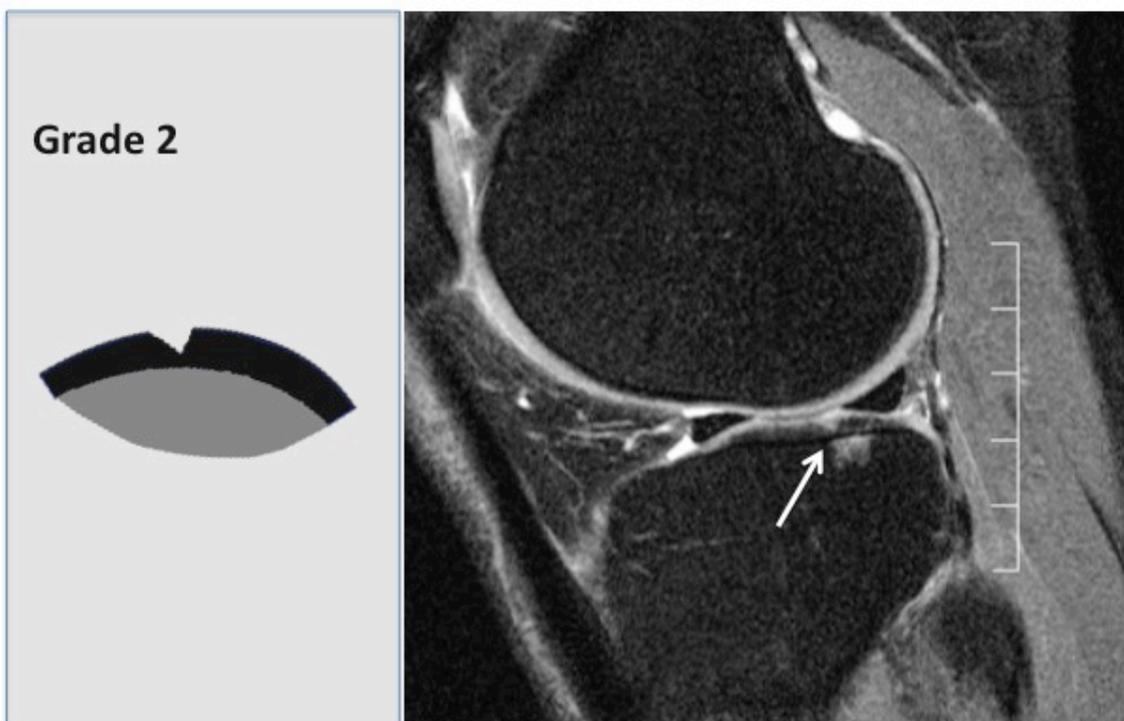
Alterations in meniscal morphology can also be assessed with the WORMS. The different meniscal regions (anterior and posterior horn as well as the body of both the medial and lateral meniscus) are graded separately from 0 to 4 based on both the sagittal and coronal images: grade 1 is defined as small radial tear or parrot-beak tear; grade 2 is defined as a non-displaced tear or prior surgical repair; grade 3 as a displaced tear (flap and bucket handle tears) or partial resection; finally grade 4: complete maceration/destruction or resection of the meniscus. Pathologies identified as intra-substance signal abnormality are not included in WORMS-scoring, but should be reported as they give important information about initiating degeneration. Meniscal extrusion can be graded separately as follows: 0 = none and 1 = meniscal extrusion of more than 3 mm beyond the tibial plateau.

Bone marrow edema like lesions (BME) can be evaluated in the subchondral bone and adjacent marrow if poorly margined areas of increased signal intensity are visible in the subchondral epiphyseal bone marrow on T2-weighted FSE FS MR images. BME can be graded on a four-point scale: 0 = none, 1 = 25% of the region or less, 2 = 25%–50%, and 3 = more than 50% involvement. Joint effusion can also be evaluated on a four-point scale: 0 = normal, 1 = less than 33% of maximum potential distention, 2 = 33% – 66% involvement; grade 3 = greater than 66%. The ligaments and tendons assessed by WORMS include the anterior cruciate ligament (ACL) and posterior cruciate ligament (PCL), the medial collateral ligament (MCL) and lateral collateral ligament (LCL), as well as the popliteus and patellar tendon. Mild abnormalities are defined as grade 1, grade 2 signifies signal abnormality of the tendon or ligament suggesting partial tear and grade 3 represents a complete tear, strain or sprain. Figures 3 A to N illustrate cartilage and meniscus pathology associated with OA graded by the WORMS score as published by Link [85].

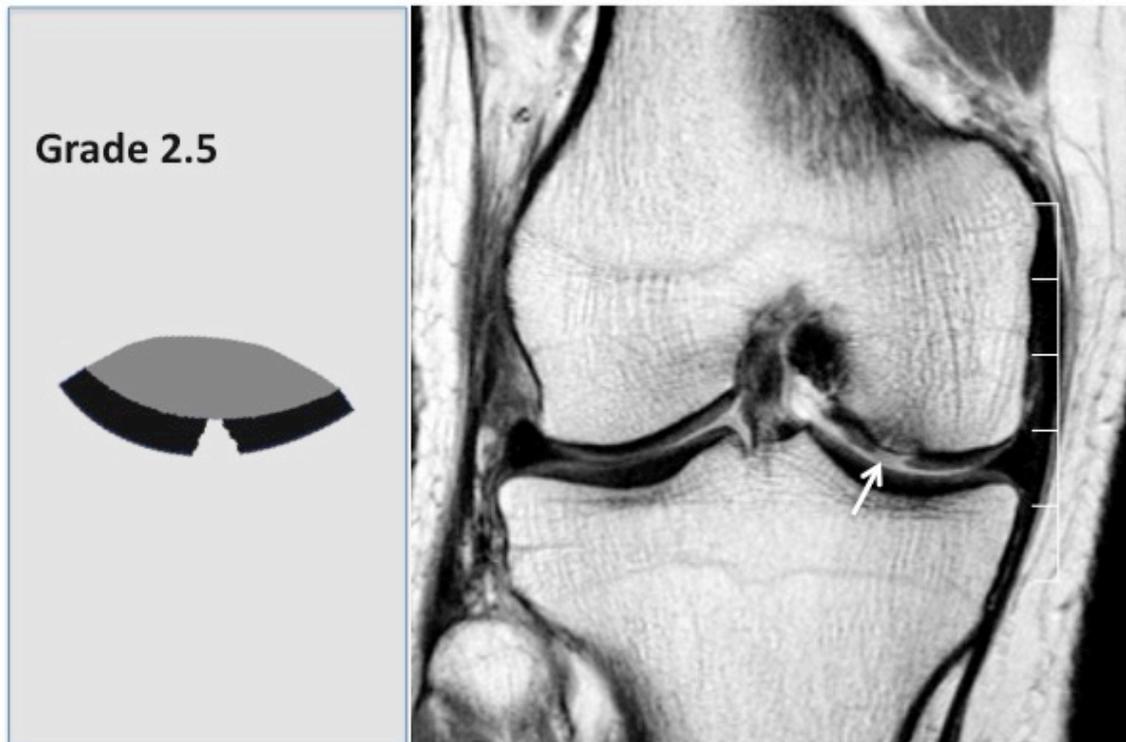
Figure 3 A-N: Illustrations of the WORMS Grading for Cartilage (3 A - H) and Meniscus Pathology (3 I - N)

A Normal Tibiofemoral Cartilage

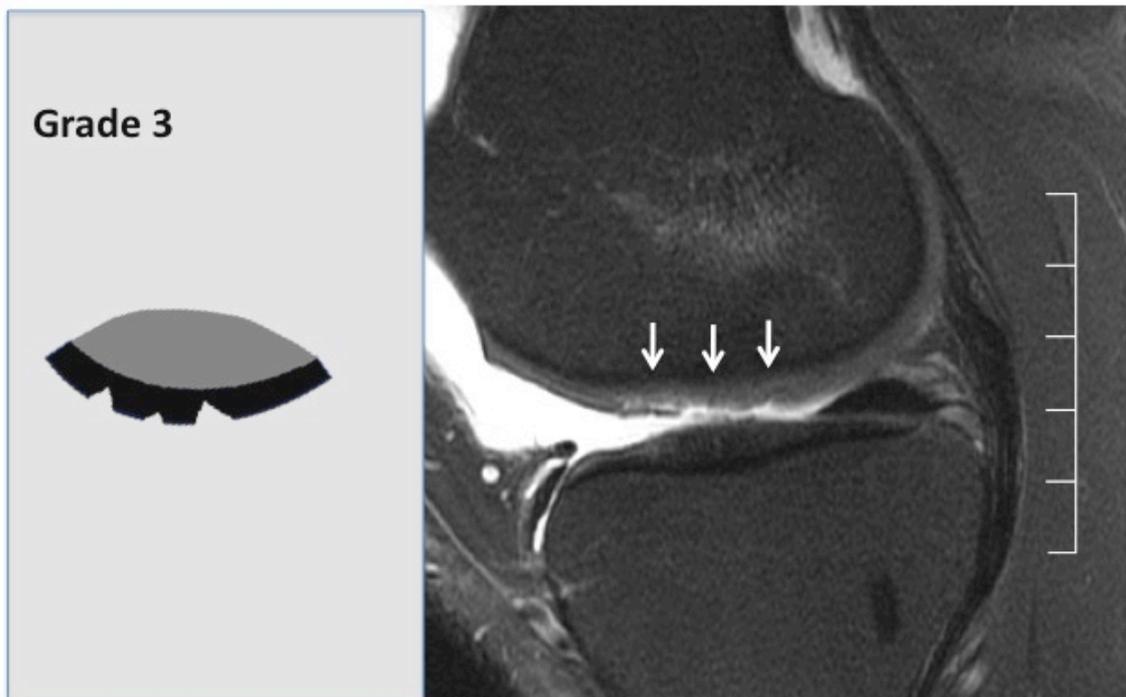


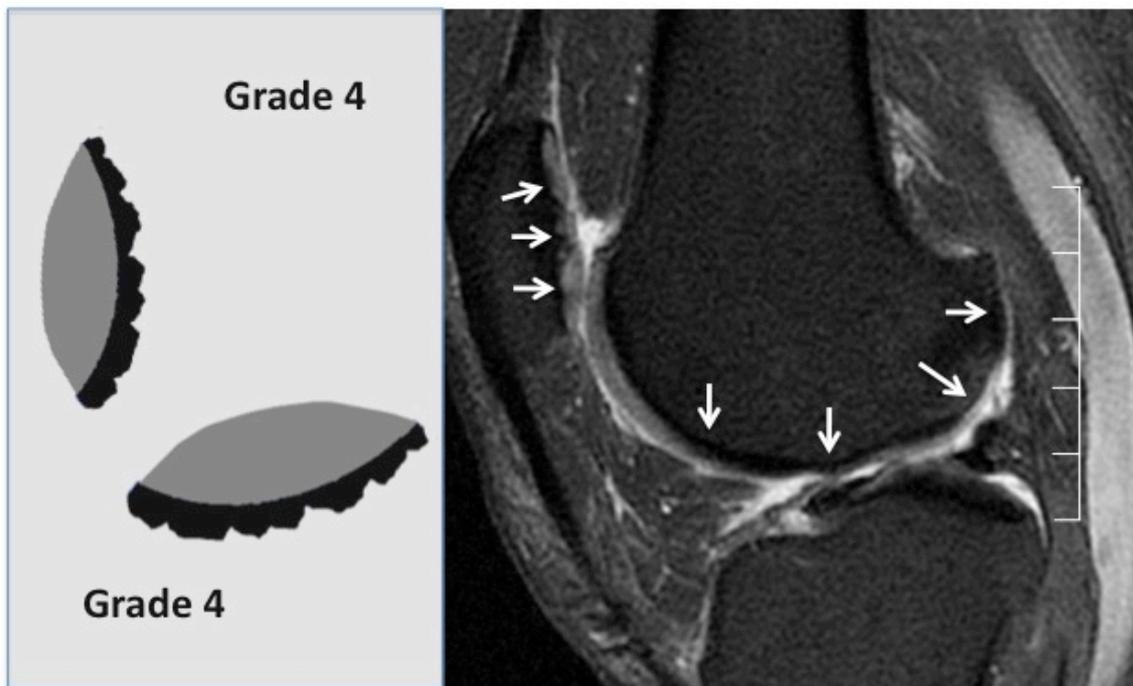
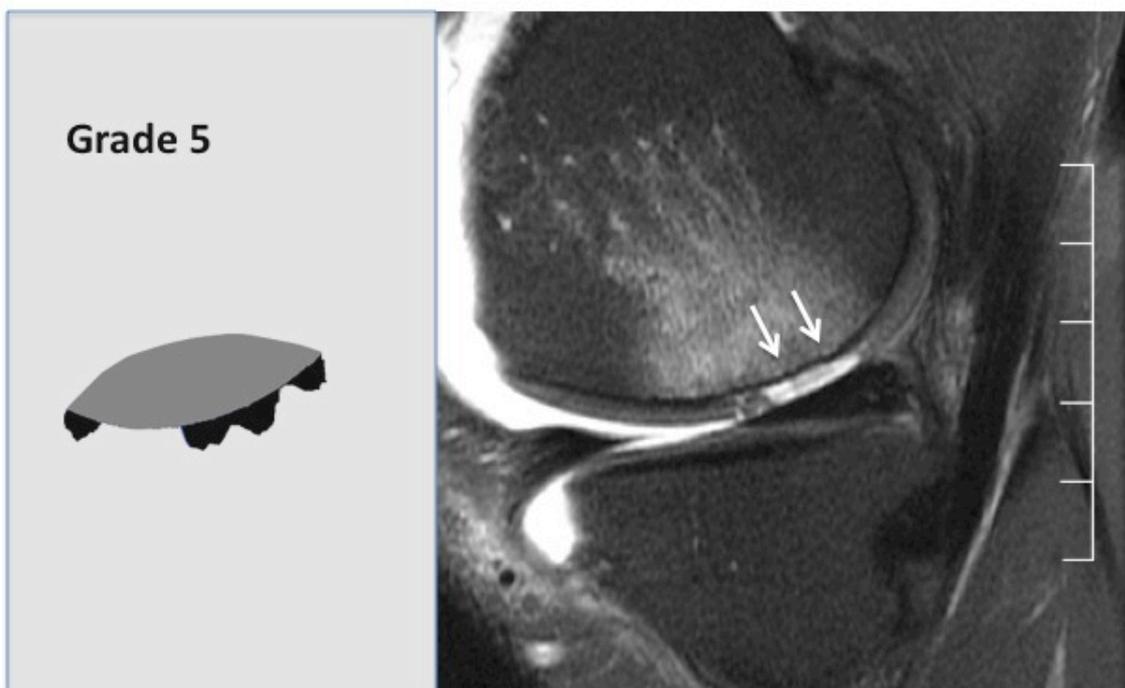
**B Signal Inhomogeneities within the Patellar Cartilage****C Partial Thickness Lesion < 1 cm in Size at the Lateral Tibia with underlying Bone Marrow Edema like Lesion**

D Full-thickness Lesion <1 cm at the Medial Femoral Condyle

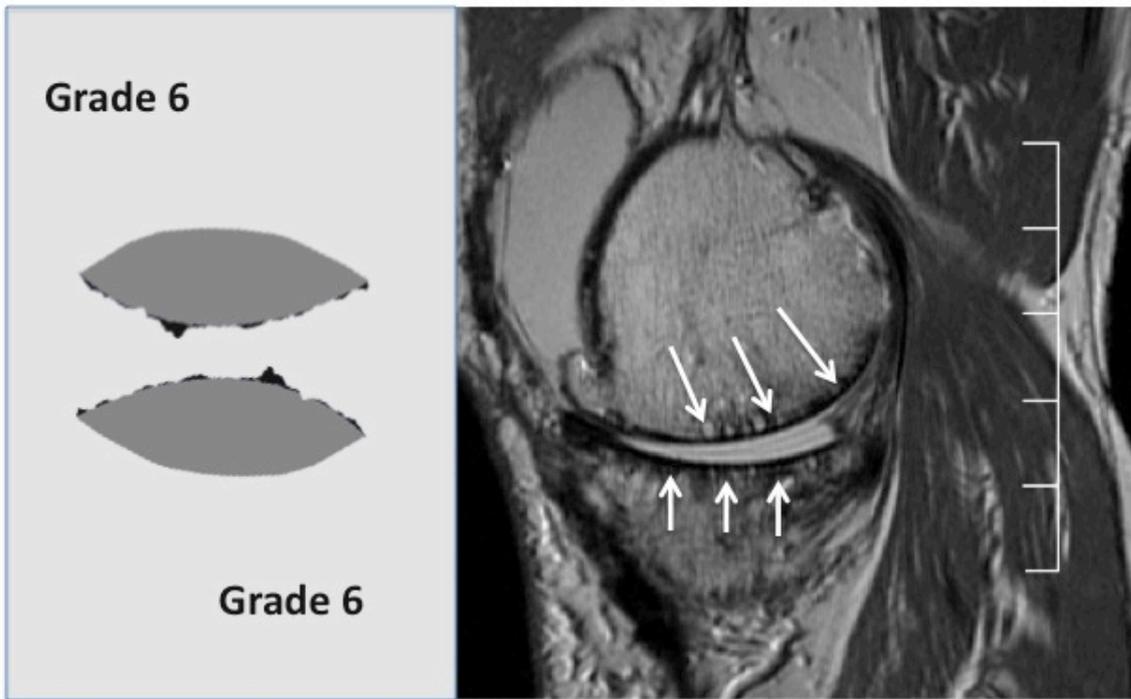


E Partial Thickness Lesion at the Medial Femoral Condyle (>1cm in Size but <75% of the Compartment)

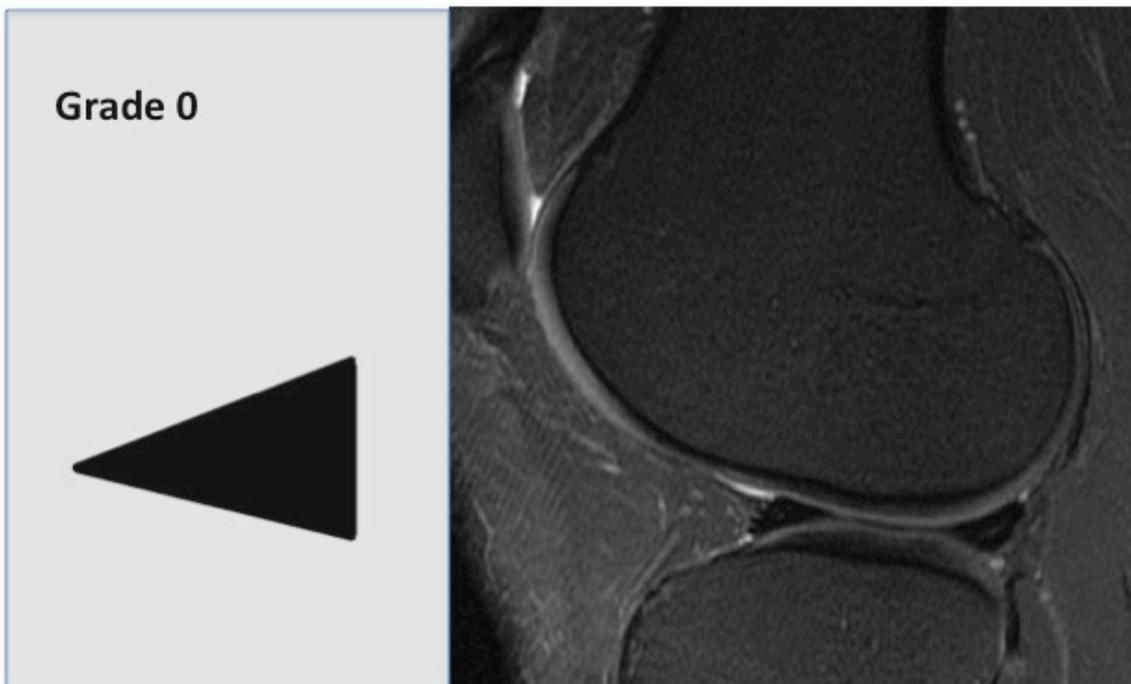


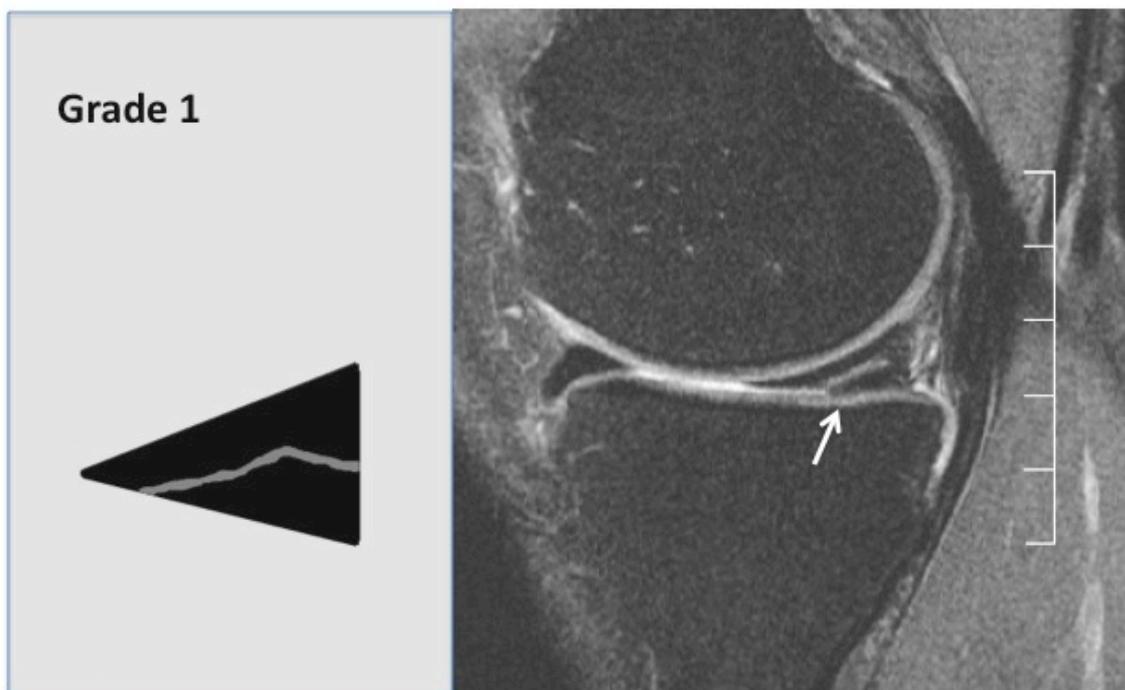
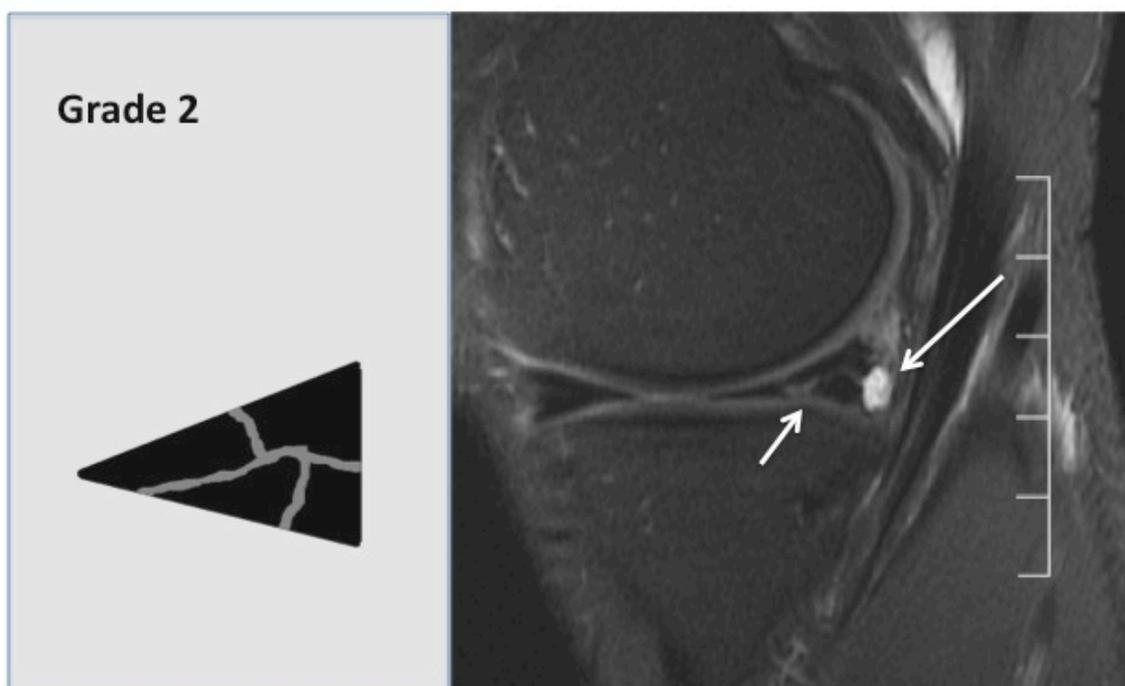
**F Multiple Areas of Partial Thickness Cartilage Loss >75% of the Compartments****G Full Thickness Cartilage Lesion at the Medial Femoral Condyle (>1cm in Size but less than 75% of the Compartment)**

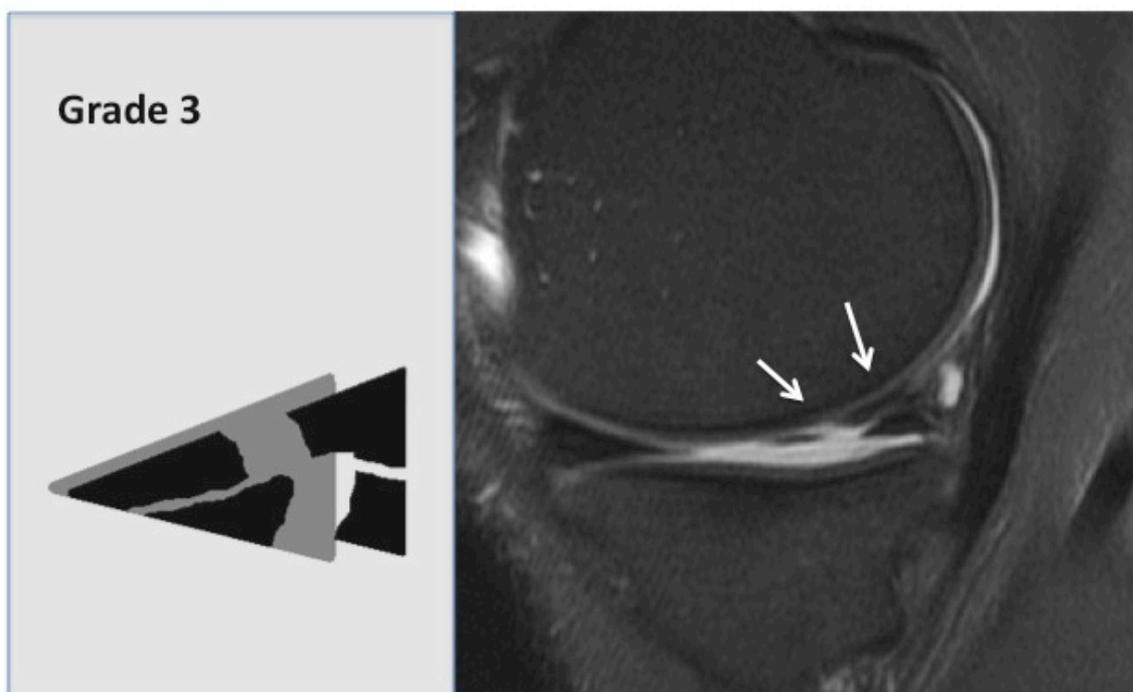
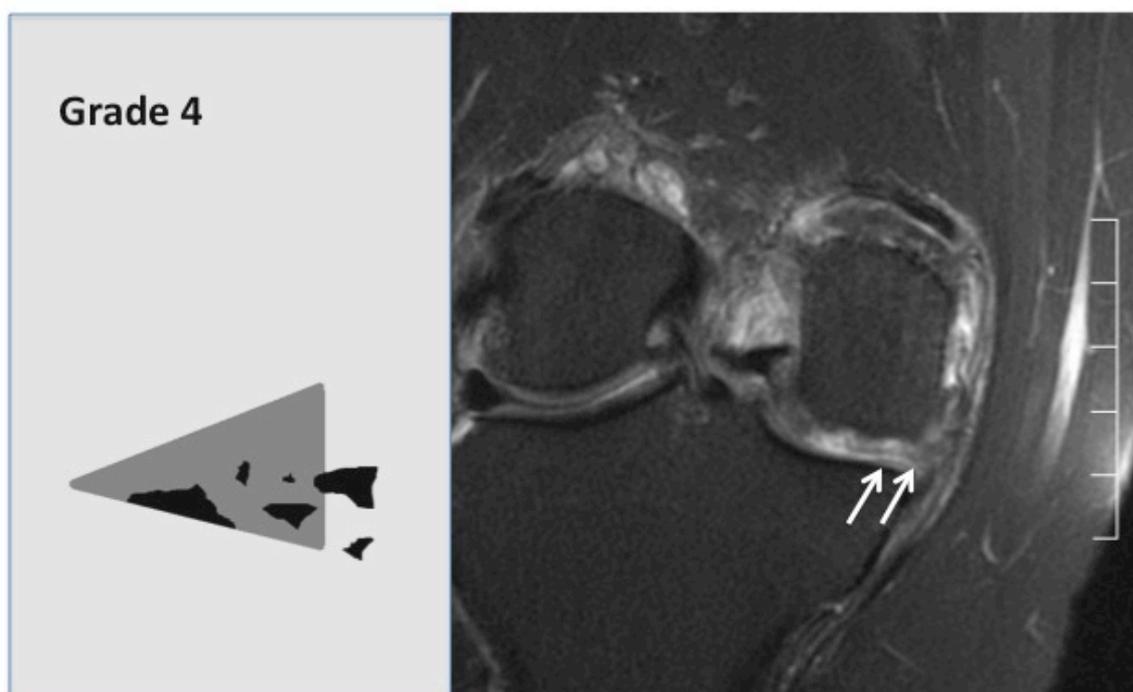
H Full Thickness Cartilage Loss at more than 75% of the Compartment



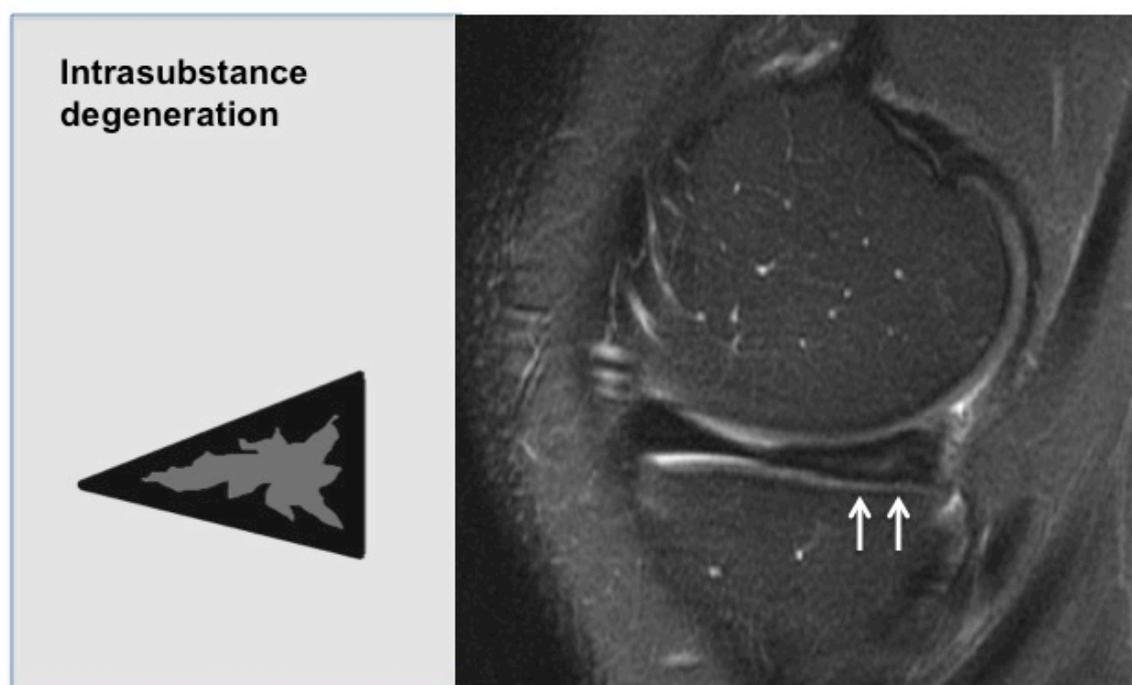
I Normal Triangular Shaped Menisci



**J Small Radial Meniscus Tear of the Posterior Horn****K Non Displaced Tear of the Posterior Horn with adjacent Meniscal Cyst**

**L Displaced Tear of the Posterior Horn****M Maceration of the Meniscal Body**

#### N Intr substance Degeneration of the Meniscus



Magnetic Resonance Images showing Pathological Findings at the Articular Cartilage Surface (Figures 3 A-H) and at the Menisci (Figures 3 I-N) illustrating the Whole-Organ-MRI-Score (WORMS) along with Graphical Illustrations outlining the Pathologies observed with the According WORMS Score Values. Meniscus Intr substance Degeneration is not included in the WORMS Grading, nevertheless it represents an import Pathological Finding and should be reported (Figure 3 N). Figures were in Part published in the Book “Cartilage Imaging” by Link et al. [85].

#### KOSS

As an alternative to the WORMS grading, in 2005 Kornaat introduced the Knee and Osteoarthritis Scoring System (KOSS) [70]. KOSS separates the subregions for evaluation differently than WORMS and differentiates lesions by the size. The score defines the following compartments: patellar crest (crista patellae), medial patellar facet and lateral patellar facet, medial femoral condyle and lateral femoral condyle (excluding the trochlear groove), medial trochlear facet and lateral trochlear facet, medial tibial plateau and lateral tibial plateau. Cartilage lesions are graded as diffuse, focal or osteochondral defects. Furthermore, the lesion depth can be qualitatively rated as diffuse or focal cartilage loss in relation to adjacent healthy cartilage: grade 0 (homogeneous normal cartilage signal); grade 1 defines lesions of less 50% cartilage thickness loss; grade 2, if 50% or more of the articular layer is affected; grade 3

signifies a full-thickness cartilage defect. The osseous component is rated separately by measuring the distance between the actual osteochondral defect boundary and the estimated subchondral bone contour. It is graded as follows: grade 0, normal bone; grade 1, minimal size (<2 mm); grade 2, moderate size (2–5 mm); grade 3, large extension (>5 mm). Furthermore, the surface extent of the osteochondral defects can be evaluated by measuring the maximal diameter and is graded as follows: grade 0, absent; grade 1, minimal (<5 mm); grade 2, moderate (5–10 mm); grade 3, severe (>10 mm). Cartilaginous defects are additionally differentiated as focal lesions in the case of crater like abrupt defects, or as diffuse lesions in the case of a gradual transition zone between normal and degenerated cartilage. The major disadvantage of the KOSS as pointed out by the authors is the time consuming evaluation estimated at approximately 30 minutes per knee, depending on the number of detectable lesions [70].

### *BLOKS*

Another semiquantitative scoring system in use specifically designed for knee OA is the Boston–Leeds osteoarthritis knee score (BLOKS) as published by Hunter et al. in 2008 [56]. It was designed to describe each morphological feature relevant for OA including the following: cartilage integrity, attrition, bone marrow edema like lesions, subchondral cysts, osteophytes, synovitis, ligaments and meniscal pathology. Two separate scoring methods were developed to provide information on both the area affected and the extent of full thickness loss at each of the evaluated regions. It is a more complex system than most other scores in use requiring the reader to assess a number of lesions to calculate the score. The score includes a grading system for cartilage thickness at selected anatomical sites where articular cartilage loss is most frequently observed. To measure the affected area of the articular cartilage, the knee is divided into 9 articular compartments. The patella is divided into 2 regions (medial and lateral patella, separated by the crista). The femur is divided into 4 regions (medial and lateral trochlea and the weight bearing medial and lateral femoral condyles including the central and posterior femur). The tibia is also divided into a medial and a lateral compartment. To grade cartilage area, a modified WORMS score is used, collapsing the WORMS cartilage score to a 0-3 scale: grade 0 with no cartilage loss; grade 1 (<10% of region of cartilage surface area); grade 2 (10-75% of the surface affected); grade 3 (>75% of the cartilage affected). The score at all five

defined regions at the tibiofemoral joint is then summed to give a score ranging from 0–20. In addition to the area affected, site-specific cartilage loss is evaluated at 11 specific sites where degeneration is commonly observed: 3 sites at the patella (medial and lateral facet and the crista) as well as 4 sites each at the weight-bearing tibia and femur. Cartilage is scored depending on the maximum focal lesion depth at the specified sites: grade 0, no cartilage loss; grade 1, partial loss; grade 2, full thickness loss.

### *CaLS (Cartilage Lesion Score)*

In extension to the existing semiquantitative scores, Alizai et al. published a novel quantitative Cartilage Lesion Score (CaLS) [1] based on preceding work from Link and Stahl at UCSF [138, 140], which is specifically tailored to evaluate early focal cartilage lesions as a more sensitive technique to longitudinally monitor cartilage lesions. It aims to better quantify progression of OA and the associated pathologic findings at the knee joint. The CaLS system was designed to measure the three-dimensional extension of cartilage lesions with a WOMBS grade of more than 2. The volume of the cartilage defects is quantified by multiplication of five features of the lesions:  $CaLS = L \times N \times T \times D \times S$  (L: largest diameter in millimeters; N: number of sections where the lesion is visible; T: section thickness including the section gap in millimeters; D: lesion depth; S: shape factor). Lesions with a depth of less than 50% are assigned a value of 1, if depth exceeded 50%, they are assigned a value of 2 and full-thickness lesions are assigned a value of 3. In addition, a shape factor is introduced accounting for the different morphological defect configurations: a shape factor of 1 is assigned if the maximum depth occupies more than 50% of the lesion surface diameter; 0.5 if maximum lesion depth occupies less than half of the lesion surface [1]. Signal inhomogeneities in early OA stages however are hard to visually assess and therefore are not included in this score.

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### 3.2.4 Quantitative MRI Techniques

As outlined above, early cartilage degeneration is hardly quantified with established conventional imaging techniques. Early changes begin with biochemical degeneration of the extracellular matrix (ECM) and the occurrence of cartilage inhomogeneities, which eventually lead to a cascade of degeneration resulting in

ECM breakdown and subsequent morphologic cartilage loss. To identify the process of early cartilage breakdown at the earliest stage possible, new imaging parameters have been proposed to identify the very early matrix changes using high field MRI. Novel MRI-based methods such as delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), T1rho and T2 mapping and have been developed to detect and quantify cartilage matrix composition [75, 89, 100] and may therefore potentially be used as new tools for early diagnosis and monitoring of knee OA [45, 82, 94, 125].

Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) is a technique based on the distribution of contrast agent within the joint space after direct gadolinium injection. After application, the concentration of the contrast agent within the joint and cartilage tissue can be measured by means of T1 relaxation time mapping. The technique is based on the assumption, that anionic contrast agent such as Gadolinium-DTPA2 (Magnevist, Shering, Berlin, Germany) distributes not only within the synovial fluid but also into the articular cartilage. Studies have shown that the uptake takes place at an inverse proportion to the negatively charged glycosaminoglycan (GAG) chains, and therefore the proteoglycan content can be indirectly quantified [35, 95]. In vitro studies showed promising results demonstrating dGEMRIC to accurately assess GAG content [21, 78]. However, the measurements are based on the principle of electroneutrality and thus require full equilibration in the tissue, a hypothetical state that is hardly achievable in vivo. Thus the technique may not be very reproducible and long equilibration times as well as pre-contrast T1 measurements for comparison may be necessary to allow for useful application. Furthermore the incidence of nephrogenic systemic fibrosis (NSF) associated with the application of gadolinium contrast agent further complicates this technique.

Other novel MR modalities for cartilage imaging include ultra short echo time (UTE) sequences, which use the short echo time components of around 50-250 microseconds to acquire signal particularly at the bone-cartilage interface and in other structures such as ligaments and tendons with the ability to quantify bound water [24]. The use of Sodium ( $^{23}\text{Na}$ ) provides another interesting technique. Previous studies have shown, that the intra- and extracellular sodium uptake which was typically used for white matter analysis in brain imaging, may also be useful to investigate musculoskeletal diseases. However, specialized MR hardware is required to acquire Proton and Sodium signals because of a difference in resonance frequencies and the modality may suffer from low SNR and diffusion anisotropy

particularly in cartilage tissue [38]. Another potentially useful technique based on the quantification of water–macromolecule interactions that may be useful in the imaging of cartilage degeneration, where pathological changes occur in macromolecules, is Magnetization Transfer Contrast, but currently only few studies have investigated the potential of MTC imaging for musculoskeletal application, and its sensitivity to changes in the cartilage matrix still has to be evaluated [161].

T1rho is a technique assessing slow molecular motion and has been shown to be sensitive to proteoglycan content [83]. When measuring T1rho decay, proton spins are tilted and locked to the transversal plane where they relax by the time constant T1rho. After signal acquisition at different spin lock times the data can be fitted to an exponential equation. T1rho relaxation may relate to the molecular motion of PG macromolecules and thus may be suitable to assess PG content in articular cartilage. However, high signal absorption rates (SAR) limit the clinical applicability and molecular interactions with the collagen matrix further complicate analysis and interpretation of T1rho measurements [81].

Last but not least T2 relaxation time measurements are an emerging tool for cartilage analysis, which have shown promising results to depict changes related to osteoarthritis [7, 84, 106]. T2 relaxation time measurements are based on the interactions between proton spins and tissue hydration [81, 106]. The quantification of T2 can be performed using the tissue-specific intrinsic T2 relaxation time, as performed in this study, or as an alternative by quantifying the signal decay caused by field inhomogeneities using a gradient echo sequence (T2\*). When measuring intrinsic T2 relaxation times, spin-echo impulses are used to refocus the relaxation induced by field inhomogeneity. A sequence for T2 relaxation time acquisitions will typically consist of a 180 degree refocusing pulse followed by relaxation delays, i.e. echo times (TE). This allows for different T2-weightings and T2 relaxation can be estimated by fitting the data of multiple echo time measurements to a signal equation. Because of the dipolar coupling of the spins, which orient according to the position of the collagen fibrils, there is evidence to suggest that T2 relates to the articular collagen properties. Due to varying contents of collagen and macromolecules in the cartilage matrix, which bind large amounts of water, articular cartilage tissue shows variation of T2 relaxation times depending on the collagen content and therefore may allow for its quantification [7]. However, T2 relaxation time measurements may depend on a variety of factors that have to be taken into

account, such as the orientation of the collagen fibrils contained in the probe, specimen or joint analyzed, the different histological composition of the cartilage zones, but also the fitting algorithms used for the interpretation of the measured values. Collagen fibrils at the articular cartilage layer predominantly run parallel to the articular surface, fibrils in the transitional zone show relatively isotropic organization, whereas the deep cartilage adjacent to the subchondral bone shows fibrils that are perpendicularly oriented in relation to the cartilage–bone interface [106]. T2 relaxation time measurements have been demonstrated to relate to the mechanical properties [75, 107] of cartilage in human cartilage, to be elevated with cartilage matrix changes [49] as well as various stages of cartilage degeneration [4, 58] and to relate to changes assessing chondral repair [36, 74]. It may therefore be a valuable tool sensitive to the structural characteristics of cartilage as well as repair tissue.

### 3.3 Treatment

Given the irreversible nature of cartilage damage, most cartilage treatment options aim at the alleviation of symptoms and the prevention of progressive osteoarthritis. Ideally, reconstructing the articular cartilage would regenerate the normal composition of the three-dimensional collagen structure and the adjacent aggregated proteoglycans. However, most current techniques focus on symptomatic treatment.

Numerous pharmacological therapies have been developed to treat cartilage damage or to slow down cartilage degeneration. Pain medication is frequently prescribed and used, including drugs such as Acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), topical pain-relieving medications and drugs effective against OA related pain, e.g. narcotic analgesics such as codeine or hydrocodone. However, these medications target symptomatic relief only which allow for short-term relief, but in part have inherent side effects or even pose a potential risk for addiction (e.g. Tramadol). Other options for treatment include injectable therapies such as corticosteroids to suppress inflammation as well as a variety of agents for viscosupplementation. Although these drugs have favorable short-term benefits, they do not provide long-term therapeutical effects. Other slow-acting drugs, such as injectable chondroitin and glucosamine sulphate may be more effective and have shown promising initial results [37]. Chondroitin sulphate has been found to slow down the progression of the disease and has shown anti-inflammatory effects as well

as chondroprotective capabilities [154]. However, structural consolidation once cartilage tissue has been lost cannot be achieved either. As conventional medical treatment often does not provide satisfying results, many patients try complimentary non-drug relief therapies, such as the application of heat or cold (or a combination of both), transcutaneous electrical nerve stimulation (TENS), massage techniques, acupuncture and nutritional supplements (e.g. oral glucosamine and chondroitin sulphate).

To counter more advanced stages of disease or to treat focal defects, invasive surgical techniques have been developed aiming to stop or slow down cartilage degeneration. Commonly used techniques include drilling and microfracture procedures, which are used to treat small cartilage lesions. The damaged cartilage is debrided in arthroscopy to create vertical walls of stable articular cartilage along the defect rim to facilitate clot adhesion. Small holes are then drilled into the subchondral bone plate to stimulate the underlying bone marrow aiming to recruit mesenchymal stem cells. More recently, chondrocyte implantations with autologous chondrocytes harvested through biopsy, or using allografts seeded into bioresorbable scaffolds have been performed [2, 12, 47, 48, 54]. In these procedures, cartilage defects are debrided and then filled with a chondrocyte-impregnated scaffold or a suspension of cultured chondrocytes which is then covered by a periosteal flap or a collagen membrane. Alternative techniques for larger defect areas include mosaicplasty and osteochondral transfer, using autografts of one or more cylindrical osteochondral transplants harvested from less weight-bearing areas of the injured joint. The big advantage of these techniques are, that the repair tissue is vivid autologous articular cartilage, but they are of course limited by resulting pathologies on the donor site, the availability of material and differences in graft orientation. In some cases, surgery may be performed to remove loose pieces of bone and cartilage from the joint if they cause symptoms of locking. Furthermore repositioning of bones to correct joint alignment or the resurfacing of severely degenerated bones may also be indications requiring a surgical approach.

Finally, in cases of more advanced OA, prostheses are commonly implanted to replace severely degenerated joints to regain functionality. These numerous interventions pose a significant socioeconomic burden to our societies: over the course of twelve years (from 1990 to 2002), the rate of primary total hip arthroplasties per 100,000 persons increased by approximately 50% in the US, and the

corresponding rate of primary total knee arthroplasties almost tripled [76]. These numbers are projected to grow even further in the future and a recent study estimated the number of total hip replacements performed per year to reach 572,000 and that of total knee replacements to reach 3,481,000 procedures by 2030, a growth by 673% with immense associated costs [77].

Ideally, repair techniques would regenerate hyaline articular cartilage tissue to allow for structural repair, however, current options are limited and joint replacement numbers are on the rise. Most successful treatment programs include interventions combined with pain management through medication as well as strategies to improve function. This usually involves physical therapy and strategies on how to cope with OA related symptoms including education on responsible exercise, weight control, rest and relief from stress on joints, pain relief techniques and other complementary therapies. However, the role of physical activity in relation to osteoarthritis is controversially discussed. While muscle strengthening through physical therapy and exercise poses one of the best treatment options for osteoarthritis, decreasing stress on the joints at the same time provides one of the most effective ways to prevent pain. As a consequence there is a need to investigate the optimal level and type of activity for normal joint functionality. In addition, the on-going investigation of new drugs and therapy options increases the need for better tools to diagnose and monitor disease progression and treatment efficacy both in research trials as well as in a clinical setting to follow up patients longitudinally. Consequently there is a need for sensitive biomarkers that reliably assess stage, progression, stabilization or even healing of cartilage degeneration.

## 4 Materials & Methods

### 4.1 The Osteoarthritis Initiative

The Osteoarthritis Initiative (OAI) cohort study launched by the National Institutes of Health (NIH) is a multi-center, longitudinal, observational study focusing primarily on knee OA. The study aims to create a public archive of data, biological samples and joint images collected over time from a very well clinically characterized population of individuals comprised of two main subgroups, compared to healthy controls: those with clinically significant knee OA who are at risk of disease progression (Progression Cohort) and individuals who are at high risk of initiation of clinically significant knee OA (Incidence Cohort). As originally designed, up to 5,000 age-eligible women and men were recruited and enrolled at four recruitment centres: the University of Maryland School of Medicine (Baltimore), the Ohio State University (Columbus), the University of Pittsburgh, and the Memorial Hospital of Rhode Island (Pawtucket). The OAI consortium includes public funding from the National Institutes of Health (NIH) and private funding from several pharmaceutical company partners managed by the Foundation for the National Institutes of Health. Imaging data and clinical information used in the preparation of this work were obtained from the Incidence Cohort of the Osteoarthritis Initiative (OAI) database, which is available for public access at <http://www.oai.ucsf.edu/>. Specific datasets used were O.E.1. and O.C.1.

### 4.2 Subject Selection And Study Design

#### 4.2.1 Clinical Scores for Subject Selection

##### *Physical Activity Score for the Elderly (PASE)*

The Physical Activity Scale for the Elderly (PASE) is an established questionnaire to measure physical activity in older individuals which has been found to be a reliable and valid instrument for the assessment of physical activity in epidemiologic studies, as published by Washburn et al. [157] and has been previously used in studies by our group [142, 144]. The PASE scale was originally designed for older community dwelling adults, but has also been validated in younger subjects with good test-retest reliability and construct validity, which made it suitable for our study [147, 155-157]. The scale range of PASE is 0-400 with an average of 160 for the subjects selected

for this study (higher score value = more active). Activities contained in the PASE score include strenuous, moderate and light sports as well occupational and housework physical activities.

#### *Western Ontario and McMaster University Index (WOMAC) and Knee injury and Osteoarthritis Outcome Score (KOOS)*

The Western Ontario and McMaster University (WOMAC) osteoarthritis index is a valuable tool in a clinical setting allowing the physician to quantify, document and monitor measures of pain, stiffness and physical function in patients with osteoarthritis of the knee and hip [10, 11]. It is based on a pain score (range 0–20), and different scores assessing stiffness (range 0–8) and functional limitation (score range 0–68). In addition, physical performance questions evaluating everyday activities such as the climbing of stairs, standing up from a sitting or lying position, getting in and out of a car, bending, standing, walking, shopping, lying in bed as well as various other heavy and light household duties are assessed.

The Knee injury and Osteoarthritis Outcome Score (KOOS) was developed as an extension of the WOMAC Osteoarthritis Index with the purpose of evaluating short-term and long-term symptoms and function in subjects with knee injury and osteoarthritis. The KOOS adds three subscales to the WOMAC: other knee symptoms, physical function in sport and recreation and knee-related quality of life [130].

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#### 4.2.2 Inclusion and Exclusion Criteria for Subject Selection

For our study we focused on individuals with non-symptomatic early stages of the disease based on a low WOMAC score. Only subjects with a WOMAC pain score of zero of both knees for the 7 days preceding the baseline clinic visit were included. Participants with a WOMAC pain score higher than zero (3485 of 4796) were excluded for our study. We aimed to identify subjects without symptomatic knee OA, but risk factors for OA. These risk factors included knee symptoms (pain, aching or stiffness in or around the joints) in the past 12 months but not on most days for at least one month, as reported in the questionnaires provided by the OAI dataset. Additional defined risk factors were a history of knee surgery and injury as well as a family history of total knee replacement. Furthermore the presence of Heberden nodes and repetitive knee bending activities were included as risk factors. Exclusion

criteria were rheumatoid arthritis, severe joint space narrowing and contraindications or inability to undergo MRI. All clinical data was obtained from the OAI clinical questionnaires as provided by the OIA data coordination centre located at the University of California San Francisco (UCSF).

Specific inclusion criteria for the subjects in this project were: (a) a WOMAC pain score of zero for both knees, to focus on non-symptomatic subjects, (b) age of 45–55 years, to analyze a cohort of middle-aged subjects and (c) a normal body mass index (BMI) of 19–27 kg/m<sup>2</sup>, to avoid confounding related to obesity as a separate powerful risk-factor. Based on these criteria previously described, a total number of 120 middle-aged patients (mean age: 50.8 years  $\pm$  2.84 standard deviation (SD); age range 45–55 years; 60 women: mean age, 50.88 years  $\pm$  2.72 SD and 60 men: mean age, 50.72 years  $\pm$  2.97 SD) were identified and selected for analysis. All subjects selected had a normal BMI with an average BMI of 24.2  $\pm$  1.93 SD. To display the prevalence and severity of pathologies in dependence on high and low activity levels, subjects were analyzed in relation to their Physical Activity Scale for the Elderly (PASE scale: 0-400, average for the subjects in this study: 160). Cohorts of 60 women and 60 men were examined, divided in 2 subgroups each: 30 patients with a high activity level (strenuous sports, high PASE-Score; 200 - 400), and 30 patients with a low activity level (low PASE-Score; 0 - 200). In addition to the scoring assessments mentioned, extensive functional performance parameters were acquired from the participants. Subjects completed a 400-meter walk and isometric muscle strength was tested as part of the OAI clinical examination at the baseline visit. Study participants were asked to perform a 400 meter walk and the time (in seconds) for completion was measured for each subject [135]. In addition maximum isometric strength measurements of the right knee in maximum force flexion and extension were obtained using the Good Strength Chair (Metitur, Jyvaskyla, Finland) [120].

## 4.3 The OAI Imaging Protocol

### 4.3.1 Bilateral Radiographs

Bilateral standing PA "fixed flexion" knee radiographs were obtained from all study participants. As described in detail in the OAI imaging protocols and OAI study amendments [114], knees radiographs were acquired in a designated Plexiglas positioning frame (SynaFlexer™, CCB-R-Synarc, San Francisco, USA) with 20-30 degrees flexion and 10 degrees internal rotation of feet bilaterally. A focus-to-film distance of 72 inches was used. All radiographs were evaluated by two radiologists in consensus and graded using the Kellgren-Lawrence (KL) technique [64, 91]. Lateral radiographs of the OAI participants were not available.

### 4.3.2 Magnetic Resonance Imaging Protocol

#### *Quality Assurance*

The OAI MR protocol was specifically designed to allow thorough clinical assessment as well as research evaluation of the femorotibial and patellofemoral joints of both knees. Therefore, identical, dedicated 3 Tesla MR systems (Trio, Siemens Medical Solutions, Erlangen, Germany) installed at four clinical sites were used for this multi center study. In a longitudinal MR study it is of crucial importance to use standardized quality assurance (QA) methods to correct for problems developing during the study conduct prior to their affecting image quality or quantitative analysis results. As part of the OAI study design, the manufacturer performed monthly preventative maintenance, and additional independent QA was performed systematically using standardized phantoms, image acquisitions and analyses procedures. The OAI QA goals aimed to achieve maximum longitudinal consistency across all four scan sites for a number of key image characteristics such as signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR), signal uniformity, absence of artifacts, and geometric distortion. Utmost care was taken with the goal to acquire baseline and follow-up images suitable for direct comparison [131].

### *The Osteoarthritis Initiative MRI Protocol*

Outlined below are the sequences included in the OAI protocol including the rationale why each of the sequences was chosen. Table 1 lists the individual sequences and according imaging parameters.

1. Sagittal intermediate weighted two dimensional fast spin echo sequence with fat suppression (SAG IW 2D FSE FS)

Fat suppression enables identification of subarticular marrow edema, which is often found in OA patients and is associated with pain. Furthermore cysts can be detected and joint effusion can be quantified. The large imaging field of view (FOV = 16 cm) covers the suprapatellar bursa as well as popliteal cysts that potentially may dissect. Additionally this acquisition enables evaluation of cartilage quality, the cruciate ligaments as well as bony deformation such as osteophytes

2. Sagittal three dimensional dual echo steady state sequence with water excitation  
(SAG 3D DESS WE)

Sagittal 3D DESS (with coronal and axial reformations) with water excitation enables evaluation and quantification of cartilage volume in all knee compartments (including patellofemoral and femorotibial joints). Another advantage of this sequence is the possibility to identify osteophytes in both the original sagittal as well as in the coronal and axial planes. Subarticular bone marrow edema and bone chondral cysts can be identified in all planes. Marrow assessment is presumably less sensitive compared to fat suppressed intermediate weighted or T2 weighted sequences.

3. Coronal T1 weighted three dimensional fast low angle shot sequence with water excitation (COR T1W 3D FLASH WE)

Enables quantitation of cartilage volume over the central load-bearing compartment of the knee (femorotibial joint). Another primary use of the 3D FL acquisition is to identify medial and lateral osteophytes on the femur and tibia in the original coronal plane. Secondly, it also potentially provides assessment of subarticular marrow edema and cysts in the coronal plane (central femur and

tibia). The marrow assessment is presumably less sensitive compared to a fat suppressed IW or T2W sequence.

4. Sagittal T2 weighted two-dimensional single excitation multiecho-spin echo sequence

(SAG T2 2D MESE)

This sequence allows the creation of T2 maps based on 7-echo times (TE, acquired every 10 milliseconds) acquired using an imaging FOV of 12cm. The resulting image contrasts include PD, IW and T2-weighted. These images allow for the evaluation of subchondral bone (PD, T2W), sclerosis, cysts, edema, the menisci (PD), and for morphologic qualitative and quantitative cartilage analysis (PD, IW and T2W). In our research we used a sequence as described by Peterfy et al. [113] to allow quantification of cartilage T2 relaxation times as well as to provide non-fat-suppressed image contrasts.

5. Coronal intermediate weighted turbo spin echo sequence

(COR IW TSE)

The additional coronal IW TSE sequence provides good image contrast to evaluate the medial and lateral collateral ligaments, osteophytes, cysts and sclerosis (particularly at the central femur and tibia), as well as to assess damage of the meniscal body.

Table 1: MRI Protocol of the Osteoarthritis Initiative

Parameter	COR IW 2D FSE	SAG 3D DESS WE	COR T1 3D FLASH WE	SAG T2 2D MESE	SAG IW 2D FSE FS
Matrix phase	307	307	512	269	313
Matrix frequency	384	384	512	384	448
Number of sections	35	160	80	21	37
Field of view (mm)	140	140	160	120	160
Section thickness (mm)	3	0.7	1.5	3	3
Flip angle (degrees)	180	25	12	n/a	180
Repetition time (msec)	3700	16.3	20	2700	3200
Echo time (msec)	29	4.7	7.57	10, 20, 30, 40, 50, 60, 70	30
Bandwidth (Hz/pixel)	352	185	130	250	248
Chemical shift (pixels)	1.3	0	0	1.8	0
Number of signals acquired	1	1	1	1	1
Echo train length	7	1	1	1	5
Phase encode axis	R/L	A/P	R/L	A/P	A/P
Distance factor (%)	0	0	0	16	0
Phase oversampling	20	0	0	0	40
Slice oversampling	0	10	0	0	0
Phase resolution	80	80	100	70	70
Phase partial Fourier	1	1	1	0.875	1
Readout partial Fourier	1	1	1	1	1
Slice partial Fourier	1	0.75	0.75	0.75	1
X-axis resolution (mm)	0.365	0.365	0.313	0.313	0.357
Y-axis resolution (mm)	0.456	0.456	0.313	0.446	0.511
Note: Abbreviated MR sequence names are explained in the following paragraph with additional information; A/P = anterior/posterior, R/L = right/left.					

Parameters of the MRI Sequences acquired as part of the Osteoarthritis Initiative MR Protocol: Coronal Intermediate Weighted 2D Fast SE (COR IW 2D FSE), Sagittal 3D Dual-Echo Steady-State with Water-Excitation (SAG 3D DESS WE), Coronal T1-weighted 3D FLASH with Water-Excitation (COR T1 3D FLASH WE), Sagittal T2-weighted 2D Multiecho SE (SAG T2 2D MESE), Sagittal Intermediate Weighted 2D Fast SE Fat-suppressed (SAG IW 2D FSE FS). Data as published by Peterfy et al. [113].

## 4.4 Image Analysis

### 4.4.1 Qualitative Image Assessment

Images of the right knees from all subjects were transferred to picture archiving and communication system workstations (Agfa, Ridgefield Park, NJ) and reviewed by two musculoskeletal radiologists (T.M.L. and C.S. with > 20 and 3 years of experience in musculoskeletal radiology). If scores diverged, consensus readings were performed and no time constraints were used. All sequences acquired were used for analysis and ambient light was reduced during the readings. The radiologists were blinded to the subject information and the presence and absence of pathology. Pathologies were assessed on the MR images using the semiquantitative Whole-Organ Magnetic Resonance Imaging Score (WORMS) [112] as described above. The following structures and pathological findings of the knee joint were evaluated separately: (a) cartilage, (b) ligaments, (c) menisci, (d) bone marrow edema like lesions (BME), (e) osteophytes, (f) synovitis or effusion, (g) subarticular cysts, (h) flattening or depression of the articular surfaces, (i) loose bodies, and (j) popliteal cysts. For the cartilage assessment, the original 15 WORMS regions at the knee were condensed to six regions in our study: patella, trochlea, medial femur, lateral femur, medial tibia, and lateral tibia. Alterations in meniscal morphology were assessed separately in six regions (medial and lateral aspects of the anterior, body, and posterior portions of the meniscus) and meniscal extrusion was graded according to the semiquantitative WORMS score. In addition, subarticular bone marrow abnormalities (BME), ligaments, and the presence of joint effusion were assessed. Based on the MR findings, a knee was defined as abnormal if any of the analyzed subregions presented with a WORMS score of 1 or higher. A summary WORMS score was calculated for each abnormality by adding the scores for all subregions of each evaluated knee. In addition to the WORMS grading, cartilage lesions were also graded by using the MR imaging classification described by Recht et al. that is based on the modified the arthroscopic cartilage classification as published by Noyes and Stabler [122]. The presence and absence of pathological findings were reported along with their level of diagnostic confidence. Furthermore, the largest diameter of the cartilage lesions in the sagittal, coronal or axial plane and the two largest diameters of bone marrow edema (BME) as visible on the sagittal plane were measured. Grading results were reported along with direct measures of

physical performance taken from the OAI dataset such as muscle strength, muscle diameter at the mid thigh location, performance in a 400 m walk as well as knee function data and Knee injury and Osteoarthritis Outcome Score (KOOS) values. Data from the clinical scoring was then correlated with MRI derived morphological parameters as well as with quantitative MRI data.

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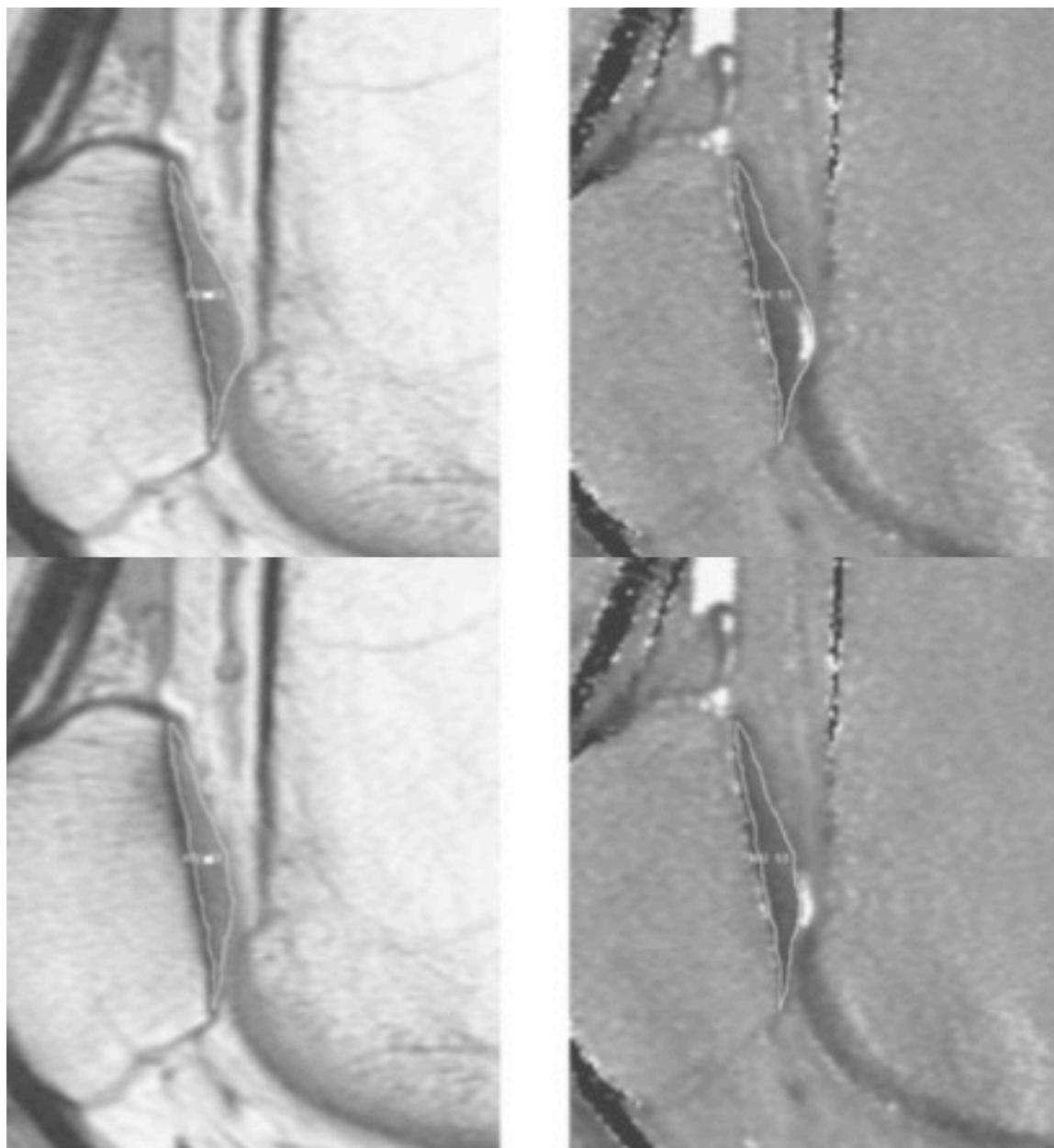
#### 4.4.2 Quantitative Image Analysis

Images were transferred to a remote workstation (SPARC; Sun Microsystems, Mountain View, USA) and T2 maps were created using the sagittal two-dimensional multiecho-spinecho images (MESE) of the right knee. Signal intensity at different echo times was calculated using the following equation:  $SI(TE) \sim \exp(-TE/T2)$ , where  $SI(TE)$  is signal intensity as a function of echo time,  $TE$  is echo time, and  $T2$  is the transverse relaxation time. Articular cartilage has a multiexponential T2 decay with a short T2 component and a longer component. However, without the use of specialized hardware, validated echo time measurements on the order of microseconds cannot be obtained. Therefore the results of our study do not represent multiexponential relaxation times. Instead, a simplified monoexponential decay model was used, that allows for T2 relaxation time calculations by fitting the acquired MRI data to a signal equation as described by Joseph et al. [59]. T2 maps were then computed on a pixel-by-pixel basis using the seven echoes ( $TE$  1: 10 ms; to  $TE$  7: 70 ms; 10 ms increments) from the MESE images and an exponential three parameter fitting routine accounting for noise.

After creation of the T2 maps, the patellar cartilage was quantified by delineating regions of interest (ROI) on the T2 maps. Segmentation was performed using in-house software developed with Matlab (Mathworks, Natick, MA, USA) and an interactive display language routine (`mrsc_image`, IDL, Research Systems, Boulder, USA). One medically trained investigator (HL) manually drew splines delineating the patellar cartilage areas. Each patella had a range of about 8–15 sections, and all well visualized artifact-free patellar cartilage was segmented and included for analysis. Tissue contrast was excellent and water-fat shift artifacts occurring at the bone-cartilage interface were well visualized on the first echo time images of the MESE sequence, whereas fluid-tissue borders were better delineated directly on the sagittal T2 maps. In order to assess cartilage precisely excluding both fluid and water-fat shift artifacts from the splines, a technique was used that allowed

to draw ROIs simultaneously on different images by opening both the T2 map and the first echo time image in one panel at the same time. Cursor, slice number and zoom were synchronized and segmentation could be performed with maximized precision using the visual advantages of both image sets. Figure 4 shows the manually drawn ROI outlining patellar cartilage as appearing in the different images. Patellar compartment mean T2 values were then calculated for the ROIs by averaging T2 values from the ROIs and by interpolation of the splines using the previously mentioned interactive display language routine.

Figure 4: Regions of Interest for Manual Patellar Cartilage Segmentation



Manually drawn ROIs (White Outline) outlining Patellar Cartilage as appearing on Sagittal First Echotime MESE Images (A, C) and the according T2 Maps (B, D). The T2 map (B) reveals Cartilage Quantification Bias due to included Fluid which would potentially bias T2 Relaxation Time Calculations. Image C and D show overlaid ROIs corrected for Fluid Artifacts by synchronized simultaneous Segmentation.

## 4.5 Statistics

### 4.5.1 Statistical Analyses

Statistical analysis was performed using JMP software Version 6 (SAS Institute, Cary, NC). The level of significance for all calculations was defined as  $p < 0.05$ .

Statistical significance of group differences were determined using one-way analysis of variance (ANOVA). Post-hoc Student's t-tests and Chi Square test were used to evaluate group differences. Associations between continuous and ordinal variables were assessed using Pearson and Spearman correlation coefficients tests as well as a multi-regression model. The regression analysis was adjusted for age, sex, BMI, history of knee injury or surgery, family history of knee replacement, and Herbeden nodes in hands, to correct for a potential confounding influence of these variables. A p value of 0.05 was used to determine the level of statistical significance for all analyses.

#### 4.5.2 Reproducibility

Precision errors have been defined to characterize the reproducibility of a diagnostic technique. Contrary to intuition and common practice, the correct estimate of a technique's precision error is not given by the (arithmetic) mean of the individual subject's precision. Instead a technique's precision error is given by the coefficient of variation, calculated by the root-mean-square (RMS) average of the precision errors calculated by the following equation for each of the  $m$  subjects [44]:

$$CV_{SD} = \sqrt{\sum_{j=1}^m CV_j^2 / m}$$

To test intra-reader reliability the same investigator reanalyzed a number of 12 randomly selected patellae was analyzed three times by the same investigator to compare T2 values of the three measurements. Thus the coefficients of variation (CV) were calculated to determine reproducibility of the quantitative T2 measurements. Reproducibility calculations were also performed for the semiquantitative cartilage WORMS score for each compartment by our group in a sample of 12 OAI image data sets that were each assessed twice by two radiologists [112]. Each sub compartment was evaluated using the cartilage WORMS grading and results given by each radiologists were compared calculating unweighted Cohen's Kappa values for inter and intra-observer agreement.

## 5 Results

### 5.1 Patient Data

Subject characteristics of the individuals included in this study are listed in Table 2. The total number of subjects included was 120, with a mean age of 50.8 years  $\pm$  2.84 (age range 45–55 years), and included 60 women (mean age, 50.88 years) and 60 men (mean age, 50.72 years). There were no significant differences by gender regarding age, KL-scores, PASE values and time required for 400m walk. However, some gender related differences were observed: women showed significantly lower mean BMI ( $P=0.002$ ), KOOS ( $P=0.026$ ), and muscle strength ( $P=0.001$ ). Based on the physical activity level assessed by the PASE score, subjects were divided into two groups: a “low activity group” (PASE values of 0-199) and a “high activity group” defined by a PASE value of 200-400. The PASE value of 200 best separated male and female subjects and was chosen as a threshold to divide the subjects into two groups of equal numbers ( $n=60$ ). The mean PASE scores for the low- and high-activity groups were as following: low PASE group: 95.87  $\pm$  34.63 (range 27–149) and High PASE group: 295.15  $\pm$  39.4 (range 244–400). The median PASE score for all subjects was 196.5. Subjects with higher PASE values showed significantly faster times in their completion of the 400 m walk ( $p<0.05$ ) as compared to low PASE subjects. Regarding all other clinical factors chosen for subject selection, no significant differences were observed between the high and low activity groups. In particular there were no significant differences in BMI, age, KOOS values, as well as muscle strength results between subjects in the low and high PASE score groups. In addition the groups did not differ regarding the clinical risk factors (history of injury, surgery, or the presence of Heberden nodes as reported in the OAI questionnaires).

Table 2: Subject Characteristics

Characteristic	All Subjects (n=120)	Male (n=60)	Female (n=60)	P-Value
History of knee injury*	33	19	14	0.2798 <sup>*</sup>
History of knee surgery*	13	8	5	0.3782 <sup>*</sup>
Family history of knee replacement*	7	2	5	0.0993 <sup>*</sup>
Heberden nodes in hands*	26	13	13	0.0185 <sup>*</sup>
Kellgren-Lawrence score	0.6 ± 0.054	0.37 ± 0.61	0.28 ± 0.58	0.446 <sup>§</sup>
KL 0*	87	41	46	-
KL 1*	29	17	12	-
KL 2*	2	1	1	-
KL 3*	2	1	1	-
PASE score	195.51 ± 106.66	202.45 ± 98.05	188.57 ± 115.04	0.478 <sup>§</sup>
PASE score range	27 - 409	27 - 409	27 - 371	-
Age (years)	50.8 ± 2.84	50.72 ± 2.97	50.88 ± 2.72	0.749 <sup>§</sup>
BMI (kg/m <sup>2</sup> )	24.2 ± 1.93	24.75 ± 1.57	23.67 ± 2.13	0.002 <sup>§</sup>
KOOS	93.94 ± 9.34	92 ± 11.29	95.89 ± 6.41	0.026 <sup>§</sup>
400 m walk (sec)	272.57 ± 30.8	275.21 ± 34.59	269.65 ± 26.02	0.372 <sup>§</sup>
Maximum force: flexion (N)	168.46 ± 64.54	200.43 ± 64.05	137.2 ± 47.96	<0.001 <sup>§</sup>
Maximum force: extension (N)	405.61 ± 116.53	464.3 ± 118.83	348.22 ± 80.92	<0.001 <sup>§</sup>
Note: Unless otherwise specified, data are means ± standard deviations (SD).				
* Data are numbers of patients.				
* Pearson $\chi^2$ test.				
§ Analysis of variance.				

## 5.2 Qualitative Analysis

### 5.2.1 WORMS and KL Scoring Results by Gender

The radiographic evaluation showed, that subjects did not differ by Kellgren-Lawrence grade (KL) in relation to gender. KL scores of 0 were found in 87 knees, 29 knees showed a KL score of 1 and KL grades of 2 and 3 were reported for 2 knees each. Clinical data as well as KL scores for all subjects stratified by gender are listed in Table 2. The MR analyses demonstrated a high prevalence of meniscal lesions among all subjects (45.0%; 54 of 120) and a high presence of overall cartilage lesions (79.0% presenting with a WORMS >0; 95 of 120). Table 3 demonstrates distribution of the lesions stratified by gender. Meniscal lesions and joint effusion

were observed more frequently in men, whereas cartilage lesions were more prevalent in women. Bone marrow edema, ligament lesions, popliteal cysts were also found more frequently in men than in women. Ligament lesions were observed most frequently at the patellar tendon (8.3% of all subjects; 10 of 120; men: 11.7% ; women: 5.0%) and the anterior cruciate ligament (6.7% of all subjects; 8 of 120; men: 8.3%; women: 5.0%). The prevalence of popliteal cysts was independent from sex, PASE scale and the presence of cartilage lesions.

Table 3: Prevalence of Focal Knee Abnormalities on MR Images by Gender

Lesion	All Subjects (n = 120)	Men (n = 60)	Women (n = 60)	P-Value*
Meniscus	54 (45.0)	30 (50.0)	24 (40.0)	0.2709
Ligament	28 (23.3)	17 (28.3)	11 (18.3)	0.1953
Cartilage WORMS >0	95 (79.2)	45 (75.0)	50 (83.3)	0.2611
Cartilage WORMS >1	65 (54.2)	34 (56.7)	31 (51.7)	-
Bone marrow edema	51 (42.5)	29 (48.3)	22 (36.7)	0.1961
Articular surface depression	0 (0)	0 (0)	0 (0)	-
Subarticular cyst	7 (5.8)	4 (6.7)	3 (5.0)	0.6969
Osteophyte	47 (39.2)	24 (40.0)	23 (38.3)	0.8516
Joint effusion	32 (26.7)	21 (35.0)	11 (18.3)	0.039
Loose body	4 (3.3)	3 (5.0)	1 (1.7)	0.3091
Popliteal cyst	31 (25.8)	18 (30.0)	13 (21.7)	0.2971
Note: If not specified otherwise, data are numbers of subjects, with percentages in parentheses.				
* Pearson $\chi^2$ test.				

There was a high prevalence of cartilage lesions at the articular patellar surface (40.0% of subjects; 48 of 120), and lesions were more frequently found in women (45%; 27 of 60) than in men (35%; 21 of 60). If the patella showed cartilage lesions, subjects showed a greater number of more severe cartilage lesions in the other articular compartments. Significantly more lesions were observed at the medial compartments (medial femur,  $p=0.0032$ ; medial tibia,  $p=0.0051$ ) as well as at the trochlea ( $p<0.001$ ) and the lateral tibia ( $p=0.0123$ ). Table 4 shows the presence and distribution of cartilage lesions at the trochlea and the tibiofemoral articular

compartments depending on lesion presence at the patella along with the according WOMBS grading averages for each compartment.

Table 4: Prevalence of other Cartilage Lesions than at the Patella

Cartilage lesion	Subjects with no Patellar Cartilage Lesions* (n=72)	Subjects with Patellar Cartilage Lesions* (n=48)	P-Value <sup>‡</sup>
Location	Number of lesions	Number of lesions	-
Trochlea**	10 (13.89 %)	23 (47.92 %)	<0.001
Medial Femur Condyle**	13 (18.06 %)	21 (43.75 %)	0.0032
Lateral Femur Condyle**	8 (11.11 %)	11 (22.92 %)	0.0715
Medial Tibia**	4 (5.56 %)	10 (20.83 %)	0.0051
Lateral Tibia**	13 (18.06 %)	19 (39.58 %)	0.0123
WORMS Compartment	WORMS score	WORMS score	-
Trochlea	0.167 ± 0.44	1.36 ± 1.81	<0.001
Medial Femur Condyle	0.46 ± 1.14	1.61 ± 2.07	<0.001
Lateral Femur Condyle	0.25 ± 0.74	0.70 ± 1.34	0.0129
Medial Tibia	0.06 ± 0.23	0.66 ± 1.40	<0.001
Lateral Tibia	0.36 ± 0.97	0.77 ± 1.29	0.111
Note: If not specified otherwise, data are mean values ± standard deviation (SD)			
* WORMS = 0.			
* WORMS = 1–6.			
<sup>‡</sup> Linear regression analysis corrected for age, sex, BMI, history of knee injury or surgery, family history of knee replacement, and Herbeden nodes in hands			
** Data are numbers of subjects, with percentages in parentheses.			

Top: Numbers and Distribution by Location; Bottom: WOMBS Grading by Compartment in Subjects with and Those without Patellar Cartilage Lesions.

Reproducibility measurements for WOMBS grading were performed to calculate interobserver agreement (95.3%) and intraobserver agreements (95.4% and 95.1%) In addition, inter- and intraobserver agreement were evaluated using Cohen's kappa calculations. Good intraobserver reliability was demonstrated with Cohen's kappa values over 0.61: interobserver agreement Cohen's k value was 0.67, whereas intraobserver agreement Cohen's k values were 0.69 and 0.72 respectively.

### 5.2.2 Morphological Scoring Stratified by Physical Activity

Furthermore, lesion presence was evaluated with subjects stratified based on their physical activity. As previously mentioned, subjects were separated into a low-activity group (PASE score: 0–199) and a high-activity group (PASE score: 200–400). Cartilage lesions (WORMS>0) were present in 56 (93.3%) of the 60 subjects from the high activity subject group versus 39 lesions (65.0%) in the 60 low activity subjects (Table 5). Significantly higher numbers of pathological findings were found in the high-activity group at the meniscus ( $p=0.018$ ), cartilage (WORMS>0:  $p<0.001$ ; WORMS>1:  $p=0.018$ ) and ligaments ( $p=0.0111$ ). Furthermore bone marrow edema like lesions ( $p<0.001$ ) were more frequent in highly active subjects as well as the presence of joint effusion ( $p<0.001$ ). In addition, lesions in the active subject group were more severe: Active individuals showed significantly higher maximum cartilage WORMS (Table 5) and Recht scores compared to less active subjects. The maximum Recht sum score for highly active subjects was  $2.4\pm 1.39$  compared to  $1.38\pm 1.33$  in the low activity group ( $p<0.001$ ). When using PASE as a continuous scale instead of analyzing subjects by group, the results could be reproduced.

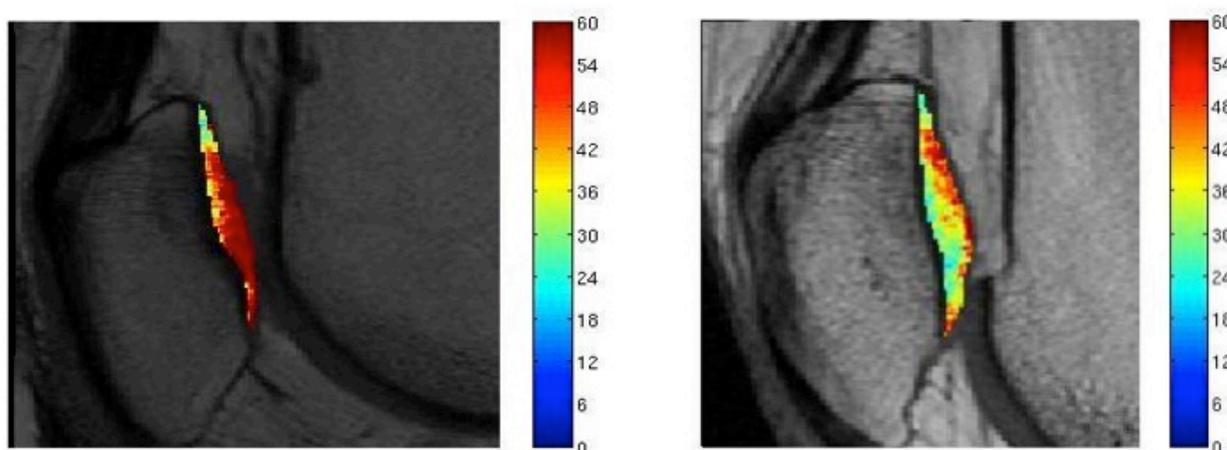
Table 5: Prevalence of Knee Abnormalities by Activity Level

Lesion	Low-Activity Group* (n=60)	High-Activity Group* (n=60)	P-Value <sup>§</sup>
Meniscus	19 (31.7 %)	35 (58.3 %)	0.0018
Ligament	9 (15 %)	19 (31.7%)	0.0111
Cartilage WORMS >0	39 (65 %)	56 (93.3 %)	<0.001
Cartilage WORMS >1	27 (45 %)	38 (63.3 %)	0.018
Bone Marrow Edema	17 (28.3 %)	34 (56.7 %)	<0.001
Articular Surface Depression	0 (0 %)	0 (0)	-
Subarticular Cysts	3 (5 %)	4 (6.7 %)	0.3447
Osteophytes	19 (31.7 %)	2 (46.7 %)	0.1727
Joint Effusion	3 (5 %)	29 (48.3 %)	<0.001
Loose Bodies	2 (3.3 %)	2 (3.3 %)	0.7685
Popliteal Cyst	15 (35 %)	16 (26.7 %)	0.8638
Note: If not specified otherwise, data are numbers of subjects, with percentages in parentheses			
* PASE score: 0–199.			
* PASE score: 200–400.			
§ Linear regression analysis corrected for age, sex, BMI, history of knee injury or surgery, family history of knee replacement, and Herbeden nodes in hands			

### 5.3 Quantitative Analysis Results: Patellar Cartilage T2

Reproducibility was evaluated as previously outlined. The coefficient of variation for T2 quantification measurements was calculated with a value of 1.17. Figure 5 shows examples of colour coded T2 maps illustrating T2 relaxation time measurements of a subject with OA compared to images of an age-matched healthy subject.

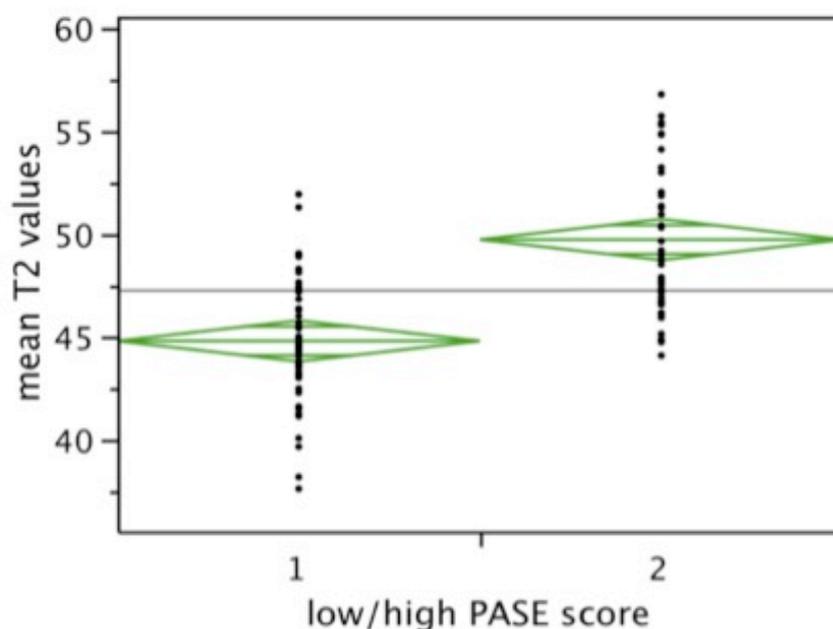
Figure 5: Color-coded T2 maps of Patellar Cartilage



Color-coded T2 maps overlaid on First Echo-time Images. Left: High T2 Values in a Patient with Osteoarthritis; Right: Low T2 values in a Healthy Subject of the same Age. Color-coded illustration demonstrating Increase in T2 Relaxation Time in ms by a Shift of Pixel Color from Blue/ Green/ Yellow to Red.

Subjects with high activity showed higher patellar cartilage T2 as the low activity group ( $48.7 \pm 4.35$  ms versus  $45.8 \pm 3.93$  ms;  $p < 0.001$ ). Figure 6 illustrates T2 value distribution of individuals stratified by physical activity level.

Figure 6: T2 Values of Individuals stratified by Activity level (PASE Score)



Mean T2 values derived from patellar cartilage in subjects in low-activity subjects (left, 1) and high-activity subjects (right, 2) stratified by PASE Score. A significant difference between activity groups ( $p=0.001$ ) was observed based on testing T2 (dependent variable) by the ordinal variable PASE using a multivariate regression model adjusted for sex, age, BMI, and OA risk factors.

Independent of activity, subjects with cartilage lesions at the whole knee showed significantly higher T2 values compared to subjects without cartilage lesions ( $47.94 \pm 4.35$  ms, versus  $44.6 \pm 3.51$  ms;  $p < 0.0025$ ). Also, when comparing T2 values of patellar cartilage in subjects with and without cartilage lesions at the patella, patellar T2 was significantly higher in the presence of lesions ( $49.94 \pm 4.75$  ms versus  $45.9 \pm 3.62$  ms;  $p < 0.001$ ). Similarly, T2 values of subjects with meniscus pathology (patellar T2:  $48.5 \pm 4.63$  ms versus  $46.2 \pm 3.92$  ms;  $p = 0.0067$ ), with joint effusion ( $49.71 \pm 4.08$  ms versus  $46.3 \pm 4.16$  ms;  $p = 0.0018$ ) and osteophytes ( $48.39 \pm 4.42$  ms versus  $46.5 \pm 4.24$  ms;  $p < 0.0213$ ) showed higher patellar T2 compared to the subjects without those pathologies.

To investigate the association of the other clinical factors depending on physical activity, linear regression analysis was performed yielding significant associations of patellar T2 with PASE grading ( $p < 0.001$ ), maximum WORMS grade ( $p < 0.001$ ) and maximum Recht score of the patellar cartilage ( $p < 0.001$ ). Subject

characteristics including all clinical variables and semiquantitative scoring results (WORMS and Reicht score) along with according T2 relaxation time measurements are shown in Table 6. All multiple regression models were adjusted for a variety of potential influences and OA risk factors such as age, sex, BMI, history of knee injury or surgery, family history of knee replacement, and Herbeden nodes in hands. One male subject from the low activity group had to be excluded from analysis due to artifacts on the T2 mapping sequence images.

## 5.4 Associations Depending on Physical Activity

Patient characteristics based on physical activity are shown in Table 6.

Table 6: Subject Characteristics, Qualitative and Quantitative Parameters by Activity Level

	Low-Activity Group* (n=60)	High-Activity Group* (n=60)	P-Value <sup>‡</sup>
Kellgren-Lawrence score	0.1 ± 0.34	0.5 ± 0.72	0.0013
KL 0**	52	35	-
KL 1**	8	21	-
KL 2**	0	2	-
KL 3**	0	2	-
KOOS	94.94 ± 9.51	93.08 ± 9.18	0.4153
400 m walk (sec)	279.3 ± 34.03	266.86 ± 26.86	0.156
Maximum force: Flexion (N)	175 ± 69.89	163.12 ± 60.03	0.9308
Maximum Force: Extension (N)	393.3 ± 133.07	415.65 ± 101.4	0.069
T2 values (msec)	45.8 ± 3.93	48.7 ± 4.35	<0.001
Cartilage WORMS (Summation score)	2.5 ± 3.34	6.3 ± 5.45	<0.001
Cartilage WORMS (Maximum score)	1.6 ± 1.59	2.8 ± 1.85	<0.001
Recht cartilage score (Summation)	2.3 ± 2.95	5.5 ± 4.37	<0.001
Recht cartilage score (Maximum)	1.38 ± 1.33	2.4 ± 1.39	<0.001
Summation WORMS Scores			
Meniscus	0.78 ± 1.54	2.4 ± 3.4	0.001
Ligament	0.3 ± 0.90	0.87 ± 1.48	0.0135
Bone marrow edema	0.88 ± 1.69	1.5 ± 1.9	0.0497
Articular surface depression	0	0	-
Subarticular cysts	0.14 ± 0.07	0.08 ± 0.06	0.7202
Osteophyte	1.5 ± 3.44	4.0 ± 7.23	0.0305
Joint effusion	0.08 ± 0.38	0.85 ± 1.02	<0.001
Loose body	0.05 ± 0.29	0.03 ± 0.18	0.8526
Popliteal cyst	0.42 ± 0.79	0.41 ± 0.77	0.7631
Note: If not specified otherwise, data are mean values ± standard deviation (SD)			
* PASE score: 0–199.			
* PASE score: 200–400.			
‡ Linear regression analysis corrected for age, sex, BMI, history of knee injury or surgery, family history of knee replacement, and Herbeden nodes in hands			
** Data represents numbers of subjects.			

As mentioned, pathological findings as assessed by Recht score and WORMS were more frequent in the high activity group compared to the low activity group. In addition, mean patellar T2 values were higher in active subjects compared to more sedentary subjects ( $48.7 \pm 4.4$  ms versus  $45.8 \pm 3.9$  ms). Figure 5 illustrates the differences for patellar cartilage T2 values by activity group derived from adjusted multivariate regression analysis. The regression model also showed, that T2 values and morphological cartilage assessment (WORMS) were independently correlated with PASE scores: both parameters were separately correlated with PASE grading (T2:  $p=0.0035$ ; cartilage WORMS:  $p=0.0022$ ).

In addition to cartilage scores (WORMS and Recht Score) and T2 findings, other evaluation results such as KL grading ( $p=0.0013$ ), meniscus WORMS ( $p<0.001$ ), ligament WORMS ( $p=0.0135$ ), osteophyte and BME assessment ( $p=0.0305$  and  $p=0.0497$ ) as well as joint effusion grading ( $p<0.001$ ) also yielded significantly higher values in the high activity group as compared to low activity subjects. Detailed data is demonstrated in Table 6.

## 5.5 Subgroup Analysis

Based on the absence or presence of cartilage lesions (WORMS > 1 in any subregion) in the entire knee, subgroups were identified in the high- and low-activity groups. The high activity group ( $n=60$ ) comprised 38 subjects showing cartilage lesions, whereas 27 of the 59 low-activity subjects demonstrated with cartilage lesions. When stratifying by lesion status, the high-activity group subjects with any cartilage lesion showed significantly higher T2 values compared to those without any lesion ( $49.72 \pm 4.42$  ms versus  $47 \pm 3.72$  ms;  $p=0.0426$ ). The low activity subjects with cartilage lesions in any compartment also had significantly higher T2 values than the subjects without lesions ( $47.0 \pm 3.77$  ms versus  $44.7 \pm 3.79$  ms;  $p=0.0361$ ). There were no significant differences in KOOS-Score, 400m walk, kneeling or for maximum extension and flexion force between the cartilage lesion versus no lesion groups.

When stratifying by activity, the subjects of the high-activity group without cartilage lesions were found to have higher T2 values compared to low-activity subjects with no lesions ( $47.0 \pm 3.72$  ms versus  $44.7 \pm 3.79$  ms;  $p=0.0275$ ). The

subjects with cartilage lesions also differed significantly depending on their activity score (high activity/ with lesions:  $49.72 \pm 4.42$  ms; versus low activity subjects/ with lesions  $47.0 \pm 3.77$  ms;  $p=0.0199$ ). The detailed differences in T2 relaxation time values are demonstrated in Table 7.

Table 7: Mean T2 Values by Activity Level and Presence of Cartilage Lesions

	Number of Subjects	T2 relaxation time (msec)	P-Value <sup>‡</sup>
Low-activity group	59	$45.8 \pm 3.93$	<b>0.0361<sup>‡</sup></b>
No cartilage lesions	32	$44.7 \pm 3.79$	-
Cartilage lesions (WORMS >1)	27	$47 \pm 3.77$	-
High-activity group	60	$48.7 \pm 4.35$	<b>0.0426<sup>¶</sup></b>
No cartilage lesions	22	$47 \pm 3.72$	<b>0.0275<sup>*</sup></b>
Cartilage lesions (WORMS >1)	38	$49.7 \pm 4.42$	<b>0.0199<sup>**</sup></b>
Note: T2 data are means $\pm$ standard deviation (SD)			
* Regression analysis corrected for age, sex, BMI, history of knee injury or surgery, family history of knee replacement, and Herbeden nodes in hands.			
<sup>‡</sup> In low-activity group, subjects with vs those without cartilage lesions.			
<sup>¶</sup> In high-activity group, subjects with vs those without cartilage lesions.			
<sup>*</sup> Versus subjects in low-activity group without cartilage lesions.			
<sup>**</sup> Versus subjects in low-activity group with cartilage lesions.			

## 6 Discussion

### 6.1 Qualitative and Quantitative Observations

The results of our study show, that middle-aged, asymptomatic individuals with risk factors for knee OA from the OAI incidence cohort had a high prevalence of osteoarthritis related knee abnormalities such as cartilage and meniscus lesions. A significant correlation between patellar cartilage T2 relaxation time values and the presence and severity of cartilage and meniscus pathology was observed. Physically active individuals showed significantly more cartilage and meniscus abnormalities compared to more sedentary subjects with lower PASE scores. In addition, a significant association between the physical activity level and patellar T2 values was demonstrated.

### 6.2 Quantitative MRI

#### 6.2.1 Cartilage Histology

For this study, we investigated articular patella cartilage. Because mature hyaline cartilage as found at articular surfaces does not regenerate, cartilage loss is irreversible, once morphological lesions have occurred. Articular cartilage is composed of a relatively small number of chondrocytes within a large extracellular matrix (ECM) composed of water (60%–80%), type II collagen (15%–20%) and negatively charged proteoglycans (PG) (3%–10%) that facilitate the binding of water molecules [106]. The composition and orientation of components varies across the depth and can be divided into four histological zones. The superficial articular layer, the transitional layer, the radial layer, and the calcified layer adjacent to the subchondral bone. It has been histologically determined that collagen fibrils run parallel to the articular surface in the superficial layer, that fibrils are distributed randomly in the transitional layer and are oriented perpendicular to the articular surface in the radial layer. Articular cartilage contains high concentrations of PG. Aggrecan, the most common PG, has a brush-shaped appearance and binds multiple glycosaminoglycan (GAG) side chains affecting the water binding properties of the matrix. Water is the largest cartilage component comprising about 80% of the gross mass at the surface and approximately 65% in the deep layers. The PG content and distribution therefore substantially affect the mechanical properties of the

cartilage. Cartilage contains different types of collagen, with type II collagen being the most prevalent in articular cartilage (90–95% of the total collagen volume). The main function of the type II collagen fibers is to stabilize the PGs and thus serve as a tensile structural framework opposing the PG's tendency to expand. Collagen and PG contents vary among the cartilage layers described above. The PG concentration is lowest at the cartilage surface, with highest concentrations found in the middle layers, which are crucial for the load-bearing capacity of cartilage tissue.

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### 6.2.2 Cartilage Evaluation

Derangement of the collagen fibrils with subsequent PG loss from the ECM and changed synthesis of matrix proteins accompanied by elevation of the water content are thought to be initiating events of early OA, before clinical symptoms and OA related changes as visible on radiographs occur [57]. These alterations of the collagen composition and integrity as well as changes of PG turnover and content can hardly be diagnosed with established clinical diagnostic techniques including plain radiography, CT and MRI arthrography, arthroscopy, and MR imaging of articular cartilage, as they precede macroscopically visible morphologic lesions [58, 98, 117]. Among these diagnostic techniques, arthroscopy is the proclaimed gold standard of joint examination, which is invasive and limited to superficial cartilage evaluation. Plain radiographs are still considered standard of care to diagnose and monitor knee OA. However, all of these techniques are limited in detecting early cartilage abnormalities.

To allow for potential interventions, to stop or slow down disease progression it is of crucial importance to identify cartilage degeneration at the initial stage of OA at the earliest time possible before cartilage loss occurs. The role of dedicated cartilage MR imaging techniques is evolving and at present novel quantitative MRI parameters have been introduced to non-invasively investigate the cartilage matrix. MRI provides a variety of advantages such as multi-planar imaging, excellent soft tissue contrast, non-invasiveness, the lack of ionizing radiation and the possibility for quantitative tissue evaluation. Non-invasive quantitative MRI parameters such as T2, T2\* and T1rho may reflect early biochemical changes of the cartilage preceding morphologically detectable damage [3, 90, 148]. Link and colleagues suggested that quantitative MRI techniques are able to detect cartilage damage at a stage before cartilage tissue is lost [90]. Their data showed an overall increase in cartilage

parameters (T1rho and T2 values) in patients with early stages of OA. More recent studies have shown, that T2 values are primarily effective in quantifying changes associated with the collagen component of the cartilage matrix and have reported conflicting results on whether T2 can reflect changes in PG content [123, 158]. In contrast to proton-based methods such as T2, T1rho mapping has been shown to be sensitive to the changes of PG content in the ECM, allowing for direct visualization of PG content and its different spatial distribution within the cartilage layers [81, 83]. T1rho describes the spin-lattice relaxation in the rotating frame and may reflect changes in the extracellular cartilage matrix due to less restricted motion of water protons in regions with degenerative changes. Stahl et al have reported T1rho to be well suited to differentiate healthy subjects and early OA patients. Thus T1rho may provide valuable complementary information regarding degeneration in OA, particularly on the PG content [139]. Their data suggested that T1rho is more sensitive than T2, but also reported a dependency of T1rho on age. Aside from T1rho, other quantitative MRI techniques such as delayed gadolinium-enhanced MRI (dGEMRIC), glycosaminoglycan chemical exchange dependent saturation transfer (gagCEST) and Sodium imaging may also provide promising approaches and have been shown to be associated with the biomechanical composition of cartilage in vivo [18, 51, 73, 105]. Sodium MR imaging of cartilage and dGEMRIC have been shown to be useful in quantifying changes of PG content. However, dGEMRIC is an invasive technique requiring contrast agent associated with the risk of nephrogenic systemic fibrosis and a relatively long waiting time is necessary for patients before the scan for contrast agent to distribute within the joint. Sodium MRI is hampered by low image contrast and resolution and requires extra hardware to allow acquisitions with a sodium coil. GagCEST has also shown promising initial results to quantify glycosaminoglycan content [88], however, T2 seems to be better suited to monitor longitudinal changes as shown in a study conducted in 2012 evaluating cartilage after osteochondral transplantation [72]. T2\* is another emerging parameter based on T2 relaxation using a gradient echo sequence that has shown to differentiate subjects versus healthy controls and has been shown to be sensitive to meniscal pathology [67, 96, 104].

As a result of the promising initial experiences with quantitative MRI, a T2 mapping sequence was included in the OAI MRI protocol [114], which allows for cross-sectional as well as longitudinal investigation of T2 in relation to the evolution

and progress of cartilage degeneration related to OA. Unfortunately no other quantitative sequence such as T1rho was included; therefore the quantitative data presented in this work is based on T2 data only.

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### 6.2.3 T2 Relaxation Time Measurements

As previously outlined, T2 mapping has been shown to be sensitive to a wide range of water interactions in tissue and in particular depends on the content, orientation and anisotropy of the collagen fibril network [106, 137]. The potential of T2 to depict ECM changes at initial stages of OA has been demonstrated in numerous in-vivo studies [4, 17, 31], as well as in animal studies [134, 159] and has been confirmed in vitro by histology in specimen studies [42, 124, 126]. A number of previous studies have found elevated T2 values in knees with diagnosed OA and in knees of individuals with risk factors for OA [4, 6, 32, 60, 145]. In addition, more recent studies suggest that T2 may predict radiographic changes and MRI manifestation of OA. In a recently conducted study by Liebl et al. using data from the OAI dataset it was shown, that T2 measurements in articular cartilage of radiographically normal tibiofemoral knee compartments were able to predict the later onset of radiographic tibiofemoral OA [84]. Their results suggest that changes in biochemical cartilage composition reflected by elevated T2 measurements precede radiological manifestations of OA, as detectable by KL grading. Joseph et al. reported T2 to predict longitudinal changes related to OA assessed by WOMBS [59].

However, other studies have not found T2 values to predict progression of OA assessed by quantitative methods in knees with KL grade of 2 or 3 [33]. A possible explanation may be, that cartilage T2 values in knees with more advanced OA are more uniformly elevated and therefore do not discriminate well for further cartilage loss. Also, there are conflicting results on the interpretation on cross sectional differences and longitudinal changes of T2. Baum et al. have compared subjects with and without OA risk factors and have found a T2 increase for both groups over 24 months, but found no significant association between the presence of OA risk factors or the presence of cartilage lesions with baseline T2 [8]. The interpretation of T2 values is hampered by the natural increase of T2 with ageing, and morphological damage to the cartilage with subsequent volume loss additionally complicates interpretation. Jungmann et al. have found an inverse correlation of longitudinal T2

changes with baseline T2 values and morphological cartilage abnormalities at baseline, indicating a potential ceiling effect or areas with decreasing T2 values [62]. The loss of large areas of degenerated cartilage may result in a decrease of mean T2 values. In the current study, only patellar cartilage was evaluated. Segmentation of the patellar cartilage alone can be done with good precision for larger sample sizes in a feasible time frame. Stehling et al. suggested a less time consuming approach to reduce segmentation time and novel segmentation algorithms are currently being investigated to further automate and standardize the cartilage segmentation process [141]. Patellar cartilage is of particular interest, as early signal inhomogeneities and morphologic lesions in the natural history of knee OA frequently initiate at the patella, where the cartilage is thickest and therefore may be most vulnerable and sensitive to degeneration [22, 27, 59, 132, 144]. Patellar cartilage exhibits distinct biochemical and mechanical properties and is known to differ from that of the tibiofemoral joint. Patellar cartilage has been shown to present with more in vivo deformation than other weight-bearing cartilage areas at the femur and tibia [34, 53]. The knee compartment affected by OA also seems to change according to varus and valgus knee malalignment. Varus knee malalignment typically is typically accompanied by a loss of joint space in medial tibiofemoral joint OA. Patellar malalignment within the femoral trochlea is commonly accompanied by patellofemoral joint OA [53]. In a study published by Duncan et al., early radiographic findings were demonstrated at the patellofemoral joint and the authors proposed that the onset of knee OA follows a common sequence initiating at the patellofemoral joint [26]. In the current study however, only cross sectional baseline data from the OAI was evaluated investigating patellar cartilage T2 measurements in relation to physical activity.

## **6.3 Cartilage Lesions and T2 in Relation to Physical Activity**

### **6.3.1 Osteoarthritis and Physical Activity**

Multiple risk factors have been linked to OA in epidemiology studies including age, female gender, obesity, sports activities, previous injury, proprioceptive deficits and genetic elements including anatomical alignment. Aside from predisposing genetic factors, age and gender, a complex interplay of occupational and lifestyle factors that in part have not been sufficiently investigated influences the initiation and course of

disease. The number of modifiable risk factors that are associated with the OA onset and progression is limited. Trauma and previous joint injury impose additional risks for OA onset [71], but for a majority of the population loading habits and load distribution may be the main determinants of cartilage health. Joint strain highly depends on a subject's body weight, but also on joint stress related to occupational and recreational activities. In multiple studies, obesity has been shown to be a risk factor for OA and that high BMI is associated with elevated T2 values [13, 61, 66]. The increased risk for OA is not only related to wear and tear due to increased loading, but may also be aggravated by changes in the lipid metabolism with detrimental effects on cartilage [68]. A loss of at least 10% of body weight, coupled with exercise, is a recognized cornerstone of OA management in obese patients and has been shown to lead to an improvement of symptoms [15]. However, the role of exercise and physical activity with inherent joint stress has been controversially discussed both in relation to the onset and the therapeutical management of OA [19, 118, 127, 146, 149, 150, 152, 153]. It has been shown that the femoropatellar joint may be particularly affected by weight-bearing physical activities [139], but as previously outlined, studies investigating the various effects of physical activity may have on weight bearing joints report conflicting results [23, 32, 39, 41, 133]. There is a paucity of data on physical activity and its association with quantitative and qualitative cartilage loss determined with MRI.

Therefore, in this study we assessed the prevalence of cartilage damage, meniscal and ligamentous pathology as well as bone marrow edema pattern in relation to cartilage T2 in relatively healthy, young subjects from the incidence cohort of the OAI with high and low levels of physical activity and no clinical symptoms of pain. This study focused on middle-aged subjects as these could potentially benefit most from a preventive intervention. Despite being asymptomatic, the middle-aged individuals analyzed in our study also showed a high prevalence of cartilage and meniscus lesions. Stahl et al. recently showed data from 10 marathon runners compared to 12 physically active asymptomatic subjects and also found a high prevalence of cartilage abnormalities both in the marathon runners (60%) and the active controls (50%) [140]. However, our data demonstrates, that physically active individuals showed significantly more knee abnormalities including cartilage, meniscus and ligament lesions, BME and joint effusion compared to more sedentary subjects. Similar results have been shown by studies on smaller populations and in

younger subjects with high physical activity levels [9, 16, 52, 151, 163]. Vignon et al stated in their review that the activities of daily life, as well as sports and recreational activities, are risk factors for knee OA and that OA risk increases with duration and intensity of activity [153].

When examining the association of physical activity and OA it is also important to take the influence of age into account. A number of studies have examined OA in physically active individuals, usually in subjects at a specific stage of their lifespan. A lower prevalence of OA related changes was reported in middle-aged physically active teachers (aged 48-60 years) compared with controls [160]. McAlindon examined the level of physical activity and the prevalence of radiographic and symptomatic knee osteoarthritis in an elderly population as part of the Framingham Study and identified heavy physical activity as an important risk factor for the development of knee OA in the elderly [99]. Their data however, based their diagnosis on radiography, which may reflect advanced disease stages, but is limited in detecting early disease. Findings in several studies have demonstrated age dependency of cartilage T2 relaxation time measurements [102, 103]. Mosher et. al indicated, that aging is associated with an increase in T2 when studying cartilage of asymptomatic male and female volunteers [103]. Aging may also change the amount of load generated by body size as compared to load related to activity and subject-specific gait mechanics [14]. Our study only included middle-aged individuals and no association of age and T2 values or age and cartilage lesions was found in our small age range.

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### 6.3.2 Physical Activity and Cartilage Morphology

Only a small number of studies have used MRI to assess the relationship between physical activity and knee cartilage morphology. In a smaller cohort compared to our study, Stahl et al. examined the relationship of physically active subjects with cartilage abnormalities in a young group of subjects (mean age 33 years): they found, that physically active individuals showed a higher prevalence of focal lesions [139]. Some studies report other pathological findings in physically active subjects to be more dominant than cartilage abnormalities, such as meniscal signal intensity or tears (13%-50%), bone marrow edema pattern (up to 41%) or joint effusion (up to 35%) [63, 92, 93]. Kaplan et al. also reported cartilage lesions in an study performed at 1.5 T MRI [63]: They examined the knees of 20 basketball players bilaterally and

detected articular cartilage lesions in 47.5% of the knees. The highest number of lesions was seen at the patella (35%) and at the trochlea (25%). In another study, Major and Helms evaluated the knees of 17 varsity basketball players [93]: eight (24%) of the 34 knees showed abnormal signal intensity at the patellar and trochlear cartilage and six (18%) showed focal cartilage lesions. Consistent with these findings our study reports a higher prevalence of lesions in physically active individuals, and demonstrates even higher lesion prevalence, which is most likely related to differences in age between studies. Furthermore we also found an association between T2 values and the prevalence of cartilage lesions. Interestingly, this association was observed in both activity groups. In the presence of cartilage lesions, T2 values elevated. Recently, Stehling et al. confirmed these findings, showing that physically active subjects present with significantly more and more severe knee abnormalities independently of gender, age, BMI, KL score and OA risk factors compared to less active subjects [143]. These studies indicate, that vigorous physical activity in young and middle aged individuals is associated with the presence of cartilage lesions.

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### 6.3.3 Physical Activity in Relation to T2

In addition to the cartilage lesion findings, our data shows elevated T2 values of the high activity level subjects compared to the more sedentary group. Furthermore, our study also reports a significant correlation between patellar cartilage T2 values and the severity of cartilage and meniscus lesions based on the WOMS and Rechscores. T2 relaxation time measurements have been shown to differentiate patients with and without OA [137] and individuals with risk factors for OA have been shown to demonstrate higher T2 values than normal controls [60]. In a study with asymptomatic physically active and sedentary subjects, Stahl et al. found that T1 rho and T2 relaxation times were not different between younger active subjects and sedentary controls, however, significant T1rho and T2 differences between active subjects with and without cartilage defects were observed [139]. In contrast to their findings, our study demonstrates a significant correlation between the physical activity level and T2 values.

T2 values are known to react differently to acute and chronic loading conditions. Acute static loading has been linked to a decrease of T2 as published by Souza et al., potentially indicating a loss of water from the ECM under loading

conditions [136]. Luke et al. reported elevated T1rho and T2 values in knees of runners directly after a marathon, suggesting different biochemical changes in the articular cartilage as a result to repetitive vigorous mechanical stress on the joint [145]. Therefore the elevated T2 values may represent adaption to biomechanical load in the form of previously reported increased water content [31]. Stehling et al. reported the according meniscal changes in marathon runners and showed both T1rho and T2 to increase acutely after the race [145]. Interestingly, their data also demonstrated that T2 values returned to the pre-race level in the 3-month follow-up. While the correct interpretation of acutely elevated or depressed T2 values has yet to be elucidated, persisting changes of T2 values have been linked to degenerative changes related to OA as previously outlined.

In an extensive review, Mosher indicated that longer T2 times may reflect chronic mechanical stimulation [101]. In a study published in 2011, Hovis et al. reported lower T2 values for light exercising individuals based on their PASE scores compared with sedentary and moderate/strenuous exercisers [55]. Their study also found, that frequent knee bending activities were associated with elevated T2 values indicating detrimental effects on cartilage. More recently, Lin et al. assessed T2 values of 205 subjects of the OAI incidence and normal cohorts with no knee pain at enrollment and evaluated the follow-up MRIs of these individuals 2 and 4 years after the baseline exam. Interestingly, they found that high and very low PASE scores were associated with greater progression of cartilage T2 measurements in asymptomatic, middle-aged individuals, suggesting accelerated cartilage matrix biochemical degeneration over time [87]. Unfortunately their study did not include morphological cartilage analysis grading using WOMBS. However, the data from these studies indicate, that there may be a physiological level of activity with beneficial effects on the articular cartilage. Moderate exercise is an important component of most OA management strategies and is known to alleviate pain and to strengthen surrounding muscles [30]. Dunlop et al. have investigated objective accelerometer data as part of the OAI and have found adults with knee OA to be particularly inactive compared to American physical activity guidelines [29, 30, 80]. Moderate activity may even be crucial for OA prevention and cartilage health, as cyclic loading is thought to be needed for nutrient transport by the synovial fluid and has been shown to be particularly important for the desorption of larger molecules [109].

In summary our data shows, that physically more active subjects show more cartilage lesions and elevated T2. Based on these results, we hypothesize that subjects develop cartilage lesions as a result of vigorous physical activity and that higher T2 values reflect cartilage quality. Substances released to the synovial fluid during the process of focal cartilage lesion development may serve as mediators and initiate cartilage breakdown in areas previously not affected by the focal lesion, thus leading to OA onset and progression. Since for the analysis of our study only asymptomatic subjects without any pain were included, our findings indicate that higher T2 values are associated with higher risk for development of morphologic cartilage lesions and that T2 may therefore serve as an indicator for early stages of initiating OA.

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#### 6.3.4 Limitations

A limitation of our study was, that we only obtained T2 values of the patella. Cartilage segmentation is a very time-consuming process, which may take up to four hours for one knee. More automated and faster segmentation techniques that would also potentially allow for clinical application of T2 quantification in the future are currently being investigated. All cases were drawn from the same pool of eligible knees. However, our results may still be influenced by uncontrolled covariates including any that resulted from the selection process. Another limitation is that we only used T2 mapping for assessing the biochemical composition of cartilage. The OAI protocol unfortunately only includes a T2 mapping sequence, without the possibility to compare T2 to other promising techniques like T1rho or dGEMRIC. Although images were scored separately, a consensus reading was performed if scores were not identical. A separate reading for both observers with subsequent comparison of the results might be a better approach. Reproducibility measurements were performed for 12 subjects and the inter- and intra observer agreements were calculated for the WOMBS cartilage score only. As WOMBS does not include the patellar tendon, we defined patella tendinosis as a grade 2 sprain and added the score to the WOMBS summation for ligaments to include the patella in our scoring system.

## 6.4 Implications for Patient Care and Future Development

Treatment options for OA are currently limited, but early identification of pre-radiographic knee OA could prove valuable once more effective disease-modifying interventions are available, since by the time even mild radiographic changes are apparent, destruction of joint tissues may already be irreversible. The potential of T2 to non-invasively evaluate biochemical and biophysical changes in the ECM of articular cartilage allow for the potential detection of early OA. T2 has been shown to be a sensitive parameter, particularly related to changes in water and collagen content as well as tissue anisotropy. In addition to diagnosis, potential applications for T2 may be therapy monitoring of newly developed pharmaceuticals or surgical techniques. The sensitivity of T2 to the integrity and properties of the collagen fibril network supports its potential usefulness for evaluating posttraumatic cartilage damage or to monitor the success of chondral repair procedures. In vivo cartilage evaluation can help to improve the understanding of cartilage function, its response to exercise, cartilage degeneration and treatment. T2 therefore may play an important future role as a marker for internal joint derangement in terms of cartilage and meniscal lesions.

At present however, the individual implications of elevated T2 values for prevention and treatment are uncertain. Paralleling the interpretation of decreased or increased T2 values, there is currently no consensus about normal T2 reference values. Significant T2 differences can be observed between studies, that may mainly be related to varying acquisition and post-processing parameters. In addition, T2 highly depends on the hardware and coils used for acquisition [111]. Hannila et al. reported initial results on the topographical variation of T2 values among young, healthy volunteers, to assess normal variation and physiological T2 distribution, which is of crucial importance [50]. In a larger frame, the NIH launched the Osteoarthritis Initiative, which includes a T2 mapping sequence and provides an extensive valuable research database [114].

Future studies will have to determine whether T2 may be used as a reliable surrogate measure for cartilage health. In particular, further longitudinal multiple time point studies are necessary to determine the changes of T2 over time in healthy individuals as well as in OA patients. Moreover, investigation of focal T2 changes at the site where cartilage lesions occur are warranted to determine whether baseline

T2 values predict the onset of morphologic cartilage lesions in knees without any detectable morphologic cartilage damage. More studies measuring T2 are therefore needed to establish the role of T2 in the sequence of pathological events in cartilage and other tissues leading to onset of OA.

## 7 Conclusion

In conclusion our study demonstrates, that non-symptomatic individuals with risk factors for knee OA show a high prevalence of knee abnormalities on MRI, particularly at the articular cartilage and meniscus lesions. It was shown, that physically active individuals present with significantly higher numbers of cartilage and meniscus abnormalities as well as higher patellar cartilage T2 values. The results of our study indicate that elevated T2 relaxation time measurements at the patella may be a marker for cartilage and meniscal degeneration.

The individual implications of elevated T2 values for diagnosis, prevention and treatment are presently uncertain, however, this study is part of our effort to support a paradigm shift in osteoarthritis research and treatment from palliation of late disease towards diagnosis at the earliest time possible to allow for early disease modifying interventions, even if treatment options may currently be limited.

## 8 Summary/ Abstract

### 8.1 Abstract in English

#### *Analysis of the Osteoarthritis Initiative Incidence Cohort: Patellar Cartilage T2 and Focal Knee Pathology Derived from 3T MRI in Relation to Physical Activity*

**Purpose:** The aim of this study was to evaluate the interrelationship between patellar cartilage T2 relaxation time measurements derived from 3T MRI, focal knee abnormalities assessed with WOMBS grading, and physical activity levels in clinically asymptomatic subjects from the Osteoarthritis Initiative (OAI) incidence cohort.

**Materials and Methods:** Institutional review board approval was obtained and the study complied with all regulations. One hundred twenty subjects without knee pain (WOMAC score of 0) aged 45–55 years with risk factors for knee osteoarthritis (OA) were randomly selected from the OAI Incidence Cohort. Subjects were studied by using knee radiographs, 3.0 Tesla knee magnetic resonance (MR) images including intermediate-weighted fast spin echo and T2 mapping sequences. Furthermore the Physical Activity Scale for the Elderly (PASE) score result for each subject was obtained from the OAI database. Two musculoskeletal radiologists assessed the MR images of the right knee for the presence and grade of abnormalities using WOMBS grading. Manual segmentation of the patellar cartilage was performed on the T2 maps and T2 relaxation time measurements were calculated from the generated regions of interest. Statistical significance was determined by using analysis of variance (ANOVA) and a multiple linear regression model adjusted for age, sex, BMI and clinical risk factors. Reproducibility was assessed calculation the correlation coefficient using Cohen's Kappa. Post-hoc Student's t-test and Chi Square test were used to evaluate group differences. A p value of 0.05 was used to determine the level of statistical significance for all analyses.

**Results:** Cartilage lesions were found in 95 (79.0%) of 120 knees, and meniscal lesions were found in 54 (45%) of 120 knees. Subjects with high activity levels (higher PASE score) had significantly higher prevalence and grade of abnormalities. Furthermore, subjects with high activity levels showed significantly higher patellar T2 values than subjects with lower PASE score ( $48.7 \pm 4.35$  ms versus

45.8±3.93 ms;  $p < 0.001$ ). Significant associations of patellar T2 with PASE grading ( $p < 0.001$ ) and the severity and grade of cartilage and meniscus lesions were found (association of patellar T2 with maximum WOMBS grade:  $p < 0.001$ ; association of patellar T2 with maximum Reicht score:  $p < 0.001$ ). Stratified by lesion status, patellar T2 values differed significantly depending on physical activity levels both in subjects with and without lesions (T2 of subjects with cartilage lesions/ high activity: 49.72±4.42 ms; subjects with lesions/ low activity: 47.0±3.77 ms;  $p = 0.0199$ ; subjects without lesions / high activity: 47.0±3.72 ms versus subjects without lesions / low activity: 44.7±3.79 ms;  $p = 0.0275$ ).

Conclusion: Middle-aged asymptomatic individuals with risk factors for knee OA were shown to have a high prevalence of cartilage and meniscus knee lesions. Physically active individuals had more and more severe knee abnormalities as well as higher patellar T2 values compared to more sedentary subjects. Causality and significance of elevated T2 values have yet to be determined, however, T2 may serve as an important non-invasive biomarker for early degenerative cartilage changes associated with osteoarthritis.

## 8.2 Summary in German / Zusammenfassung

*Analyse der "Osteoarthritis Initiative Incidence Cohort": 3T MRT basierte Messungen der T2 Relaxationszeit des Patellarknorpels und fokale Kniegelenkläsionen in Zusammenhang mit körperlicher Aktivität*

Zielsetzung: Ziel der Studie war es, den Zusammenhang von 3 Tesla Magnetresonanztomografie (MRT) basierten Messungen der T2 Relaxationszeit des Patellarknorpels mit der Prävalenz fokaler Gelenkläsionen sowie der Höhe körperlicher Aktivität in einem asymptomatischen Patientenkollektiv der "Osteoarthritis Initiative (OAI) Incidence Cohort" zu untersuchen.

Material und Methoden: Die Durchführung der Studie erfolgte mit Zustimmung der lokalen Ethikkommission. Einhundertzwanzig Personen im Alter von 45–55 Jahren, mit Risikofaktoren für die Entwicklung von Kniearthrose, jedoch ohne Knieschmerzen (WOMAC Score von 0), wurden randomisiert aus der "OAI Incidence Cohort" ausgewählt. Es wurden die Röntgenbilder sowie 3.0 Tesla MRT Daten der Probanden mit intermediate-weighted fast spin echo Sequenzen und einer T2 mapping Sequenz ausgewertet. Desweiteren wurde der im Rahmen der "OAI" erhobene Aktivitätsindex "Physical Activity Scale for the Elderly" (PASE) verwendet. Zwei muskuloskelettal spezialisierte Radiologen evaluierten die Prävalenz und Schwere von Gelenkpathologien mit Hilfe der WOMMS Einteilung im jeweils rechten Knie der Probanden. Nach der manuellen Segmentierung des Patellarknorpels wurden die T2 Relaxationszeiten in den Segmentierungsarealen berechnet. Statistisch signifikante Unterschiede wurden mit Varianzanalysen (ANOVA) sowie mit Hilfe eines linearen Regressionsmodells, das für mehrere klinische Riskikofaktoren sowie die Variablen Alter, Geschlecht und Gewicht (Body Mass Index) adjustiert wurde, berechnet. Die Reproduzierbarkeit wurde durch Berechnung des Cohen's Kappa Korrelationskoeffizienten bestimmt. Weitere Unterschiede zwischen den Gruppen wurden mittels Post-hoc Student's t-Test und Chi Square Test bestimmt, wobei für alle Berechnungen ein Signifikanzniveau mit einem p- Wert von  $<0.05$  festgelegt wurde.

Ergebnisse: Der Anteil der Knie mit Knorpelläsionen betrug 95 (79.0%) von 120 untersuchten Probanden, Meniskuspathologien wurden in 54 (45%) Fällen beobachtet. Probanden mit höherer körperlicher Aktivität (hoher PASE Score) zeigten

eine höhere Anzahl und Schwere von Knorpelläsionen sowie höhere patellare T2 Werte als Probanden mit niedrigem PASE Score ( $48.7 \pm 4.35$  ms versus  $45.8 \pm 3.93$  ms;  $p < 0.001$ ). Es zeigten sich statistisch signifikante Zusammenhänge zwischen patellaren T2 Werten und PASE Score Werten ( $p < 0.001$ ), sowie mit der Prävalanz und Schwere von Knorpel- und Meniskusläsionen (Zusammenhang Patella T2 und maximaler WORMS Wert:  $p < 0.001$ ; Zusammenhang Patella T2 und maximaler Recht Score:  $p < 0.001$ ). Eine Stratifikation der Probanden basierend auf der Prävalenz von Knorpelläsionen zeigte eine Abhängigkeit der patellaren T2 Werte vom körperlichen Aktivitätsniveau sowohl in der Gruppe mit Knorpelläsionen (T2 Werte in ms; Gruppe mit hohem PASE Score und Läsionen:  $49.72 \pm 4.42$ ; Gruppe mit niedrigem PASE Score und Läsionen:  $47.0 \pm 3.77$ ;  $p = 0.0199$ ) als auch in der Gruppe ohne Knorpelläsionen (T2 Werte in ms; Gruppe mit hohem PASE Score ohne Läsionen:  $47.0 \pm 3.72$  versus Gruppe mit niedrigem PASE Score ohne Läsionen:  $44.7 \pm 3.79$ ;  $p = 0.0275$ ).

Schlussfolgerung: Asymptomatische Probanden mittleren Alters mit Riskofaktoren für Gonarthrose zeigten eine hohe Prävalenz von Knorpel- und Meniskuspathologien. Probanden mit höherem körperlichem Aktivitätsniveau zeigten in Anzahl und Schwere vermehrte pathologische Veränderungen des Kniegelenkes, sowie erhöhte patellare T2 Werte im Vergleich zu weniger aktiven Probanden. Ursache und Bedeutung erhöhter T2 Werte wurden noch nicht vollständig geklärt, jedoch könnte T2 Relaxationszeit zukünftig eine wichtige Rolle als nicht invasiver Parameter für frühe degenerative Knorpelveränderungen in Zusammenhang mit Arthrose spielen.

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## 10 Appendices

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### 10.3 Clinical Readout Sheet

## Clinical Score Sheet

Menisci	Location	Visualization	WORMS	Other pathology	Size	
	1					
	2					
	3					
	4					
	5					
	6					
Ligaments/Tendons	Location	Visualization	WORMS			
	1					
	2					
	3					
	4					
	5					
	6					
Cartilage	Location	Visualization	WORMS	RECHT	Size	
	1					
	2					
	3					
	4					
	5					
	6					
Bone marrow edema	Location	Visualisation	WORMS-Mink	Additional morphological finding	Size	Signal intensity
	1					
	2					
	3					
	4					
	5					
	6					
Articular surface	Location	Visualization	WORMS		Size	
	1					
	2					
	3					
	4					
	5					
	6					
Articular cysts	Location	Visualization	WORMS	Numbers	Size	
	1					
	2					
	3					
	4					
	5					
	6					
Osteophytes	Location	Visualisation	WORMS		Size	
	1					
	2					
	3					
	4					
	5					
	6					
Synovial thickening	Location	Visualization	WORMS		Size	
Loose bodies	Location	Visualization	WORMS	Numbers	Size	
	1					
	2					
	3					
	4					
	5					
	6					
Popliteal Cysts		Visualisation	WORMS	Numbers	Size	

## 10.4 Acknowledgement

### 10.4.1 Data Use Agreement

Part of the data presented in this manuscript was prepared using an Osteoarthritis Initiative (OAI) public use data set (available for public access at <http://www.oai.ucsf.edu/>) and does not necessarily reflect the opinions or views of the

OAI investigators, the NIH, or the private funding partners. The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health.

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#### 10.4.2 Data Published prior to Submission of the Thesis

Data and results presented in this thesis have been previously published in the journal article by Stehling, Liebl et al. "Patellar Cartilage: T2 Values and Morphologic Abnormalities at 3.0-Tesla - MR Imaging in Relation to Physical Activity in Asymptomatic Subjects from the Osteoarthritis Initiative" as published in "Radiology" [144]. The figures illustrating the cartilage WOMBS score have in part been published in the book "Cartilage Imaging – Significance, Techniques and New Developments" edited by Thomas Link [85].

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