TECHNISCHE UNIVERSITÄT MÜNCHEN

Abteilung für Radiologie

Analysis of Cartilage T2 Values of the Patella and Trochlea Derived from 3T MRI in Asymptomatic Subjects and the Correlation with Muscle Strength and Physical Activity

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INTRODUCTION

Osteoarthritis (OA) is the most common form of arthritis, a chronic disease and the major cause of activity limitation and physical disability in elderly people. Today, nearly 27 million individuals in the United States have clinically symptomatic OA and radiographic evidence is seen in at least 70% of the population over the age of 65 years(1). 35 million people are 65 and older, and more than half of them have radiological evidence of OA in at least one joint. According to the U.S. Census Bureau, by 2025, 18.5 % of the population will be elderly persons and at risk for OA. The elderly are projected to be more than three times as many in 2050 as today, and to comprise nearly 17 percent of global population, compared with seven percent in 2002(2).

Despite of the fact that OA is a disease of the elderly population, age alone does not cause a degeneration of joints. Besides mostly age associated loss of muscle strength, there are also other risk factors such as female gender, overweight/obesity and knee injury that lead to an increased susceptibility to this disease(3).

OA is a slowly progressing disease characterised clinically by pain, enlargement and deformity of the joints and limitation of joint motion. It is the leading cause of disability and work limitation among adults. The disease occurs usually late in life and most commonly affects the hand and large weight bearing joints. Even though the hands are one of the most commonly affected sites in OA, the knee is the major source of reported disability and loss of function. It is diagnosed by a combination of joint symptoms and radiographic changes(4).

Pain, stiffness, and limited function are the most common problems caused by OA. In addition to clinical findings, the disease is characterised by typical findings in radiographs and magnetic resonance imaging (MRI), which can be semi-quantitatively evaluated by using Kellgren-Lawrence scale (KL) and the Whole-Organ Magnetic Resonance Imaging Score (WORMS). By using these scales, findings as osteophytes, joint space narrowing, cartilage defects, meniscal and ligamentous abnormalities, bone marrow oedema, and subchondral cysts can be rated in an internationally approved system(5).

However, there is a lack of knowledge of factors initiating the process of OA(6). One of the major reasons is that ancient conventional radiographic studies did not allow the analysis of early

stages of the disease. Therefore, a method detecting a subclinical stage before the occurrence of pain stiffness and limitation of range of motion would be helpful to assess the individual predisposition or the progress of OA.

Especially, studies have shown the potential of MR imaging parameters to reflect changes in the biochemical composition of cartilage in early OA. These techniques include T2, T1rho quantification and delayed gadolinium-enhanced MRI of cartilage (dGEMRIC). They allow a characterisation of the cartilage matrix, probably already before morphological damage occurs(7).

GOALS

The study is based on the data of the Osteoarthritis Initiative (OAI), a longitudinal multicentre and NIH funded study. It focuses on healthy, middle-aged subjects (45-55 years) from the Incidence Cohort with high and low levels of physical activity and no clinical symptoms of pain. The subjects were analysed at baseline and after 24 months.

The specific aims were defined as follows:

1. To study whether T2 relaxation times of the trochlea and patella are related to the severity of focal cartilage and meniscus lesions as determined by semi-quantitative WORMS scores using 3Tesla knee MRI and to KL scores determined on radiographs of the knee.

2. To analyse if asymptomatic subjects with higher cartilage T2 relaxation time or with morphological knee abnormalities at baseline were more likely to develop increased pain, limited function, and reduced physical activity after 24 months compared to subjects with low T2 values and without knee abnormalities.

3. To correlate cartilage T2 values with physical activity levels (PASE scale) and thigh muscle volume and strength to examine whether muscle strength has a protective impact on the knee joint.

The idea of using a novel direct segmentation technique for T2 maps was encouraged by the findings of Stehling et al.(8). They demonstrated that this way of measuring the thickness and the T2 values, but not the volume of cartilage in the knee, is equal to a segmentation in T1 echotime sequences but less time consuming (45 min. compared to 5h for one knee).

BACKGROUND

OSTEOARTHRITIS

Osteoarthritis is the most common form of arthritis and a slowly progressing joint disease that is characterised, as mentioned before by pain, enlargement of the joints, and limitation of the range of motion. OA is considered to be a degenerative osteoarticular disease with multiple affected targets including articular cartilage (AC), synovium, and subchondral bone(9). During OA major damage of the AC is observed at the morphological, cellular, and molecular levels combined with alterations of the synovium and the subchondral bone(9, 10). AC is a slick, white tissue that covers joint surfaces. It lacks blood vessels and nerves and is composed of an extracellular matrix (ECM) produced by chondrocytes. As cartilage is an avascular tissue it has a low oxygen tension, ranging from 1 to 7%. Therefore, the chondrocytes are developmentally adapted to these hypoxic conditions and have an enhanced anaerobic glycolysis and thereby play a central role in the equilibrium between ECM synthesis (anabolism) and degradation (catabolism)(9).

AC is organized into four layers according to the morphology of the chondrocytes, the orientation of collagen fibres, and the amount of proteoglycans (PG) and water(9). The outer surface is in contact with the synovial fluid and provides a frictionless surface. In the transitional area, the network is less dense and less hydrated than that of the outer articular surface and chondrocytes have a round morphology (figure 1)(9). In the deep area of the AC, chondrocytes form radial columns and are aligned along the collagen fibres perpendicular to the subchondral bone. In the

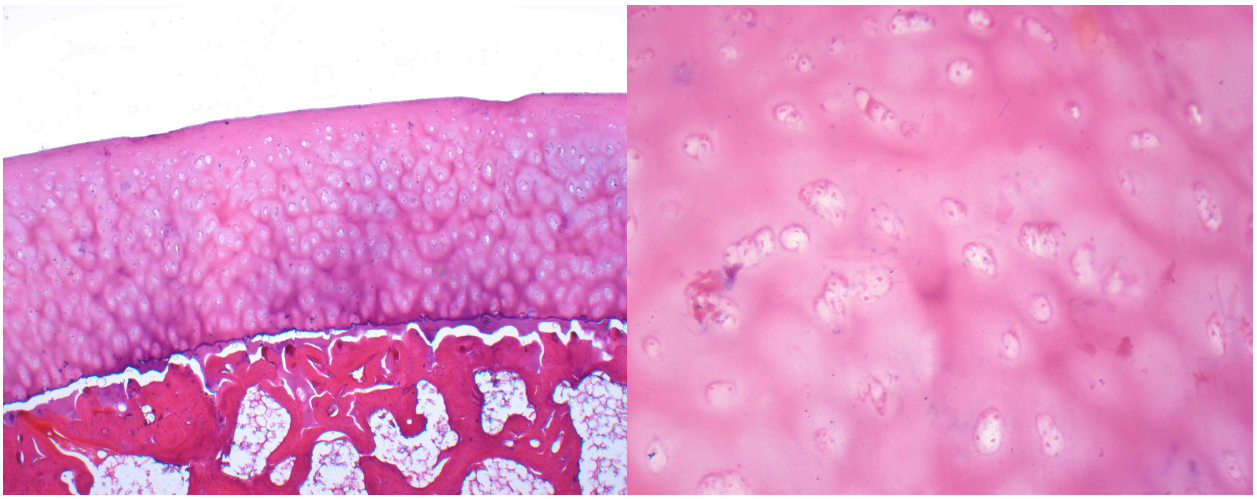


Figure 1: Left side: Low magnification of articular cartilage with subchondral bone. Right side: Higher magnification of the basal proliferative zone, with the chondrocytes showing a broad rounded eosinophil cytoplasm (hematoxylin-eosin stain). With permission of the Institute of Pathology of the Ludwig Maximilians University Munich.

basal area the collagen fibres calcify and thereby, the cartilage is anchored to the subchondral bone. This histological organisation relates to the biomechanical properties of cartilage. The orientation of the collagen fibres reduces the intra-cartilagenous friction and compression is mainly restricted to the surface and the deep area of the AC(9).

The ECM is mainly composed of collagen type I in bone and synovia, type II in cartilage, associated with PGs, and structural glycoproteins(11). Interposed within the collagen framework are PGs, which are negatively charged and bind cations, mainly sodium. Thereby, the osmolarity of the ECM increases by drawing water into the cartilage and by causing the hydrated PGs to swell(12). These aggregates are constricted in their extension within the collagen framework and thereby place the network under tension. The capacity of cartilage to withstand and adapt to repetitive compression is achieved by the movement of water through the solid matrix(13).

At equilibrium in a healthy cartilage, the collagen framework balances the swelling pressure of the proteoglycans and provides cartilage with compressive stiffness(12). Thereby, the compressive load is dissipated and the ECM is protected(12). When this balance is impaired, the PGs are no longer constrained by the tension of the collagen network, and thereby can bind a higher amount of water, resulting in a higher compressibility of the matrix(10). This leads to the fact, that a greater portion of the load is carried by the solid components of the ECM(12). After years, this impairment leads to increased stress, structural fatigue and fragmentation of cartilage. Finally, these changes of the cartilage matrix result in cartilage fibrillation, proliferation, and ulceration (illustrated in figure 4/5, page 11/12)(12).

ETIOLOGY OF OSTEOARTHRITIS

If a primary insult occurs regardless of whether it is inflammatory, mechanical or immunogenic in character, the balance between synthesis and degradation of ECM, normally controlled by chondrocytes, is disturbed and cartilage degeneration ensues(10).

Once established, OA is characterised by changes in the morphological structure. Characteristic changes are the decrease in articular cartilage thickness, subchondral bone sclerosis (bone thickening), formation of osteophytes (bone outgrowth on the joint margin), and modification of the synovial fluid composition (figure 2, (14))(9).

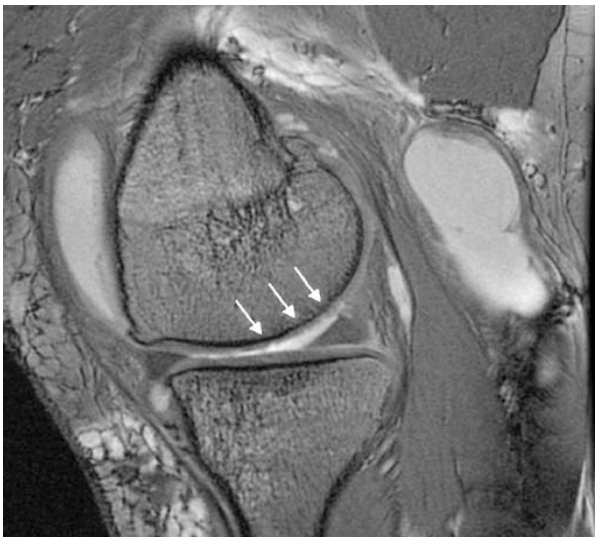


Figure 2: Sagittal MR image in a patient with osteoarthritis and extensive cartilage lesions at the medial femoral condyle of the knee joint (arrows). The image was obtained with a SSFP sequence (5.5/1.9 ms/15 degrees) without fat saturation. Cartilage is intermediate to low in signal and fluid is bright; note large joint effusion and baker cyst as well as osteophytes. Taken from (14).

Looking at the cartilage, loss of volume and average thickness is found during the progress of OA(15). Additionally, a progressive degradation of components of the ECM, an increased bone turnover accompanied by secondary inflammatory factors is commonly seen. The major component of cartilage is water, increasing from 67% near subchondral bone to 74% near the articular surface(12, 16). The remaining 25% to 35% are solid matrix, primarily type II collagen fibres and large aggregating proteoglycans(12, 17).

As mentioned before, the composition and distribution of the solid matrix influences the tissue permeability and thereby produces a regional variation in cartilage compressibility(12, 18). Typical consequences in the development of cartilage matrix breakdown are the loss of PGs, changes in water content (increase and loss), molecular alteration of collagen and consequently swelling of the cartilage. This results in a change of the functional activity of the chondrocytes(14).

Especially during aging, chondrocytes lose their responsiveness to stimuli from growth factors so that a dynamic load (physical activity), that would lead to a reparative matrix synthesis, does no longer take place(3). Loss of PGs is an initiating event in early OA, whereas neither the content nor the type of collagen is altered in early OA(10). Complicating is the fact that AC lacks nerves and therefore can be damaged without leading to a sensation of pain(19, 20).

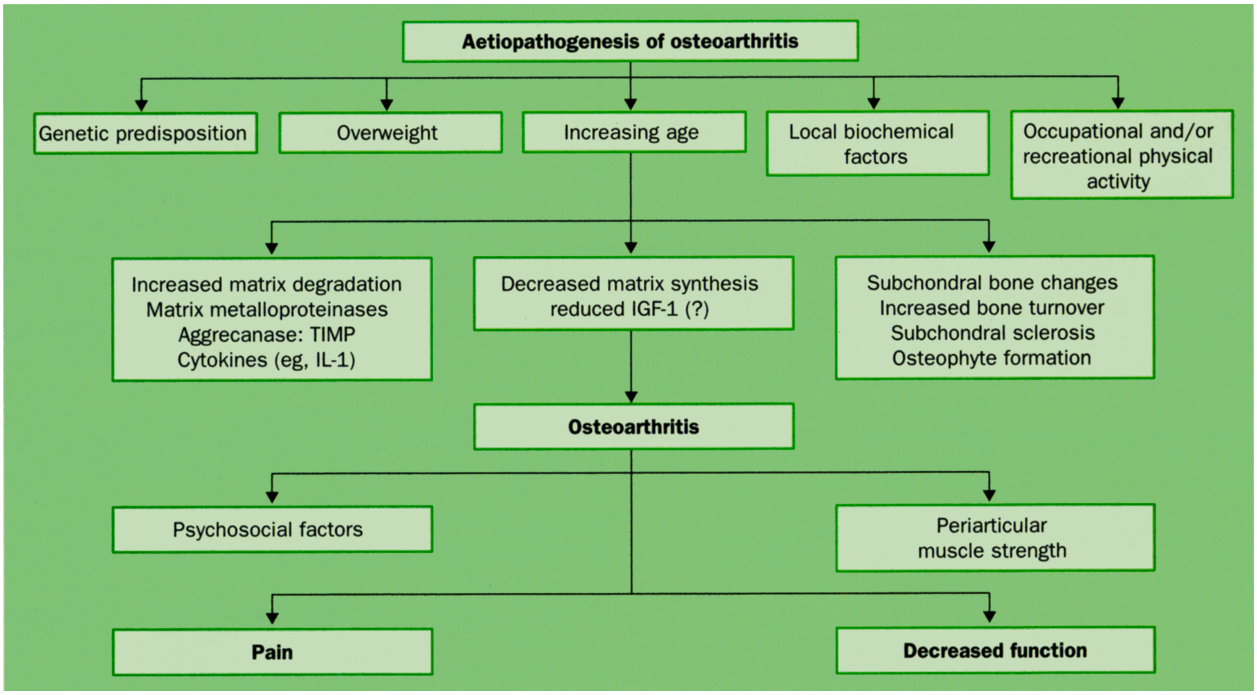


Table 1: Etiopathogenesis of osteoarthritis, according to(21).

Besides cartilage loss, a number of other findings are frequently associated with OA, such as bone marrow oedema (BMEP) and synovial and ligamentous lesions. These lesions coming along with cartilage loss have a substantial influence on the progression of the disease and the ensuing loss of clinical function(5). Searching for disease causing influences, there are different intrinsic and extrinsic factors that are acting on the joint(table1 (21)). More specific, obesity, muscle weakness, joint laxity, and joint overuse are leading causes(21-24). In this respect, it was found that a high Body Mass Index (BMI), previous knee pain, presence of Heberden' s nodes, hand OA, female gender, older age, certain physical occupational activities (e.g. kneeling, squatting), and increased bone mineral density are risk factors for the onset of knee OA in older adults(25).

Looking at the pathogenesis of osteoarthritis and the change in cartilage matrix, different stages can be detected. The main biochemical characterisations in the initial stage of OA are the

reparative processes involving increased synthesis of ECM, the proliferation of chondrocytes, and the loss of PGs (figure 3)(23).

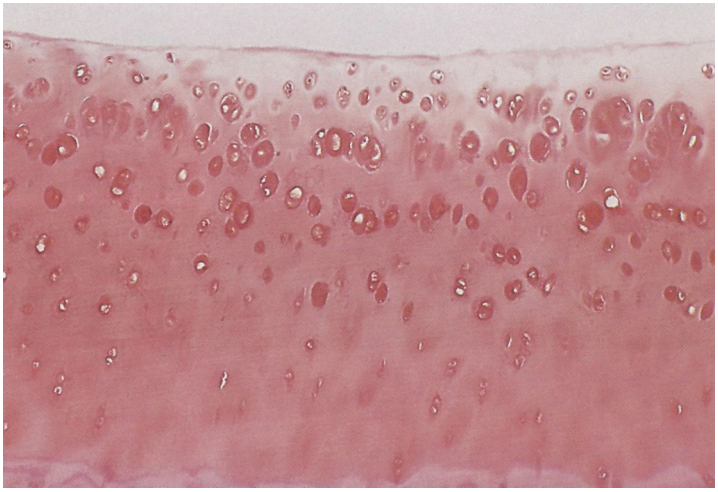


Figure 3: The early stage of OA. Loss of PG in the superior zone coming along with proliferation of chondrocytes in the adjacent zone which is a characteristic feature of cartilage repair. (SafranO stain). With permission of the Institute of Pathology of the Ludwig Maximilians University Munich.

In the early stage of the degeneration, an increased synthesis and activity of proteases is predominant, resulting in loss of cartilage. This is associated with focal swelling and subsequent irregularities in the surface. On the other hand, the cartilage still tries to adapt to the degeneration by increasing the synthesis of structural glycoproteins, collagen, and PGs(9, 10). However, the newly produced cartilage does not show as much resistance to physical stress. This is manifested by alterations of the chain length of glycosaminoglycan (GAG) and proteoglycan subunits and by the decreased capacity of forming aggregations with hyaloronic acid(10). In consequence, the reparative process leads to an insufficient repair of the cartilage. Additionally, due to proteolytic enzymes and mechanical wear, there is disorganisation of the collagen network including cleavage, thinning, vertical and horizontal splitting of the collagen fibrils (figure 4)(10, 17, 26, 27). This regrouping is mainly present in cartilage in the intermediate phase of OA.

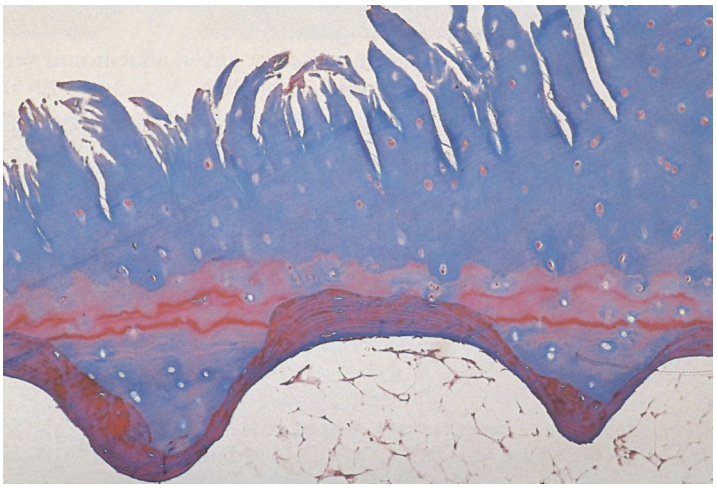


Figure 4: Progressed OA stage. Deeper fissures in the cartilage layer with multiplication of the tidemarks. With permission of the Institute of Pathology of the Ludwig Maximilians University Munich.

In progressive disease, the loss of proteoglycans is accentuated proportionally to the severity of the osteoarthritic degeneration(17). This loss also results in decreased water content, which is of

great pathogenetic importance since, as already mentioned, cartilage consists approximately of 70% water. The loss of water consequently attributes to decreased resilience and elasticity(10, 14, 17).

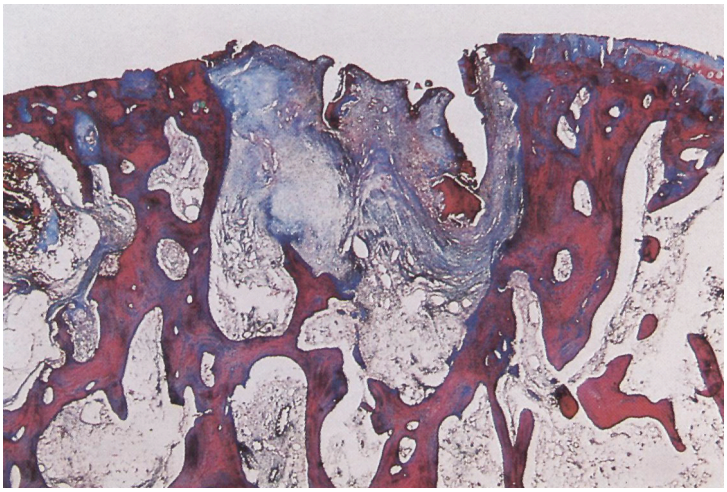


Figure 5: Late stage of OA showing loss of articular cartilage on the surface with denudation of the subchondral bone and cyst formation of the bone marrow. Azan stain. With permission of the Institute of Pathology of the Ludwig Maximilians University Munich.

In the late stage of the disease with manifested clinical pain, loss of articular cartilage progresses and results in extensive defibrillation, chondrocyte necrosis, disorganised collagen network, and a denudation of subchondral bone and cyst formation appear (figure 5)(10, 12).

As osteoarthritis does not only affect the joint itself but also the adjacent structures, thickening of the subchondral bone is frequently seen and blood vessels penetrate the subchondral bone. Furthermore, bone marrow oedema (BMEP) and cavities are common features(28). Summarising, the osteoarthritic progress does not only affect the cartilage but also the surrounding bone structure and the synovial membrane.

To diagnose osteoarthritis there are several ways like radiographs, magnetic resonance tomography and biomedical markers. Biomedical markers such as cartilage oligometric matrix protein (COMP), bone sialoprotein (BSP), chondroitin sulphate chains of PGs or propeptides of type II procollagen (PIICP and PIINP) show changes in osteoarthritis(29). These markers are not unique to OA and show considerable variability across individuals, so that they may be more useful as a complement to clinical and radiological criteria(11, 30). More specifically, chondrocyte-derived matrix metalloproteinases (MMPs-2,-7,-8,-9,-13,-14), a catabolic enzyme family involved in the degradation of cartilage collagens and PGs in OA, have mostly been found to be elevated in synovia and cartilage in patients suffering from OA(9, 31).

Remarkably, also adipokines like leptin, adiponectin and resistin, normally produced by white adipose tissue, have been found to be elevated in synovial fluid of patients with OA(32). Therefore, fat tissue can be regarded as an active organ involved in immuno/inflammatory

processes during degenerative processes in OA(9).

Joint pain, morning stiffness, instability, and loss of function depict the clinical criteria. In addition, impairment of the range of motion, crepitus or bony enlargement of the joint are common features(21). As these criteria are very subjective and have a high inter-individual variability, radiography has been the most valid and reliable non-invasive method to diagnose OA until now. Using Western Ontario Mc Master Osteoarthritis Index (WOMAC) and Kellgren-Lawrence Scale the range of osteoarthritic degradation is standardised. Knowing that X- Rays may not show the early stage of the disease before severe cartilage loss has taken place, MRI has become more important in the diagnostic analysis of OA, especially in early stages.

DIAGNOSTIC TECHNIQUES

RADIOGRAPHS

Radiography is the gold standard for the diagnosis of the advanced, more progressed stage of OA where cartilage is irreversibly damaged or lost. This morphological imaging is used to depict a degeneration of the bone structures, whereas it is not suitable for the detection of cartilage degeneration itself. Hence, radiographs are notoriously insensitive to the earliest pathologic features of the knee OA. The absence of positive radiographic findings therefore should not be interpreted as confirming the absence of the disease. Controversially, the presence of positive radiographic findings does not guarantee that an osteoarthritic joint is the active source of the patient's current knee symptoms(33, 34). The most commonly used radiographic scoring system of OA is the Kellgren-Lawrence scale (see Appendix) based on the presence of osteophytes, loss of joint space width, subchondral sclerosis and attrition of the bone (figure 6,(5)). In contrast, MRI based technologies are most promising since they give information about the quality and quantity of cartilage(5). Therefore, they might allow the imaging of matrix changes and cartilage destruction in an early stage of OA.

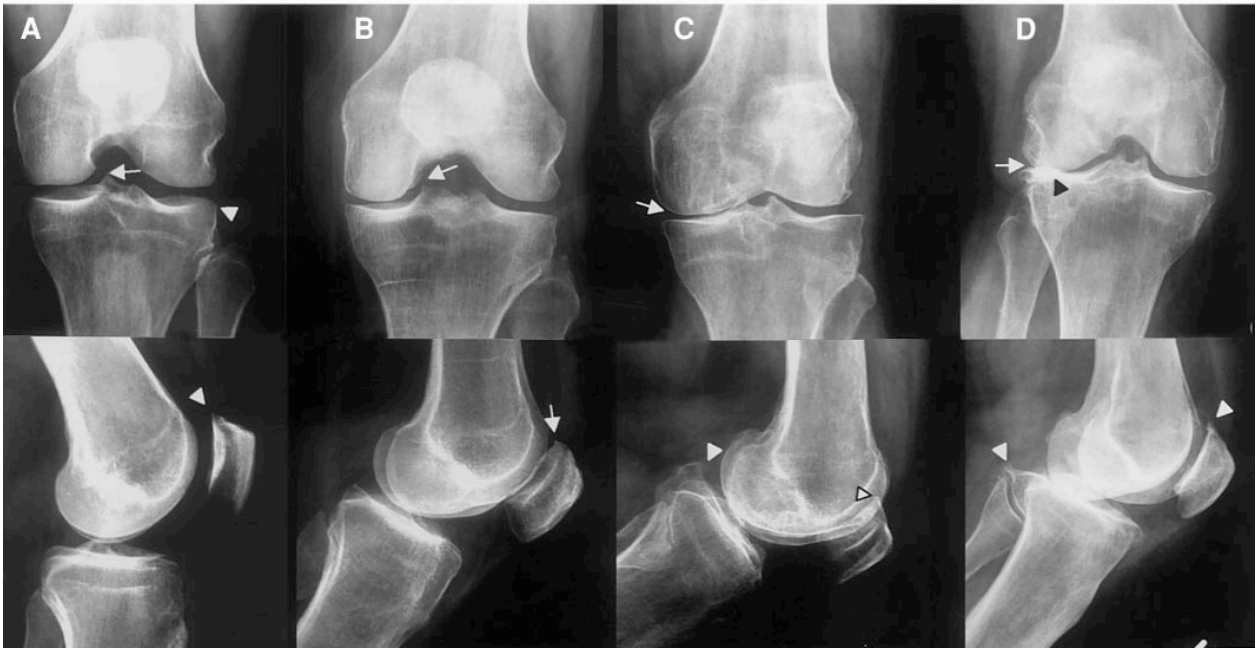


Figure 6: Conventional radiography. Anteroposterior (top) and lateral (bottom) radiographs of knees with KL scores of 1–4. *A,* Knee with a KL score of 1 with minimal osteophytes at the medial femoral condyle (arrowhead in anteroposterior view) and the patellar joint surface (arrowhead in lateral view), 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 narrowed joint space (arrow) and osteophytes (arrowheads). *D,* Knee with a KL score of 4 with substantially narrowed joint space (arrow), severe osteophytes (white arrowheads), and sclerosis of subchondral bone (black arrowhead). Taken from(5).

There are some other advantages of MRI compared to radiography besides no radiation. Because of the tomographic viewing perspective, it can delineate osteophytes more reproducibly than radiography and detect osteophytes in locations that would otherwise be obscured by projectional superimposition in conventional radiographs(35).

The MRI produces a magnetic field and radiofrequency that aligns the atoms of the scanned body. Thereby, a good soft tissue contrast is provided by forcing the nuclei to produce a rotating magnetic field. The magnetic field is detected by the scanner and recorded as an image of the scanned area.

MRI has two different sequences, the longitudinal relaxation time (T1) and the transversal relaxation time (T2). In a T2 weighted scan water and fluid containing tissues, such as cysts and oedema or the liquor, are hyperintense/bright and can be distinguished from fatty tissue, which is hypointense/dark. T2 MRI reflects the ability of free water proton molecules to move and to exchange energy. Therefore, estimation of cartilage T2 relaxation times is sensitive to a wide range of water interactions in tissue. As damaged tissue tends to have an increased water content T2 weighted sequences are sensitive to tissue pathologies(36). For tissues, such as cartilage, that have restricted water mobility T2 relaxation time is best suited(37). In contrast, T1 is well suited for the illustration of the anatomic structures and fatty tissue, such as bone marrow, by imaging fat as hyperintense and water as hypointense signal(36).

In addition to different sequences, there is also the possibility to use different field strengths. Though the standard is 1.5 T imaging, a number of studies(38-43) have demonstrated that 3.0 T MRI allows better visualisation of cartilage lesions and may therefore be more suitable for the overall assessment of OA. Link et al.(14) showed in an animal model that cartilage lesions were visualised in a better way and diagnostic performance was improved at 3.0 T compared to 1.5 T using optimised high resolution MRI sequences. Figure 7(14) shows two corresponding intermediate-weighted fat-saturated MRI obtained at 1.5 and 3.0 T in a pig knee demonstrating a superficial cartilage defect at the patella (arrow), which was better visualised at 3.0 T.

Similarly studies on human cadaver ankles also showed an improved diagnostic performance and a significantly higher specificity and accuracy ($p < 0.05$) in assessing cartilage lesions at 3.0 T versus 1.5 T. The same applies to ligamentous and tendon pathology(38, 39, 44).

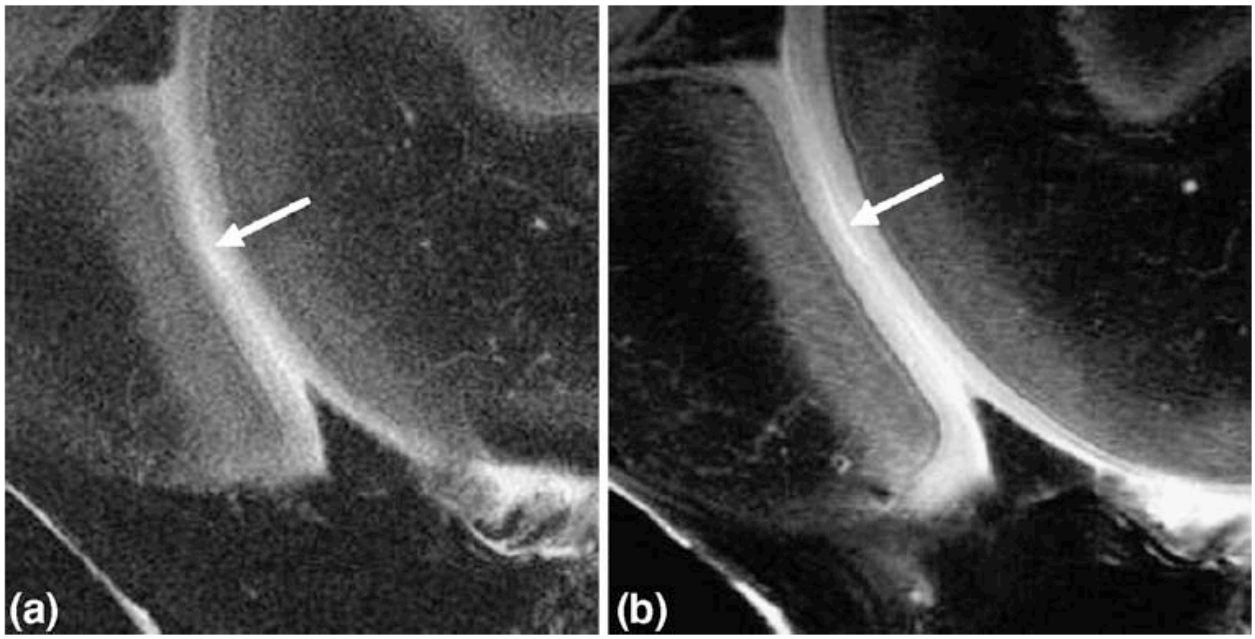


Figure 7: Sagittal MR images of a pig knee with artificially created patellar cartilage defect obtained at (A) 1.5 T and (B) 3.0 T using fat-suppressed IM-weighted FSE sequences (4000/35 ms; TR/TE for both 1.5; 3.0 T). Superficial cartilage defect at the patella (arrows) is well shown on the 3.0-T image (B) but is not well visualised on the 1.5-T image (A). Taken from(14).

QUANTITATIVE IMAGING OF THE CARTILAGE MATRIX

Searching for a marker that reflects the structural and molecular composition of cartilage is very important. In addition to assessing cartilage pathology as well as thickness and volume, recent studies have shown the potential of MRI parameters to reflect changes in biochemical composition of cartilage in early OA. These techniques include T2 quantification(45), T1rho quantification(46, 47), and delayed Gadolinium enhanced MRI of cartilage(48, 49). They also allow characterisation of the cartilage matrix and, potentially, of its quality before morphological damage occurs.

T2 QUANTIFICATION

Current clinical MRI evaluation of articular cartilage relies primarily on identification of morphological changes in damaged cartilage(50). These include determination of cartilage thickness and volume using three-dimensional T1-weighted fat-suppressed gradient-echo imaging and detection of superficial cartilage lesions, primarily with two-dimensional proton density-weighted fast spin-echo sequences. In addition to these anatomic techniques, new MRI parametric mapping techniques, such as cartilage transverse relaxation time (T2) mapping (figure 8), are being developed that exploit the sensitivity of MRI to biophysical properties of the tissue(12, 51).

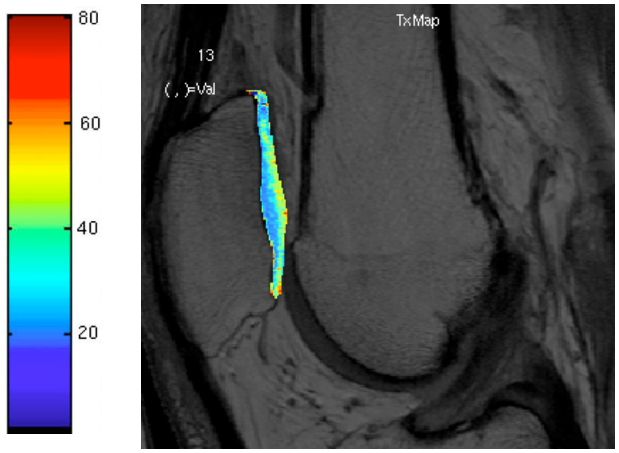


Figure 8: Colourmap of the patello-femoral joint. Taken from the OAI cohort. Subject with low PASE scale. Showing an early stage of osteoarthritic changes in the cartilage of the patella.

As water has a central role in the biochemical properties of cartilage, it is an ideal biomarker of cartilage damage and is used in MRI relaxation parameters, such as T2. It is used to provide a quantitative and non invasive facility for the study of cartilage water and of the interaction with ECM at a molecular level(12). The T2 values of cartilage are influenced by the anisotropy and the fiber orientation of the collagen tissue matrix and therefore T2 may be a marker for the integrity of the collagen

framework(12, 52). Additionally, T2 is sensitive to slow molecular motions of water protons and thereby to the process that occurs during the earlier stages of cartilage damage and in OA(12, 53). It was shown that increasing T2 relaxation time is proportional to the distribution of cartilage water and is sensitive to small water content changes(53). The spatial variation of in vivo cartilage T2 in young asymptomatic adults was examined and a reproducible pattern of increasing T2 that was proportional to the known spatial variation in cartilage water was found. Moreover, it was inversely proportional to the distribution of PGs(54). Therefore, it was postulated that the regional T2 differences might reflect the restricted mobility of cartilage water within the solid matrix. Thus, measurement of the spatial distribution of the T2 reflecting areas of increased and decreased water content may be used to quantify cartilage degeneration by quantifying the water content, macromolecular changes, and collagen anisotropy before morphological changes have occurred(52).

To summarise, there are three major modifications in cartilage that correlate with higher cartilage T2 values(12):

1. The fragmentation of collagen matrix and the loss of tissue anisotropy
2. The cartilage water content
3. The augmenting ECM permeability and thereby the higher water mobility

T1RHO QUANTIFICATION

A different parameter that has been proposed to measure cartilage composition is 3D-T1rho-relaxation mapping. T1rho describes the spin-lattice relaxation in the rotating frame in contrast to conventional spin-lattice relaxation time (T1). It is sensitive and specific to the slow macromolecular interactions especially at low frequency range (0–100 kHz). Changes in the cartilage ECM (loss of GAG and PG) may be reflected by increasing values(14, 52). Preliminary studies on T1rho using 1.5 T clinical scanner demonstrated also the in vivo feasibility of quantifying early biochemical changes in symptomatic OA participants(46, 47).

This method is mainly concentrating on loss of GAG and PG, while T2 mapping uses distribution of collagen and the variation on intrinsic water as a probe to study the structural integrity of the extracellular matrix(12, 54, 55). In a study with a limited number of symptomatic participants it was shown that T1rho-weighted MRI provided a marker for quantification of early degenerative

changes of cartilage in vivo(47). It was also detected that subjects with and without focal cartilage pathology had different T1rho and T2 composition of cartilage. Thereby, it was concluded that T1rho and T2 may be parameters suitable to identify asymptomatic subjects at higher risk for developing cartilage degeneration(56).

DELAYED GADOLINIUM - ENHANCED PROTON MRI

Delayed Gadolinium enhanced proton MRI (dGEMRIC) is a technique that measures changes of GAG and PG in ECM, and has been successful in quantifying PG changes(52). As mentioned before, cartilage consists of approximately 70% water, the remainder is predominantly composed of type II collagen fibers and GAG. These GAG macromolecules contain negative charges that attract sodium ions (NA^{+}).

One of the most commonly used MRI contrast agents Gadopentetate dimeglumine (Gd-$DTPA^{2}$; Magnevist®, Schering, Berlin, Germany) has a negative charge and does therefore not accumulate in areas of high GAG concentrations. In fact, it is distributed in higher concentrations in areas with lower GAG concentration and thus reflects pathologic alteration of the cartilage. Summarising, the lower the GAG content of the cartilage the higher the contrast enhancement of the agents and therefore the pathologic cartilage composition(14). Gd-$DTPA^{2-}$ concentrations in cartilage can be quantified. This technique has been defined as dGEMRIC.

Studies have shown that the dGEMRIC measurement of GAG corresponds to the true GAG concentration as measured biochemically and histologically(7, 48, 57). But it can not be used universally as gadolinium has toxic potential especially in patients with renal insufficiency by causing the irreversible so-called systemic nephrogenic fibrosis syndrome. Therefore, the main advantage of the T1rho and T2 MRI is that it can be used without the requirement of exogenous contrast agent and that it can easily be implemented on any clinical scanner without special radiofrequency and hardware modification(52).

SEQUENCE PROTOCOLS

Given the fact that different tissues are involved in OA a number of different sequences have been developed for "whole-organ" assessment of OA. All those sequences have in common that both morphological and quantitative analyses are required. Standard sequences to gather good results in morphological imaging of cartilage and subchondral pathology in MRI are the T2-weighted-, 2D proton density (PD)- and intermediate- (IM) fast-spin-echo (FSE), the 3D spoiled gradient-echo (SPGR), and the fast low angle shot (FLASH) gradient echo sequences.

FAST-SPIN-ECHO SEQUENCES

The most commonly used sequences for morphological joint imaging are fast-spin-echo sequences(7). These sequences are most commonly used for the evaluation of the knee ligaments and the menisci(14, 58). T2- and PD-FSE have a high sensitivity (96%) and specificity (98%) depicting internal pathology by having an intermediate signal with high intrinsic cartilage contrast. With IM- and T2-weighted FSE sequences, normal hyaline cartilage is intermediate in signal and fluid is bright. Thereby, a good contrast allows to identify surface abnormalities as well as pathologies of the cartilage matrix (figure 9, long arrows(7)). In particular, fluid sensitive fat-suppressed sequences have been found to be useful for the imaging of osteoarthritic joints(7, 14). Especially, fat-suppressed IM-FSE sequences provide good visualisation of cartilage, menisci ligaments, and tendons. They clarify cartilage pathology by being fluid sensitive and still allow assessment of the bone marrow (figure 9(7), short arrow)(7). The IM-FSE sequences thereby provide better visualisation of anatomic structures than only T2-FSE sequences. Standard parameters used for this sequence are as follows: Repetition time (TR): 3000-4000 ms, TE: 30-60 ms. Slice thickness varies

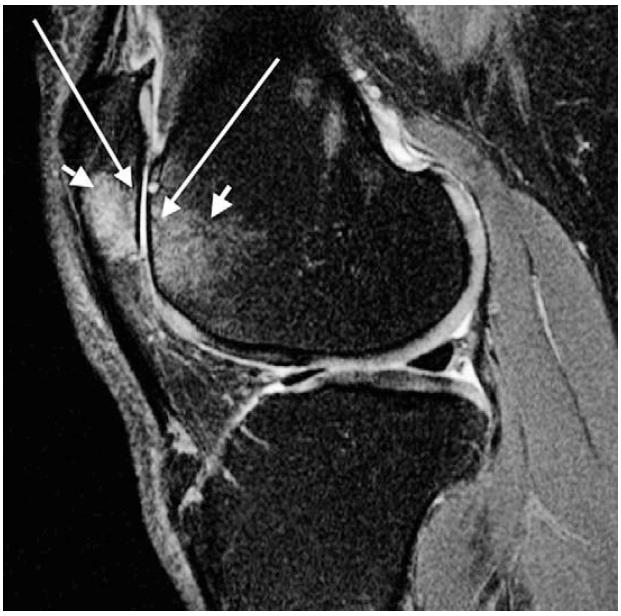


Figure 9: Sagittal fat-suppressed IM-weighted FSE (3200/30 ms.) MR image of the knee obtained in a 48-year-old man who had advanced degenerative disease of the femoropatellar joint. Cartilage lesions (long arrows), bone marrow oedema pattern (short arrows) at the trochlea and patella, osteophytes, tendons, menisci, and ligaments are well visualised with this fluid-sensitive sequence. Taken from(7).

around 2-4 mm, but in a clinical setting usually 3 mm are used. The acquisition time is in the order of 3-6 minutes. On the contrary, proton density-weighted sequences have a shorter TE: 10-30 ms, are less fluid sensitive and thereby seem to be more helpful in assessing the anatomical structure of the menisci. In addition, they thus can give additional information concerning tendons and ligaments(7).

IM-FSE is commonly used in clinical context not only because of the fact that the acquisition time is usually lower than in SPGR and FLASH (7-12min. compared to 9-14min.), but also because the image quality of the gradient echo sequences can be degraded by motion artefacts(14). To analyse the image performance of IM-weighted sequences, arthroscopy was used as a comparison. In this study intra-operatively obtained specimens underwent histological analysis and morphology was matched with preoperative MRIs(59). The parameters that were assessed included thinning of cartilage, < 50%, > 50% and full thickness lesions. Furthermore, the surface integrity including fissuring and fraying as well as signal pattern abnormalities of the cartilage were analysed. Histological findings in areas of bone marrow oedema and cartilage swelling were also documented. It was found a sensitivity of 72%, specificity of 69%, and an accuracy of 70% for cartilage thinning, 69%, 74% and 73% for surface irregularities, and 36%, 62% and 45% for intra-cartilaginous signal abnormalities(59). The results point out that FS-IM-weighted FSE sequences show good performance in assessing cartilage thickness and are very effective in depicting surface defects of the cartilage. However, the cartilage signal changes do not characterise the extent of cartilage degeneration(5, 7).

3D SPGR AND FLASH SEQUENCES

FLASH and 3D SPGR sequences are suitable to depict cartilage volume and, fairly the cartilage surface. Sequence parameters used to visualize cartilage are in the range of TR: 20-35 ms, TE: 7-12 ms and flip angle: 12-30 degrees. The visualisation of internal cartilage pathology is limited by the bright signal of the cartilage in the SPGR and FLASH images. Therefore, subtle fissures may not be as good depicted.

It should be noted that these gradient-echo sequences are very limited in assessing menisci, ligaments, and tendons and have limited performance in visualising bone marrow pathology. Additionally, they are sensitive to susceptibility artefacts, which should be considered after previous surgerys, especially after cartilage repair procedures.

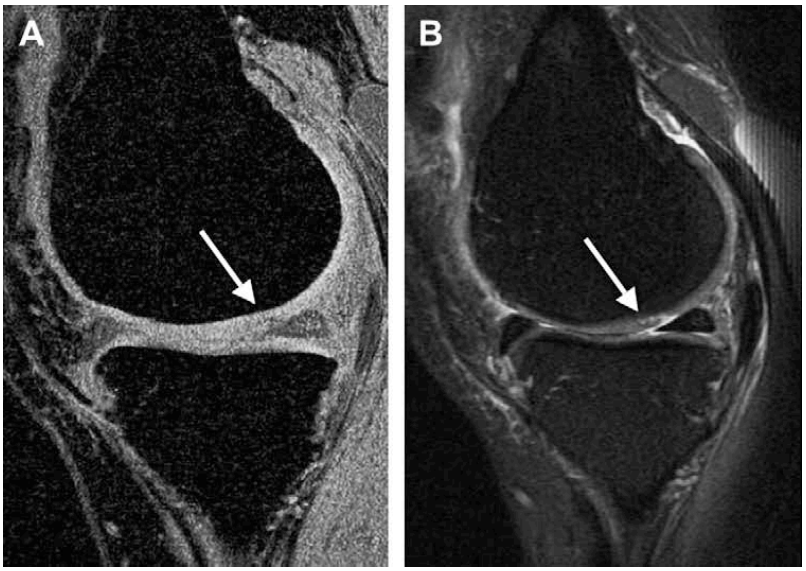


Figure 10: Sagittal MR images of the knee obtained in a middle-aged runner using (A) fat-suppressed SPGR (21/12.5 ms., flip angle: 15), (B) IM-weighted FSE sequence (4300/51 ms.). Cartilage delamination (arrow) is well visualised on the fluid-sensitive sequence (B) but not on the SPGR sequence (A) in which the cartilage appears uniformly bright. Taken from(7).

Still, 3D SPGR and FLASH sequences have been found useful for cartilage segmentation in order to assess quantitative measurements of volume and thickness(60-62). However, imaging time with these sequences is usually fairly high (9-14 min.) and image quality can be degraded by motion artefacts. Therefore, as mentioned above, IM-weighted FSE sequences seem to be more effective in visualising subtle cartilage abnormalities compared to SPGR sequences (figure 10, (7))(7, 38, 39).

OTHER SEQUENCES

A number of other sequences, like 3D Double Echo Steady State Sequence (3D DESS), Driven Equilibrium Fourier Transform (DEFT), and Steady State Free Precision (SSFP) imaging have been developed to improve morphological depiction of cartilage.

DESS is a mixed T1/T2*-w sequence in which the cartilage appears more intermediate in signal. When 3D DESS and T2-weighted FSE sequences were compared concerning the depiction of patellar cartilage abnormalities, the DESS showed a more accurate performance in diagnosing cartilage softening but seemed to be less suitable for the detection of cartilage abnormalities(14, 63, 64).

DEFT imaging provides a much higher cartilage-to-fluid contrast than other sequences. More specific, the signal of cartilage is higher than in T2-FSE sequences and thereby provides a better visualisation of the full cartilage thickness(7). Furthermore, the signal of synovial fluid is higher than in SPGR sequences and thereby provides a high synovial to cartilage contrast.

This leads to a high signal to noise ratio for the cartilage while preserving signal from cartilage which might lead to a better visualisation of cartilage pathology(7, 65).

SSFP is a high signal method that provides 3D images. When SSFP was compared to SPGR the cartilage delamination was better visualised in the former one. Nevertheless SSFP is a sequence that needs further studies to explore its potential for the depiction of cartilage(7, 66).

Summarising, it may be concluded that each of the sequences discussed above do have an application field where they perform the best. The choice of the sequence depends on the demands that are made on the image, such as signal to noise ratio, acquisition time, fluid to cartilage ratio, superficial versus deeper layer imaging, or softening of the cartilage.

TREATMENT

The treatment of osteoarthritis is depending on several parameters, starting with the degree of degeneration and destruction of the joint at the moment of the detection of the disease. The treatment should be tailored according to four major factors(67):

1. Knee risk factors (obesity, adverse mechanical factors, physical activity)
2. Level of pain intensity and disability and general risk factors (age, comorbidity, polypharmacy)
3. Signs of inflammation- including effusion
4. Location and degree of structural damage

Since a curative state can not be achieved yet, current therapeutic modalities are aimed primarily at reducing pain and improving joint function by targeting relief of symptoms. However, they do not lead to any improvement in joint structure itself. Furthermore, actual therapy does not delay progression since there are no disease modifying drugs yet(33).
Therefore, the goals of the contemporary management of the patients with OA are, as mentioned before the control of pain, the functional improvement, and thereby the amelioration of health-related quality of life. Further goals are to avoid toxic effects of the pharmacological therapy and to alter the natural course of the disease(68).

NON PHARMACOLOGIC MODALITIES

Conservative non-pharmacological modalities are implemented to improve joint range of motion, muscle strength, joint stability, and mobility. In addition, there is supportive care like bracing, orthotics or assistive devices and weight loss maneuvers(68).

WEIGHT LOSS

Patients with overweight/obesity who have knee OA should be encouraged to lose weight through a combination of diet and exercise. Weight loss reduces the load on the weight-bearing joints. The Arthritis, Diet and Activity Promotion Trial(69) showed that diet and exercise lead to an overall improvement of self reported measures of pain in 30,3 % of the patients, even in those who lost only 5% of their body weight over 18 months. The within-group change of WOMAC

score and thereby of the physical function revealed significant improvements of 24% in the diet plus exercise group (mean 5.73; 95% confidence interval 2.63, 8.83) and 18% in the diet-only group (mean 4.23; 95% CI 1.27, 7.19)(69, 70).

EXERCISE

Exercise facilitates weight loss by increasing aerobic capacity, muscle strength, and endurance. All persons that are capable of exercise should be encouraged to take part in a low-impact aerobic exercise program(70). Randomised controlled trials(71-73) in patients with knee OA demonstrated that strengthening of thigh muscles with either isometric, isotonic or resistive exercises was associated with significant improvement in quadriceps strength, and function and reduction in knee pain, compared to controls(74).

Besides the Arthritis, Diet and Activity Promotion Trial(69) it was shown that muscle strength has an impact on the joint protection associated with less cartilage damage or loss(75). In other studies, also higher quadriceps strength was found to be associated with significantly reduced risk of developing knee OA in women(76). Plus it was found to be protective against cartilage degeneration in the lateral compartment of the patello-femoral joint(77). Lower extremity muscle strength has been shown to influence knee joint loading and dynamic stability(78-80). Therefore, it was suggested that quadriceps weakness precedes the onset of knee OA and hence could increase the risk of disease development, particularly in women(81, 82).

PHYSICAL THERAPY

Physical therapy consists of a number of strategies to facilitate symptom resolution and improve functional deficits, including range-of-motion exercise, muscle strengthening, muscle stretching, and soft tissue mobilisation. All in all, it helps to stabilise the joint and to improve life quality even though there is pain or limitations in the range of motion.

KNEE BRACES AND ORTHOTICS

As the medial tibio-femoral compartment often is involved in OA, interventions, such as valgus bracing, whose goal is to realign the knee to reduce transarticular loading on the medial compartment are used. Patients who have persistent ambulatory pain from hip or knee OA should consider to use a walking cane in the contralateral hand to the painful joint(70). In addition, patients may benefit from shoe inserts to correct abnormal biomechanics due to angular

deformities of the knees. Another useful maneuver for patients with OA of the knee is the medial taping of the patella, to improve the patellar slide inside the trochlea. Finally, the use of light-weight knee braces may also be helpful in patients with tibio-femoral disease, especially if complicated by lateral instability(73).

PHARMACOLOGIC THERAPY

Even though the physical and occupational therapy are the cornerstones, both the EULAR (European League Against Rheumatism)(67) and the OARSI (Osteoarthritis Research Society International)(83, 84) issued new guidelines in 2007 and 2008 recommending a combination of non-pharmacological and pharmacological modalities to manage OA effectively. Non-steroidal anti-inflammatory drugs (NSAIDs) as Ibuprofen or Paracetamol or cyclooxigenase 2(COX2)-specific inhibitors such as celecoxib and rofecoxib are endorsed drugs.

The drugs can be devided into two groups, the fast-acting drug family (NSAIDs, acetaminophen, COX2, glucosteroids, opioids) mainly used for pain relief and the slow-acting group (glucosamine, chondroitin sulfate, S-adenosyl methionine, hyaluronic acid) dedicated to the prevention of pain as well as the slowing down of the cartilage destruction(9).

NSAIDs have a good impact on pain suppression but do come with a significant higher risk of dyspepsia, gastrointestinal bleeding and ulcera, therefore they are usually combined with proton pump inhibitors(85). Also acetaminophen reduces pain substantially but triggers adverse hepatic events in patients with hepatic insufficiency(9).

The major advantages of COX2-specific inhibitors with respect to upper gastrointestinal bleeding is that neither of them has a clinically significant effect on platelet aggregation or bleeding time. Accordingly, these agents appear preferable especially in pre- and perioperative management of patients with OA, as well as patients taking warfarin sodium(68, 86).

Chondroitin sulfate is one of the major components of cartilaginous ECM. Oral administration of chondroitin sulfate has been reported to decrease the activity of catabolic enzymes in osteoarthritic cartilage and to stimulate the synthesis of GAGs and collagens(9).

However, structure-modifying efficacy has not been demonstrated convincingly for any of the existing pharmacological agents. An alternative approach to the use of oral agents in the palliation of joint pain is the use of intra-articular injection such as hyaluronic acid (HA), tidal irrigation or glucocorticosteroids(68). HA is a polysaccharide ubiquitously found in ECMs. The therapeutic concept of visco-supplementation suggests that the intra-articular injections of HA

can help restore the viscoelastic and tribologic properties of the synovial fluid. Intra-articular injection of HA has been shown to decrease the symptoms of OA with significant improvements in pain and functional outcomes. This effect appears from 2 to 5 weeks after injection and can persist for up to 12 months(9).

All in all, there is a need for individual treatment and a need to balance between cardiovascular, gastrointestinal and renal risks by considering the safest therapeutic agent for individual patients with OA.

SURGICAL THERAPY

Surgery should be resisted when symptoms can be managed by non-surgical means. Indications for surgical intervention are debilitating pain and major limits on daily activities and walking distance, or impaired ability to sleep or work. Surgery, including joint replacement, is recommended only as a last resort for the reason that it comes along with various risks, such as peroneal nerve injury, vascular injury including local haemorrhage, limb ischaemia, and asymptomatic deep vein thrombosis(87).

Surgical opportunities are (ranked by plan of action):

1. Arthroscopic washout and debridement
2. Osteotomy of the proximal tibia or distal femur
3. Unicompartmental knee replacement
4. Patello-femoral replacement
5. Total knee replacement

The clinical outcome depends on various factors like the timing of the surgery, the experience of the surgeon, and the patient's preoperative medical status as well as the peri- and postoperative management and rehabilitation. Cartilage repair using mesenchymal stem cells (osteochondral transplantation) and autologous osteochondral plugs (so called mosaic plasty) and other cartilage replacement techniques are being investigated for the repair of focal chondral defects(68).

MATERIAL AND METHODS

OSTEOARTHRITIS INITIATIVE

The Osteoarthritis Initiative (OAI) is a multi-centre, longitudinal, prospective observational study of knee osteoarthritis (OA) that provides a large dataset of clinical information, questionnaires, radiographs, and MR imaging studies obtained from nearly 5000 participants (4796 participants at baseline) who are followed up every 12 months for a period of 48 months. This study is the only one, besides the MOST study (Multicentre Osteoarthritis Study) that includes incidence, progression, and disability in the same study(88). The overall aim of the OAI is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. The study protocol, amendments and informed consent documentation were reviewed and approved by the local institutional review boards. Data is available for public access at http://www.oai.ucsf.edu/. Specific datasets used are baseline clinical datasets 0.2.2 and baseline image dataset 0.E.1., 24 month follow-up clinical dataset 3.2.1 and 24 month follow-up imaging dataset 3.E.1.

The subjects included in this analysis were a subset of the 4796 participants of the OAI study and were divided in two groups. Participants with symptomatic knee pain corresponding to a clinical diagnosis of knee osteoarthritis with the need of prevention or the risk of worsening were recruited for the Progression Group. Participants without symptomatic or prevalent knee pain but on the basis of having specific characteristics, which give them an increased risk of developing symptomatic knee pain during the study, were selected for the Incidence Group. The third group used as a reference includes a small number of participants who at baseline did not have any of the eligibility factors, lacked knee symptoms and did not have radiographic findings of Knee Osteoarthritis (defined as a definite tibio-femoral osteophyte) in any knee(4).

The knee MRI acquisition consisted of a coronal intermediate-weighted (IW) 2D fast spin-echo, sagittal 3D dual-echo in steady state with selective water excitation (WE), sagittal 2D IW FSE with fat suppression (FS) and sagittal 2D multi-echo (ME) spin-echo (SE) sequences(89). MR images were evaluated by two musculoskeletal radiologists separately. If scores were not identical by both observers, consensus readings were performed. Pathology of cartilage surfaces was analysed using the WORMS-score (see Appendix)(90, 91). Cartilage abnormality was counted using a threshold of one and higher. Segmentation of trochlea and patellar cartilage was

performed to generate T2 maps from the sagittal 3.0 T MR images of the knee at baseline and after 24 months.

SUBJECTS

The right knees of two-hundred-seventeen subjects were included in this analysis. Subjects analysed were from the Incidence Subcohort, characterised by absence of symptomatic knee OA, defined as frequent symptoms and radiographic OA in the same or either knee at baseline. However, they did have at least one of the following OA risk factors at baseline: knee symptoms ("pain, aching, or stiffness in or around the knee" in the past 12 months), overweight or obesity, history of knee injury, history of knee surgery, family history of total knee replacement or Heberden nodes, and repetitive knee bending activities. 3T MRI (Siemens Trio) of the right knee was obtained in every subject at baseline and after 24 months. Incident symptomatic knee pain was defined as (a) the occurrence of frequent knee pain on most days of the month, (b) a Kellgren and Lawrence grade of 2 or more on the AP radiograph meaning definite tibio-femoral osteophytes in the same knee(4). Other specific inclusion eligibility criteria for the subjects in this project besides (i) baseline Western Ontario and McMaster University pain score of zero for both knees, were (ii) age range: 45–55 years and (iii) body mass index (BMI) of 19–27kg/m^2. These specific inclusion criteria were applied to exclude obesity as an OA risk factor and to focus on younger, relatively asymptomatic subjects. Exclusion criteria were rheumatoid/inflammatory arthritis, bilateral severe knee joint space narrowing/endstage osteoarthritis and contraindications or inability for MRI. Based on these criteria 4560 subjects from the OAI cohort were excluded as shown in figure 11 at baseline.

136 women and 100 men (N=236) were identified and included. Due to artefacts in the T2 mapping MR images at both time points 19 subjects with artefacts in the T2 multi-echo sequence in at least one cartilage knee compartment had to be excluded, resulting in 217 individuals that were analysed.

For the 24 month follow-up the data of 211 subjects was available. Due to slightly more artefacts in the follow-up images another 16 subjects had to be excluded additionally, resulting in the data of 182 for the follow-up cohort (figure 11 follow-up).

Subjects had different activity levels, as determined with the Physical Activity Scale for the Elderly (PASE). Based on their physical activity level (PASE from 27 to 378) subjects were divided into three groups with the same PASE range of 117 and were defined as low activity group with PASE values of 27-144, as medium activity group with PASE values of 145-261, and as a high activity group subjects with PASE values of 262-378.

Only baseline muscle data of 76 men and 98 women (N=174 were available at the time point of the study, 24 months follow up muscle data was not launched yet. In the following, subjects were divided by gender, cross sectional muscle area and the ratio of vastus lateralis to vastus medialis. Furthermore, the data was correlated to T2 values as well as to physical activity and morphological scores, such as WORMS and Recht score.

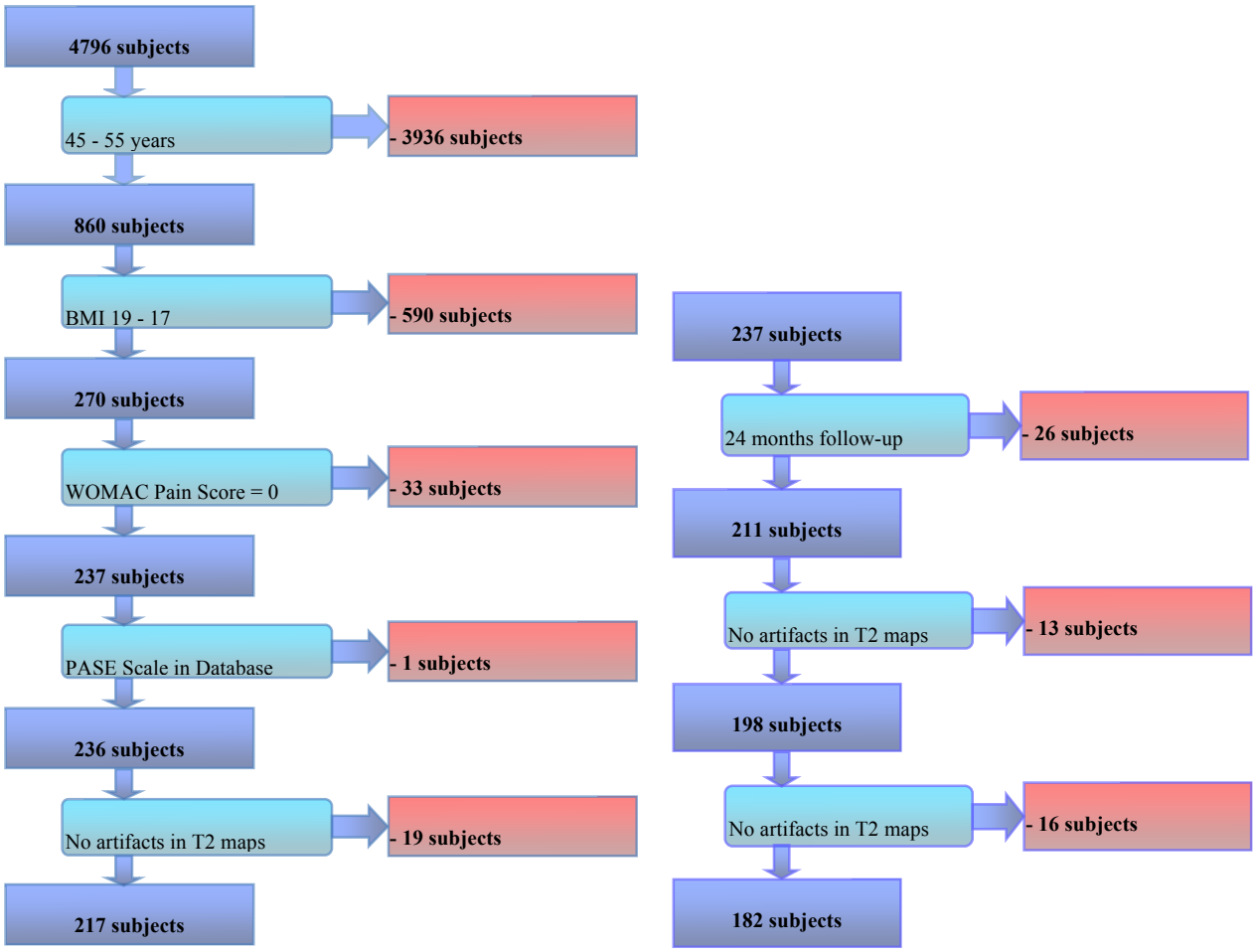


Figure 11: Subject selection at baseline (left) and follow-up (right).

CLINICAL QUESTIONNAIRES

WESTERN ONTARIO AND MCMASTER UNIVERSITY SCORE

One of the best established instruments developed to assess symptoms related to osteoarthritis is the Western Ontario and McMaster University (WOMAC) Osteoarthritis Index, a multidimensional health status instrument that quantifies the degree of pain, functional impairment, and stiffness in patients with osteoarthritis of the knee and hip(92, 93). In this study, only subjects with WOMAC pain score of zero of both knees for the past 7 days at the baseline clinic visit were included.

PHYSICAL ACTIVITY SCALE FOR THE ELDERLY

Physical activity levels were assessed using the Physical Activity Scale for the Elderly (PASE), an established questionnaire to measure physical activity in older individuals(94). Washburn et al. found the PASE to be a reliable and valid instrument for the assessment of physical activity in epidemiologic studies(94). The scale ranges from 0-400, with 400 being the highest. In this study an average of 160 was measured.

KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE

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 score: other knee symptoms, physical function in sport, and recreation and knee-related quality of life(95).

KELLGREN-LAWRENCE SCORE

The Kellgren-Lawrence Score (KL) is a standard radiologic grading system for osteoarthritis that is quantifying evidence of osteophytes in the joint margins, narrowing of the space joint, and subchondral sclerosis(96). The following features were defined: 0, no features of osteoarthritis; 1, doubtful osteoarthritis, with minute osteophytes of doubtful importance; 2, minimal osteoarthritis, with definite osteophytes but unimpaired joint space; 3, moderate osteoarthritis, with osteophytes

and moderate diminution of joint space; and 4, severe osteoarthritis, with greatly impaired joint space and sclerosis of subchondral bone(5).

WHOLE-ORGAN MAGNETIC RESONANCE IMAGING SCORE

The Whole-Organ Magnetic Resonance Imaging Score (WORMS) was based on the method used in the Osteoarthritis Research Society International (OARSI) Atlas for radiographic assessment of osteophytes in the knee and represents an initial semi-quantitative scoring system for whole-organ assessment of the knee in OA using MRI(90, 97). This system incorporates 14 features: articular cartilage integrity, subarticular bone marrow abnormality, subarticular cysts, subarticular bone attrition, marginal osteophytes, medial and lateral meniscal integrity, anterior and posterior cruciate ligament integrity, medial and lateral collateral ligament integrity, synovitis/effusion, intraarticular loose bodies, and periarticular cysts/bursitis(98). The quantification of meniscal damage is based on the distribution of magnetic resonance imaging signal intensity and its relation to the articular surface, and on surgically and histologically validated MRI grading schemes that have been used in clinical practise(90).

CLINICAL EXAMINATIONS

Subjects completed a 400 meter walk and isometric muscle strength tests. The time in seconds for a 400 meter walk of each subject was measured(99, 100). The maximum isometric strength of the right knee was obtained in Newtons in maximum force flexion and extension using the Good Strength Chair (Metitur, Jyvaskyla, Finland)(101).

IMAGING

BILATERAL RADIOGRAPHS

Bilateral standing PA ”fixed flexion” knee radiographs were obtained. Knees were radiographed in a plexiglass positioning frame (SynaFlexerTM) 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 and graded by two radiologists using the KL scoring system (see Appendix)(5, 96).

MAGNETIC RESONANCE IMAGING

MRI examinations were obtained at baseline and in a 24 months follow-up with identical 3T MRI systems (Trio, Siemens, Erlangen, Germany), which were specifically acquired for the OAI. Both knees were examined with standard morphological sequences, and T2 mapping sequences were obtained of the right knee only. Identical knee coils were used for all studies at all scanners. Following sequences were used for morphological analysis of the knee studies: (i) a coronal 2D IW FSE sequence (TE 29 ms, TR 3850 ms), (ii) a sagittal 2D IW FSE sequence with fat suppression (TE 30 ms, TR 3200 ms), (iii) a sagittal 3D DESS sequence with selective WE with coronal and axial reformations (TE 4.7 ms, TR 16.3 ms, flip angle 25°) and a coronal 3D T1-weighted fast low-angle shot (FLASH) sequence with water excitation (TE 7.57 ms., TR 20 ms.). For quantitative T2 relaxation time assessment a (iv) sagittal 2D multi-slice multi-echo (MSME) sequences (TE 10, 20, 30, 40, 50, 60, and 70 ms, and TR 2700) was used (table 2)(89) .

An additional 10 minutes of MRI scan time per participant at selected visits was used to obtain measures of skeletal muscle and fat distribution in the mid thigh designed to complete the measures of muscle strength. Components of the protocol were optimised for segmentation of subcutaneous and inter-muscular fat depots, skeletal muscle, and specific muscle groups. The thigh MRI is consisting of a 15 slice contiguous axial T1-weighted acquisition of the quadriceps region centred at 100 mm above the medial femoral epiphysis(4). For MR imaging of the right thigh, participants were asked to lie in a supine position on the table with their legs in a neutral position. The patella apex was palpated and the landmark position was defined as 15 cm above the patella apex so that the mid thigh region would be in the centre of the field of view. A bi-planar (axial and coronal) localizer was used to visualize the right femoral epiphysis. Axial T1-

weighted scans (T1W) (TE 13 ms, TE 600 ms) were positioned such that the bottom slice was at the medial femoral growth plate. A set of 15 contiguous axial images was generated(75).

Scan	Cor IW 2D TSE	Sag 3D DESS WE	Cor T1W 3D FLASH WE	Sag 2D MESE	Sag IW 2D TSE FS
Plane	Coronal	Sagittal	Coronal	Sagittal	Sagittal
FS	No	WE	WE	No	FS
Matrix (phase)	307	307	512	269	313
Matrix (frequency)	384	384	512	384	448
No. of slices	35	160	80	21	37
FOV (mm)	140	140	160	120	160
Slice thickness/gap (mm/mm)	3/0	0.7/0	1.5/0	3/0.5	3/0
Flip angle (°)	180	25	12	n/a	180
TE/TR (ms/ms)	29/3700	4.7/16.3	7.57/20	10, 20, 30, 40, 50, 60, 70/2700	30/3200
Bandwidth (Hz/pixel)	352	185	130	250	248
Chemical shift (pixels)	1.3	0	0	1.8	0
No. excitations averaged	1	1	1	1	1
ETL	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 (8/8 = 1)	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-resolution (mm)	0.365	0.365	0.313	0.313	0.357
Y-resolution (mm)	0.456	0.456	0.313	0.446	0.511

Table 2: OAI knee MRI protocol of acquisition parameters. Taken from the OAI Protocol.

IMAGE ASSESSMENT

CLINICAL READINGS, SEMI-QUANTITATIVE, MORPHOLOGICAL ANALYSES

MR images of the right knee were reviewed on picture archiving communication system (PACS) workstations (Agfa, Ridgefield Park, NJ, USA) by two musculoskeletal radiologists separately, one of them with 20, the other with 4 years of experience in musculoskeletal imaging. If scores were not identical, both radiologists performed consensus readings. During the reading session ambient light was reduced and no time constraints were used. Radiologists had access to all sequences acquired of the subjects and the sequences listed in table 2 were used for the analysis.

A WORMS score was used to evaluate the images for OA-related abnormalities of the knee(90, 98). Findings in six regions of the knee were recorded, at the patella, trochlea, medial and lateral femur, and medial and lateral tibia, condensing the original regions described in WORMS scores

from 15 to 6 because of the small number of lesions expected in the asymptomatic study population. Using the semi-quantitative scoring system the following joint structures were separately evaluated: (i) cartilage, (ii) ligaments, (iii) menisci, (iv) bone marrow oedema pattern, (v) osteophytes, (vi) synovitis/effusion, (vii) subarticular cysts, (viii) flattening or depression of the articular surfaces, (ix) loose bodies, and (x) popliteal cysts.

Cartilage signal and morphology was scored using an eight-point scale (see Appendix**):** 0, normal thickness and signal intensity; 1, normal thickness or swelling with abnormal signal on fluid sensitive sequences; 2.0, partial-thickness focal defect <1 cm in greatest width; 2.5, full-thickness focal defect <1 cm in greatest width; 3, 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 <75% of the region; 4, diffuse (≥75% of the region) partial-thickness loss; 5, multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region; 6, diffuse (≥75% of the region) full-thickness loss. Condensing the anatomical regions from 15 to 6 would have potentially affected the frequency of grade 4 and 6 lesions. However, grade 4 lesions are very rare and usually if there is >75% partial-thickness cartilage loss, full-thickness lesions are present and grade 6 lesions were not expected in this cohort.

Alterations in meniscal morphology were assessed separately in six regions (medial and lateral: anterior, body, posterior) using a four-level scale (0, normal; 1, intrasubstance abnormalities; 2, non-displaced tear; 3, displaced or complex tear; 4, complete destruction/maceration). Meniscal extrusion was graded as follows: 0, none; 1, meniscal extrusion of more than 3 mm beyond the tibia plateau. Compared to the original WORMS score system, grade 1 was added to better reflect presence of early degenerative meniscal disease.

Subarticular bone marrow abnormalities were defined as poorly marginated areas of increased signal intensity in the normal subchondral and epiphyseal bone marrow on fat-suppressed T2-weighted FSE images. This feature was graded from 0 to 3 based on the extent of regional involvement: 0, none; 1, <25% of the region; 2, 25% to 50% of the region; 3, >50% of the region. Ligaments and joint effusion were evaluated using a four point scale from 0 to 3 (0, no lesion;

1, grade 1 sprain; 2, grade 2 sprain; 3, grade 3 sprain for ligaments; 0, normal; 1, <33% of maximum potential distention; 2, 33%-66% of maximum potential distention; 3, >66% of maximum potential distention for joint effusion). Based on the MR findings, a knee was defined

as abnormal if a WORMS score value of ≥ 1 was found in any of the sub-regions evaluated. An overall WORMS score for each abnormality was calculated by adding the scores for all the sub-regions in a knee.

Cartilage lesions were also graded using the MRI classification described by Recht et al.(5, 102) based on the arthroscopic Noyes and Stabler(103) scoring system: grade I lesions were defined as having areas of inhomogeneous signal intensity on fat-saturated IW FSE sequences; grade II lesions, as cartilage defects that involved less than half of the articular cartilage thickness; grade III lesions as cartilage defects involving more than half of the cartilage but less than full thickness; and grade IV lesions as full thickness cartilage defects exposing the bone. In addition, the largest diameter of the cartilage lesion in the sagittal, coronal or axial plane, and the two largest diameters of bone marrow oedema pattern in the sagittal plane were measured.

CARTILAGE SEGMENTATION AND T2 MEASUREMENTS

Segmentation of the patellar cartilage was performed to generate T2 maps from the sagittal 2D MSME sequences of the right knee. Images were transferred to a remote SUN/SPARC workstation (Sun Microsystems, Mountain View, CA, USA) and analysed with software developed at the University of San Francisco using an Interactive Display Language (IDL) (Research Systems, Boulder, CO, USA) environment.

An IDL routine was used to simplify the manual drawing of splines delineating cartilage areas. Tissue contrast was excellent and water-fat shift artefacts occurring at the bone-cartilage interface were well visualised on the first echo time images of the ME sequence, whereas fluid was well shown on the sagittal T2 maps. In order to exclude both fluid and water-fat shift artefacts from the regions of interests (ROIs**),** a technique was used that allowed adjustment of the splines simultaneously in both images

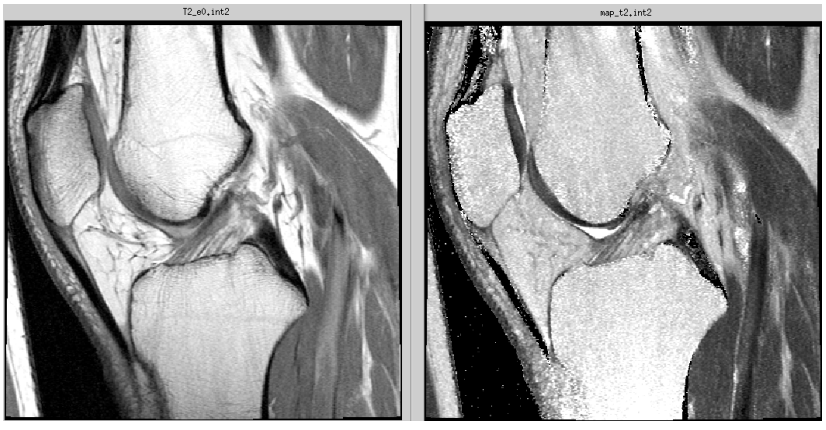


Figure 12: Right knee of a subject of the Incidence Cohort. Comparing echo-sequence e0 (left side) to map-sequence in the same slice (right side) in a parallel panel. Segmentation was processed in the map-sequence, in which the oedema is more apparent.

by opening two images panels at the same time with synchronised cursor, slice number and time if necessary (figure 12/13).

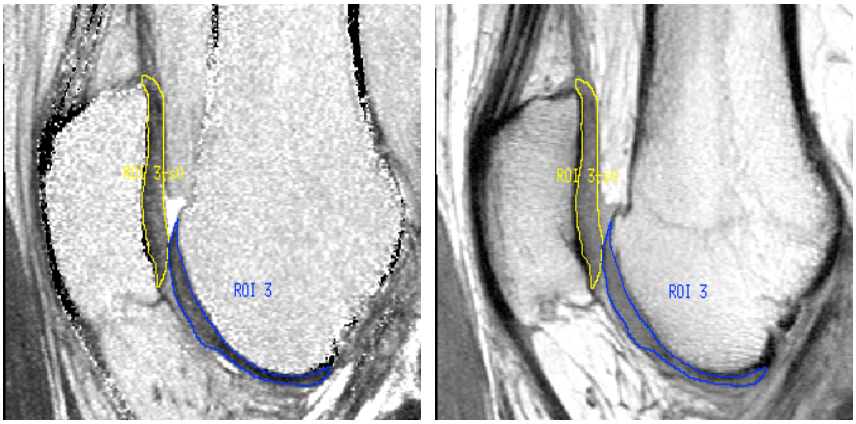


Figure 13: Segmentation in T2 map (left side) and corresponding T2_e0 (right side). This points out the better visualisation of oedema and cartilage barrier in the T2 map sequence while segmenting simultaneously.

One important methodological goal was to discriminate artificial partial volume effects from oedema. In order to achieve this, in doubtful cases both sequences (T2 maps and T2_e0) were analysed simultaneously to prevent false T2 values. T2 maps were segmented by one operator and supervised by a radiologist. Mean T2 values for each compartment were calculated after completed segmentation. An IDL routine was used to calculate the mean T2 values from the ROIs created in the T2 maps. The relaxation time, T2, was estimated using the formula:

$$SI(TE) = S_{oe}\, e^{-\frac{TE}{T_2}} \left(1 - e^{-\frac{TR}{T_1}}\right)$$

THIGH-MUSCLE-VOLUME MEASUREMENT

Using a semi-automatic, standardised segmentation technique, volumes of hamstring and quadriceps muscles were obtained. The three central sections (image slice 7-9) of the 15 standardised axial T1W images through the right mid thigh region were used for segmentation of the thigh muscle groups. Segmentation was performed on a SUN/SPARC workstation using the Qbrain software. The volume and area of the quadriceps, hamstring, vastus lateralis, and vastus medialis were calculated (figure 14).

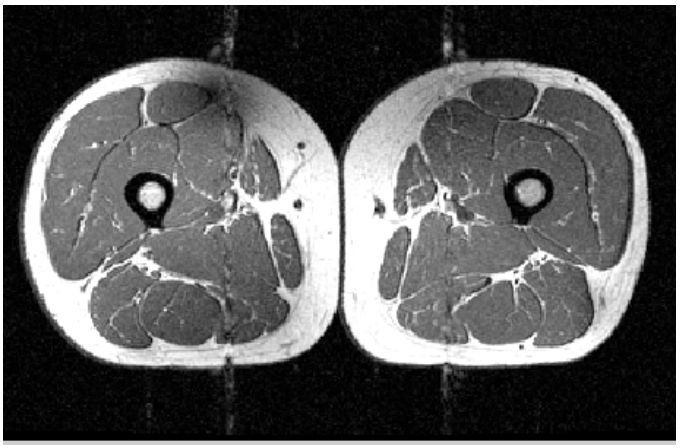


Figure 14: Segmental view of both legs. The right leg was used for the segmentation.

Segmentation was performed spline based and separately for the muscles described above. Sartorius and gracilis muscles were not included in the analysis (figure 15). While subcutaneous and peripheral fat was excluded during segmentation, fatty infiltration within each muscle group was not evaluated separately. To exclude variation in body size as a confounding factor, the relative or corrected cross-sectional area of these muscles was also measured by calculating the ratio of muscle cross-sectional area to body surface area (BSA). BSA was calculated using the Mosteller formula(104). Corrected muscle cross-sectional area showed no significant residual correlation with either body mass index or body weight.

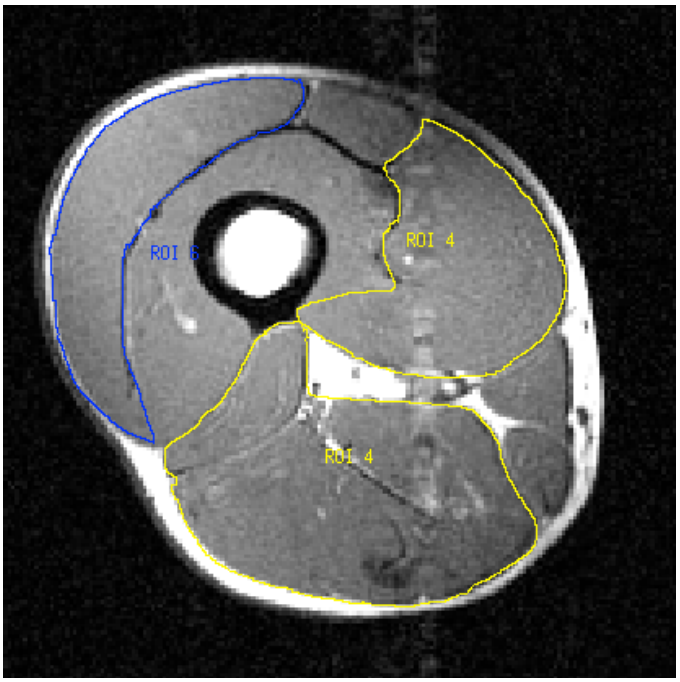


Figure 15: Segmentation of the right leg. Right thigh marked with Rois. Roi 6 (blue) musculus vastus lateralis, Roi 4 (yellow, above) musculus vastus medialis, Roi 4 (yellow, below) musculus biceps femoris. Musculus gracilis and musculus sartorius without Roi.

STATISTICAL ANALYSIS

All statistical processing was performed with JMP software Version 8 (SAS Institute, Cary, NC). The level of significance was defined for all calculations as $p < 0.05$. Statistical significance of group differences was determined using Student's *t*-test, one-way analysis of variance (ANOVA), Pearson and Spearman correlation coefficient test, and multiple regression models.

A multivariate regression model and bivariate linear and second degree polynomial regression models were used for correlations between morphological and clinical parameters in order to correct the data for the impact of age, gender and BMI. T-ratios were measured in the correlations. The T-ratio is the ratio of the estimate to its standard error. T-values greater than 2 in absolute value usually correspond to significance probabilities of less than 0.05.

Also a paired *t*-test was performed to calculate the differences in PASE, KOOS and WOMAC scores over time between subject groups with different T2 values and grade of morphological knee abnormalities over time.

REPRODUCIBILITY MEASUREMENTS FOR THE CARTILAGE

Reproducibility for the semi-quantitative analyses of different knee abnormalities using the WORMS score for each compartment was calculated in a sample of 12 OAI image data sets that were each assessed twice by each of the two radiologists. Each sub-region was graded using the WORMS score and grades given by each radiologist were compared. Cohen's Kappa values were calculated for inter-and-intra-observer agreement. The inter-and-intra-observer agreement was based on the exact rating of each feature, not just the presence or absence of each feature and expressed as intra-class correlation coefficients (ICC) by treating the data as continuous variables(98).

The coefficient of variation (CV) was determined using root-mean-square averages of standard deviations of repeated measurements. The CV was calculated for both knee compartments to determine reproducibility of the quantitative T2 measurements(105). To test intra-observer reliability 10% (48 subjects) of the data were randomly selected and segmented three times by the same investigator. CV was calculated for patellar cartilage with a root mean square of 0,692 and trochlea cartilage with a root mean square of 0,388(105).

Briefly, the WORMS score analysis inter-observer agreement was 95.3%, and the intra-observer agreement was 95.4% and 95.1% respectively. The inter-rater agreement had a Cohen's Kappa value of 0.67, and the intra-rater agreements had Cohen's Kappa values of 0.69 and 0.72, respectively. The CV for T2 quantification measurements was 1.17%.

REPRODUCIBILITY MEASUREMENTS FOR THE THIGH MUSCLE

Reproducibility for the quantitative analyses of the muscle cross-sectional area for each muscle group separately and all groups combined was calculated in a random sample of 12 OAI image data sets that were assessed three times by the same investigator. The CV for total thigh muscle cross-sectional area measurements (quadriceps and hamstring combined) was 0.72%. The CV for cross-sectional area measurements of quadriceps, hamstring, vastus medialis, and vastus lateralis muscle were 0.92%, 0.96%, 1.34%, and 1.67%, respectively.

RESULTS

CARTILAGE RESULTS

To evaluate the association of T2 relaxation times and cartilage abnormalities WORMS, PASE and WOMAC score were correlated with T2 values. As a result, at baseline a high correlation between MR-based cartilage and meniscus lesions, joint effusion and osteophytes (WORMS) with physical activity (PASE) and clinical symptoms (WOMAC) was found.

Furthermore, an increase in pain, stiffness, and a loss of the joint function, quantified using the WOMAC scores after 24 months, could be predicted by the KL-Score, the BMEP, and osteophytes at baseline. Moreover, a trend was shown for the correlation between T2 values and knee symptoms calculated with the WOMAC Score.

The most pertinent findings are summarised in table 3. It shows the PASE values at baseline and follow-up of all subjects divided in separate subject groups. Subjects were divided into two groups with presence (WORMS=1, KL score=1) or absence (WORMS=0, KL score=0) of cartilage or meniscus lesions, BMEP, osteophytes, and joint effusion. Then for both compartments (trochlea, patella) all subjects were divided into groups with T2 values above and below the median T2 value (43,805 for the patella and 45,361 for the trochlea) of all 198 subjects. The total number of subjects was 198, since not all PASE Scale values at 24 months were available and some T2 maps could not be analysed because of artifacts. In the following, the subjects of the patella group were divided into 97 subjects, with T2 values lower than the median and a group of 101 subjects, with higher T2 values than the median. T-ratios and the *p* values between the morphological and the clinical parameters were calculated in a multi-regression model.

Significant negative delta-values as an indicator for a significant decrease in physical activity (PASE) after 24 months in subjects with cartilage lesions and joint effusion were calculated.

Difference in PASE after 24 months	Number	PASE baseline mean	PASE 24 month mean	Delta	Statistical Analysis (p) paired T test
T2 values					
with T2 **patella** baseline < 43,805 (Median)	101	183,94	179,42	-4,52	0,5863
with T2 **patella** baseline > 43,805 (Median)	97	208,13	188,62	**-19,52**	**0,0127***
with T2 **trochlea** < 45,361 (Median)	103	190,31	187,79	-2,52	0,7491
with T2 **trochlea** > 45,361 (Median)	95	201,75	179,73	**-22,02**	**0,0078***
Knee abnormalities at baseline					
with cartilage WORMS = 0	54	161,87	164,83	2,96	0,7349
with cartilage WORMS >1	144	208,52	191,08	**-17,44**	**0,0145***
with meniscus WORMS = 0	103	178,23	169,60	-8,63	0,3065
with meniscus WORMS >1	95	214,84	199,44	**-15,40**	**0,0436***
with BMEP WORMS = 0	119	185,87	173,21	-12,66	0,0586
with BMEP WORMS >1	79	210,76	200,05	-10,71	0,2961
with osteophyte WORMS = 0	126	186,29	181,75	-4,54	0,5216
with osteophyte WORMS >1	72	212,43	187,72	**-24,71**	**0,0103***
with joint effusion WORMS = 0	146	179,05	177,84	-1,21	0,8541
with joint effusion WORMS >1	52	242,83	201,00	**-41,83**	**0,0001***
with KL-Score = 0	137	183,17	179,55	-3,62	0,5953
with KL-Score >1	61	224,16	193,74	**-30,42**	**0,0017***

Table 3: Correlation between high mean T2 values and the decrease of PASE after 24 months and the significant decrease of PASE in subjects with knee abnormalities at baseline.

Table 3 shows that subjects with higher T2 values at baseline had a higher PASE scale at baseline and furthermore showed a significant decrease of the activity level after 24 months. Additionally, subjects with WORMS >1 and KL score >1 showed a higher PASE scale at baseline, as well as a significant PASE decrease after 24 months, except for the BMEP. For a visual illustration the results are demonstrated in figure 16 and 17. PASE is displayed in blue bars at baseline and in red bars after 24 months. For the patellar compartment subjects with higher T2 values had higher PASE values at baseline (208.13 vs. 183.94). After 24 months the physical activity decreased significantly in the high T2 group compared to the low T2 group (Delta PASE

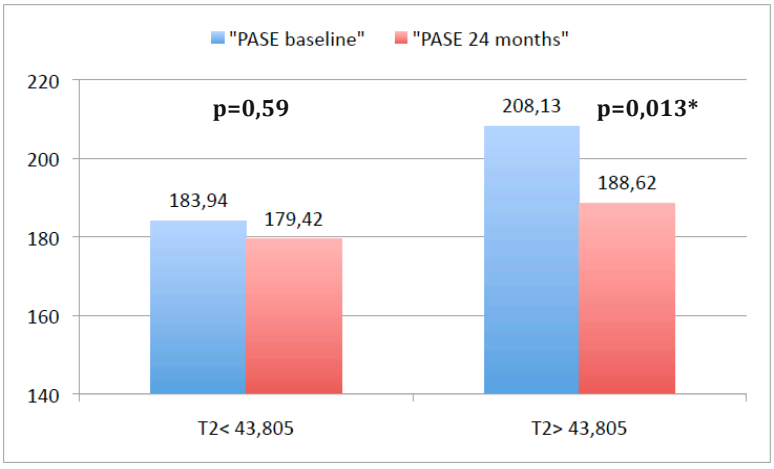


Figure 16: PASE versus patella T2 values.

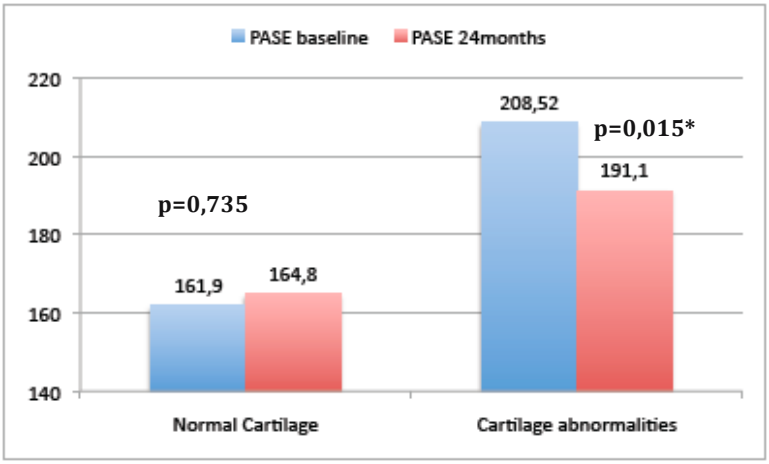
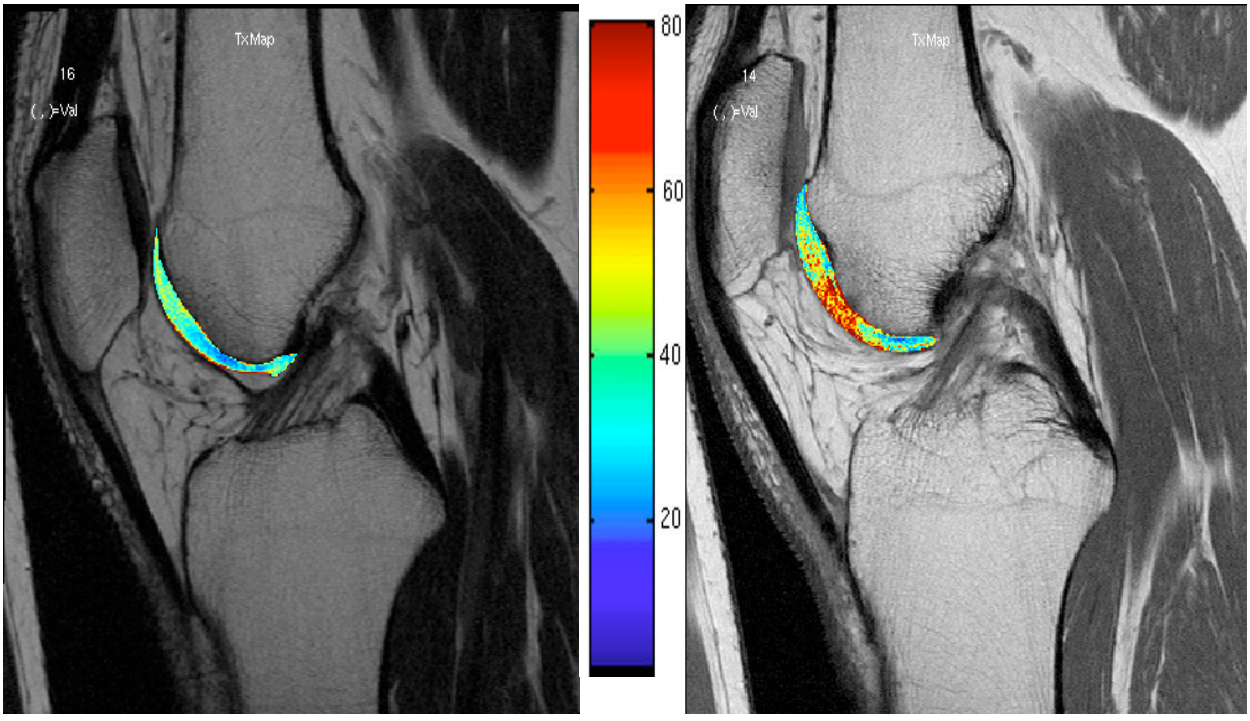


Figure 17: PASE versus cartilage abnormalities (WORMS >1).

-19.52, p = 0.0127* vs. -4.52, p = 0.5863) (figure 16). Both compartments showed a decrease in PASE over time. The results for the trochlea compartment (p = 0.0078*) were even more significant than for the patella (p = 0,0127*) (table 3). Not only subjects with higher T2 values, but also subjects with knee abnormalities, such as cartilage abnormalities (shown in figure 17) and meniscus abnormalities, osteophytes, joint effusion, and KL scores > 1 at baseline showed a significant decrease of physical activity ($p < 0.05$) after 24 months (table3).

In contrast, subjects without WORMS >1 and KL-score >1 did not show a significant decrease (p = 0.735) in PASE after two years (table 3, figure 17). Summarised, both figures illustrate that a higher T2 value at baseline leads to a significant reduction of the activity level after 24 months.



A **B**

Figure 18: T2 colour maps in MR image of the trochlea of the right knee. A: a knee of a sedentary subject with PASE scale below median. B: a knee of a subject with PASE scale above median with a visualisation of an oedema (red colour) as a sign of cartilage destruction in the trochlea.

Figure 18A shows an MR image of the trochlea with T2 values below the median in a sedentary subject with no significant change in PASE over a period of 24 months in a colour-coded T2 map. Figure 18B shows a trochlea with high T2 values above the median in an active patient of the same age with a substantial decrease in physical activity (PASE) over a period of 24 months. As a sign of cartilage abnormality, bone marrow oedema pattern is apparent in the middle of the trochlea in red colour. Both colour maps were overlaid on the first-echo image of the multi-echo spin- sequence. According to these findings, in the following it was tested whether there is also a correlation between the pain measured as WOMAC score, the T2 values and the WORMS score. Table 4 shows the WOMAC scores at baseline, follow-up and the change in WOMAC for clinical subgroups. Since not all subjects had WOMAC scores at follow-up, the number of subjects was 203. Subjects were again separated according to the presence or the absence of meniscus lesions, joint effusion, osteophytes, and degenerative changes in the radiographs (KL scores) at baseline (table 4). All subjects either with or without knee abnormalities showed an increase of knee symptoms (WOMAC score) after 24 months (table 4).

	Number	**WOMAC baseline**	**WOMAC 24 months**		**Statistical Analysis (p)**
		mean	mean	Delta	Multiregression Analysis
Knee abnormalities at baseline					
with cartilage WORMS = 0	56	0,38	1,11	0,74	0,5860
with cartilage WORMS >1	147	0,84	1,53	0,69	**0,0409***
with meniscus WORMS = 0	108	0,64	1,20	0,56	0,0351*
with meniscus WORMS >1	95	0,79	1,66	0,87	0,0744
with BMEP WORMS = 0	122	0,64	1,09	0,45	0,0951
with BMEP WORMS >1	81	0,82	1,91	1,09	**0,0415***
with osteophyte WORMS = 0	129	0,49	0,95	0,46	0,0374*
with osteophyte WORMS >1	74	1,10	2,23	1,13	0.708
with joint effusion WORMS = 0	151	0,60	1,03	0,43	0,0239*
with joint effusion WORMS >1	52	1,00	2,45	1,45	0.0921
with KL-Score = 0	151	0,60	1,04	0,44	0,0262*
with KL-Score >1	52	1,02	2,49	1,47	0,0921

Table 4: WOMAC score at baseline and follow-up in correlation to knee abnormalities (WORMS).

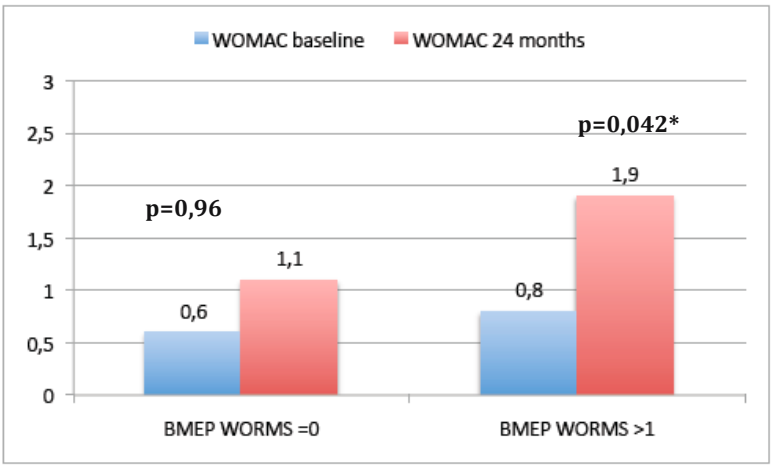


Figure 19: WOMAC versus BMEP values.

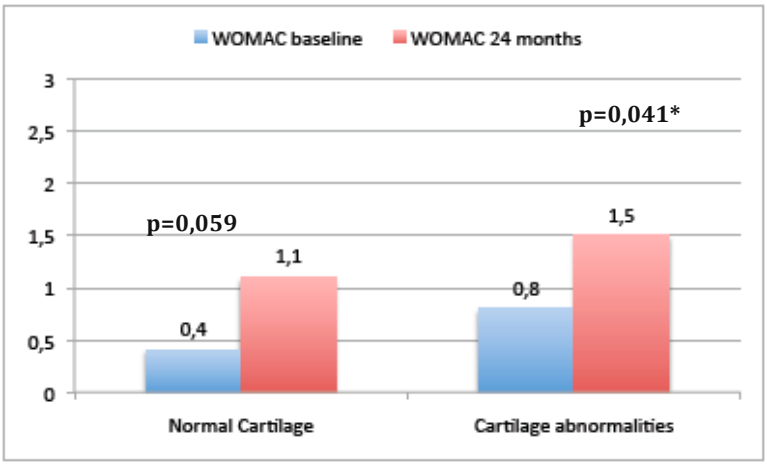


Figure 20: WOMAC versus Cartilage abnormalities.

For a visual illustration the results are demonstrated in figures 19 and 20. WOMAC scores at baseline are displayed as blue bars and as red bars after 24 months. Subjects with and without cartilage abnormalities showed both an increase of knee symptoms (WOMAC score) after 24 months. However there is only a significant increase in pain in the cartilage abnormalities group (p = 0,041* vs. p = 0,059) as well as in the BMEP WORMS >1 group (p = 0,0415* vs. 0.951) (figure 19, 20).

Furthermore, it needed to be examined whether there is also a possibility to differentiate which level of activity influences the change in T2 values the most. Therefore, all 182 subjects were separated into three groups (table 5) with the same range of activity level of 117. 51 subjects were found in the low PASE group (range 27-144) 96 subjects in the middle PASE group (range 145-261), and 35 in the high PASE group (range 262-378). Then the mean T2 values, and separately the T2 patella values and the T2 trochlea values were compared with all PASE groups.

	PASE Scale at baseline						
	low PASE Scale (1)		middle PASE Scale (2)		high PASE Scale (3)		P-values for PASE categories
	mean	SD	mean	SD	mean	SD	Multiregression Analysis1
Number (182)	51		96		35		
Range PASE per group	117		117		117		
Range PASE (0-400)	27 – 144		145 – 261		262 – 378		
mean PASE	104,59	28,36	202,03	32,63	309,06	31,78	
T2 Patella baseline	43,19	2,75	43,44	3,87	45,11	2,93	**0,0226***
T2 Patella follow up	43,98	2,55	44,49	3,63	47,53	3,04	**<,0001***
Dealta T2 Patella	0,79	2,32	1,05	2,97	2,42	2,25	**0,0150***
T2 Trochlea baseline	44,76	3,26	45,76	4,02	45,69	3,23	0,1453
T2 Trochlea follow up	46,63	2,28	47,05	3,32	48,7	3,4	**0,0080***
Delta T2 Trochlea	1,87	3,18	1,29	3,17	3,01	3,43	0,3335

[1] Correction for Age, Gender and BMI, knee injury or knee surgery in history, family history of knee replacement and Herbeden`s nodes in hands

Table 5: PASE scales at baseline in correlation to T2 values in patella and trochlea at baseline and 24 months follow-up.

The results for the patella show that the T2 values rise significantly in correlation to the higher PASE scales at baseline (p = 0.0226) and at the follow-up after 24 months (p = < 0,001). Therefore, it may be concluded that more activity/extensive activity causes a higher stress on the cartilage tissue, represented by higher T2 values as shown before in table 3. Interestingly, the ascent is higher from the middle to the high PASE group (43,44 - 45,11) than from the low to the middle PASE group (43,19 - 43,44) at baseline and even more pertinent at follow up (see table 5).

Comparing the T2 values between baseline and follow-up inside the PASE groups, it was detected that the incline of the T2 values inside each PASE group is rising too from baseline to follow up. This leads to the assumption that subjects with higher activity levels (PASE scale) at baseline acquired more cartilage destruction over time compared to people with lower PASE scales, represented by the higher incline of T2 values. The correlation for the trochlea showed similar results regarding the incline of the T2 values in between the PASE groups, but only for the T2 values after 24 months.

Therefore, it may be concluded that the patella might be more exposed to the body load in general in active subjects because of the continuous movement. In other words, higher activity seems to impact the cartilage of the patella in early stages more than the cartilage of the trochlea. However, after a constant high PASE scale over 24 months both compartments show a significant

degeneration, represented by higher T2 values, especially in subjects with a high activity level. The higher delta T2 in the high PASE group leads to the hypothesis that extreme stress/sport does have a negative impact on hyaline cartilage of the whole knee joints.

MUSCLE RESULTS

Since the study had been focusing only on the cartilage and its development over the time, it seemed commendable to evaluate additional parameters, such as the thigh muscle strength, diameter and force. Table 6 shows baseline participant characteristics, including eligibility risk factors, combined and separated by gender.

There was no gender related differences in KOOS scores, PASE values, age , repeated chair stand pace, and time required for 400-meter walk. But women had a significantly lower BMI and less flexion and extension muscle strength compared to male subjects.

	All	**Male**	**Female**	***p***
Number	174	76	98	
Risk factors				
Knee injury in history	50	27	23	
Knee surgery in history	21	15	6	
Family history of knee replacement	28	15	13	
Heberden's nodes in hands	33	5	27	
PASE scale	199.21 ± 80.39	205.18 ± 77.65	194.57 ± 83.55	0.193
PASE scale range	27 - 378	27 - 378	27 - 371	
Age	50.55 ± 2.93	50.59 ± 2.87	50.52 ± 2.99	0.436
BMI	23.88 ± 2.08	24.70 ± 1.59	23.25 ± 2.20	**<0.0001***
Repeated chair stands/sec	0.610 ± 0.156	0.607 ± 0.6	0.613 ± 0.16	0.604
400-meter walk (sec)	271.39 ± 30.53	271.06 ± 34.96	271.64 ± 26.80	0.547
Right knee flexion maximal force (Newton)	162.87 ± 68.16	191.24 ± 80.95	142.97 ± 47.97	**<0.0001***
Right knee extension maximal force (Newton)	392.45 ± 112.82	457.15 ± 111.06	345.52 ± 88.64	**<0.0001***

Table 6: Participant characteristics. Published in(78).

In the following the gender differences in thigh muscle cross-sectional area were correlated. As shown in table 7 below, there is a significant difference in total muscle cross-sectional area of the thigh muscle between male and female subjects (mean 388.17 ± 170.30 for male versus 313.10 ± 128.75 for female, p = 0.0009). Similarly, highly significant gender differences in muscle size are noted in all the muscle groups measured separately, except for the vastus lateralis (VL). After correcting for body size using BSA, no significant gender difference in total muscle cross-sectional area (mean 198.56 ± 84.75 for male versus 185.64 ± 74.78 for female, p = 0.1479) was noted. In accordance, there was also no significant gender difference in muscle size observed in any of the muscle groups, when measured separately, except for vastus medialis (VM) area. VM still demonstrated a very significant gender difference (mean 41.95 ± 16.09 for male versus 31.35 ± 12.48 for female, p < 0.0001).

	All	Male	Female	*p*
Number	174	76	98	
Area, BSA uncorrected				
Total	345.89 ± 152.52	388.17 ± 170.30	313.10 ± 128.75	**0.0009***
Quadriceps	189.40 ± 89.06	216.702 ± 101.62	168.24 ± 71.60	**0.0003***
Hamstring	156.48 ± 66.98	171.47 ± 73.17	144.86 ± 59.57	**0.0055***
Vastus lateralis	54.37 ± 27.25	57.60 ± 29.14	51.86 ± 25.55	0.0881
Vastus medialis	65.75 ± 30.77	82.18 ± 33.07	53.01 ± 21.67	**<0.0001***
Area, BSA corrected				
Total	191.28 ± 79.31	198.56 ± 84.75	185.64 ± 74.78	0.1479
Quadriceps	104.62 ± 46.17	110.86 ± 51.15	99.79 ± 41.53	0.0636
Hamstring	86.66 ± 35.17	87.70 ± 36.01	85.85 ± 34.67	0.3668
Vastus lateralis	30.26 ± 14.90	29.58 ± 14.83	30.79 ± 15.02	0.7020
Vastus medialis	35.98 ± 15.08	41.95 ± 16.09	31.35± 12.48	**<0.0001***

Table 7: Muscle cross-sectional area measurements with and without correction for body size using body surface area (BSA). Published in(78).

Furthermore, the relation of muscle size with different physical activity parameters in male and female subjects was analysed. Therefore, both the male and female subjects were divided into two groups of equal size according to their uncorrected total muscle cross-sectional area. As shown in table 8, male subjects in the large muscle size group showed significantly greater maximal knee flexion and extension forces compared to those with smaller muscle size. Female subjects with larger muscle size also demonstrated significantly higher maximal extension force, and higher mean maximal flexion force, even though this was not statistically significant. There

was no significant difference in terms of 400-meter walk time or in pace of performing repeated chair stands in any group observed. After normalisation of muscle size using BSA, no significant difference was found in any of the four tested parameters between male or female subjects with smaller and with larger muscle size.

	All	Low Muscle Volume	High Muscle Volume	*p*
Male	**76**	38	38	
400 meter walk		270.25 ± 31.22	271.83 ± 38.57	0.4229
Repeated chair stand		0.59 ± 0.13	0.62 ± 0.18	0.1855
Maximal extension force		428.19 ± 107.97	494.10 ± 105.46	**0.0077***
Maximal flexion force		173.78 ± 75.91	213.52 ± 82.98	**0.0249***
Female	**98**	49	49	
400 meter walk		270.04 ± 25.90	273.76 ± 27.83	0.2508
Repeated chair stand		0.59 ± 0.14	0.63 ± 0.17	0.1200
Maximal extension force		325.70 ± 71.68	361.41 ± 96.64	**0.0254***
Maximal flexion force		136.46 ± 46.82	147.96 ± 49.43	0.1304

Table 8: Total thigh muscle cross-sectional area (uncorrected) in relation to clinical parameters of physical activity. Published in(78).

Furthermore, subjects were separated based on their physical activity level. Subjects with PASE values of 0-199 were defined as the low activity group, and those with PASE values of 200-400 were defined as the high activity group. This time, the PASE score of 200 was used as a threshold because it represented the median of the PASE scale and was very close to the mean value of the scale (197.72). Subjects with higher PASE values had larger mean total muscle cross-sectional area and higher mean cross-sectional area of all four measured muscle groups (both corrected and uncorrected). However, this difference was not statistically significant. In addition, multivariate correlation analysis also failed to reveal a significant correlation between muscle cross-sectional area (both corrected and uncorrected) and PASE score.

Given the fact that cartilage T2 value elevation has been shown to precede development of morphological cartilage abnormalities, it may potentially be used as a biomarker for detection of early or preclinical OA(91, 106). Based on this hypothesis, cartilage T2 measurements according to total muscle cross-sectional area were analysed, before and after correction for BSA. There was no significant difference in T2 values found between subjects with smaller total muscle size and those with larger size. In the following, the effect of each of the four muscle groups on cartilage T2 values was studied. No significant difference in T2 values between subjects with low quadriceps or hamstring cross- sectional area and those with high cross-sectional area was found.

However, when the female and male subjects were divided separately into equal groups according to their VM cross-sectional area, male subjects in the high VM group demonstrated significantly higher mean T2 values when all the cartilage compartments were combined (mean 43.88 ± 2.01 vs. 45.12 ± 2.53,\ p = 0.0102) (table 9). No significant difference was found in female subjects. Based on these results, male and female data sets were combined and then divided into two groups of equal size according to their vastus lateralis/medialis cross-sectional area ratio (VL/VM ratio).

		Patella	Trochlea	Combined		Patella	Trochlea	Combined
Male (76)	**Low VM**	43.60 ± 3.76	44.91 ± 3.48	43.88 ± 2.01	**Low VL**	44.43 ± 4.08	45.57 ± 3.45	44.63 ± 2.57
	High VM	44.61 ± 3.92	47.19 ± 3.63	45.12 ± 2.53	**High VL**	43.79 ± 3.64	46.53 ± 3.94	44.37 ± 2.15
	P	0.1274	**0.0033***	**0.0102***	***p***	0.2380	0.1305	0.3121
Female (98)	**Low VM**	44.23 ± 4.17	44.82 ± 3.69	44.98 ± 2.49	**Low VL**	45.08 ± 4.30	45.51 ± 4.06	45.51 ± 2.72
	High VM	43.71 ± 3.72	45.23 ± 3.70	44.49 ± 2.32	**High VL**	42.88 ± 3.23	44.58 ± 3.25	44.02 ± 1.83
	p	0.2611	0.2978	0.1597	*p*	**0.0029***	0.1115	**0.0014***

Table 9: Comparison of cartilage T2 values (compartment specific and combined mean T2) in subject groups (separated by gender) with high and low muscle cross-sectional area. (VM=vastus medialis; VL=vastus lateralis). Published in(78).

As shown in table 10, there is a highly significant difference in mean cartilage T2 values between subjects with low VL/VM ratio and those with high VL/VM ratio (mean 45.17 ± 2.52 vs. 44.10 ± 2.12, $p = 0.0017$). Linear and second degree regression analyses of cartilage mean T2 values by VL/VM ratio also generated significant p values of 0.0301* and 0.0327*, respectively. Significant differences in T2 values were noted in all the cartilage compartments except for the medial femoral compartment. Additionally, also male and female subjects were analysed separately using their VL/VM ratio. It was found that both male and female subjects in the high VL/VM ratio group demonstrated lower combined cartilage T2 values (table 10). The cartilage compartments that demonstrated significant differences in T2 values in female subjects are the patella, medial femoral, and medial tibial compartments. In male subjects the lateral femoral and lateral tibial compartments showed significant difference in T2 values (table 10).

Representative thigh muscle images with corresponding cartilage T2 colour maps and MR morphological images from participants with low and high VL/VM ratios are shown in figure 21.

		Patella	Trochlea	Medial femural	Lateral femural	Medial tibial	Lateral tibial	Mean T2
All subjects combined (174)	**Low VL/VM**	44.76 ± 3.99	46.18 ± 3.41	51.45 ± 3.59	49.39 ± 3.74	39.79 ± 2.78	39.67 ± 3.39	45.17 ± 2.52
	High VL/VM	43.31 ± 3.66	44.81 ± 3.89	50.93 ± 3.31	48.26 ± 3.17	38.67 ± 2.73	38.64 ± 3.29	44.10 ± 2.12
	p	**0.0067***	**0.0078***	0.1593	**0.0169***	**0.0041***	**0.0216***	**0.0017***
Male (76)	**Low VL/VM**	44.03 ± 3.18	46.44 ± 3.46	50.86 ± 3.45	49.35 ± 3.72	39.67 ± 2.55	39.67 ± 2.67	45.00 ± 2.26
	High VL/VM	44.20 ± 4.47	45.66 ± 3.95	49.61 ± 3.65	47.51 ± 3.21	38.83 ± 2.60	38.19 ± 3.19	44.00 ± 2.37
	p	0.5742	0.1808	0.0657	**0.012***	0.0808	**0.0158***	**0.0317***
Female (98)	**Low VL/VM**	44.81 ± 4.33	45.14 ± 3.53	52.47 ± 3.04	49.69 ± 3.84	39.74 ± 3.18	39.86 ± 3.98	45.22 ± 2.69
	High VL/VM	43.15 ± 3.36	44.92 ± 3.84	51.41 ± 3.24	48.58 ± 2.39	38.68 ± 2.69	38.80 ±3.21	44.26 ± 2.04
	p	**0.0189***	0.3897	**0.0495***	0.057	**0.0404***	0.0777	**0.0275***

Table 10: Comparison of cartilage T2 values (compartment specific and combined mean T2) in subject groups (combined and separated by gender) with high and low vastus lateralis/vastus medialis cross-sectional area ratio (VL/VM). Published in(78).

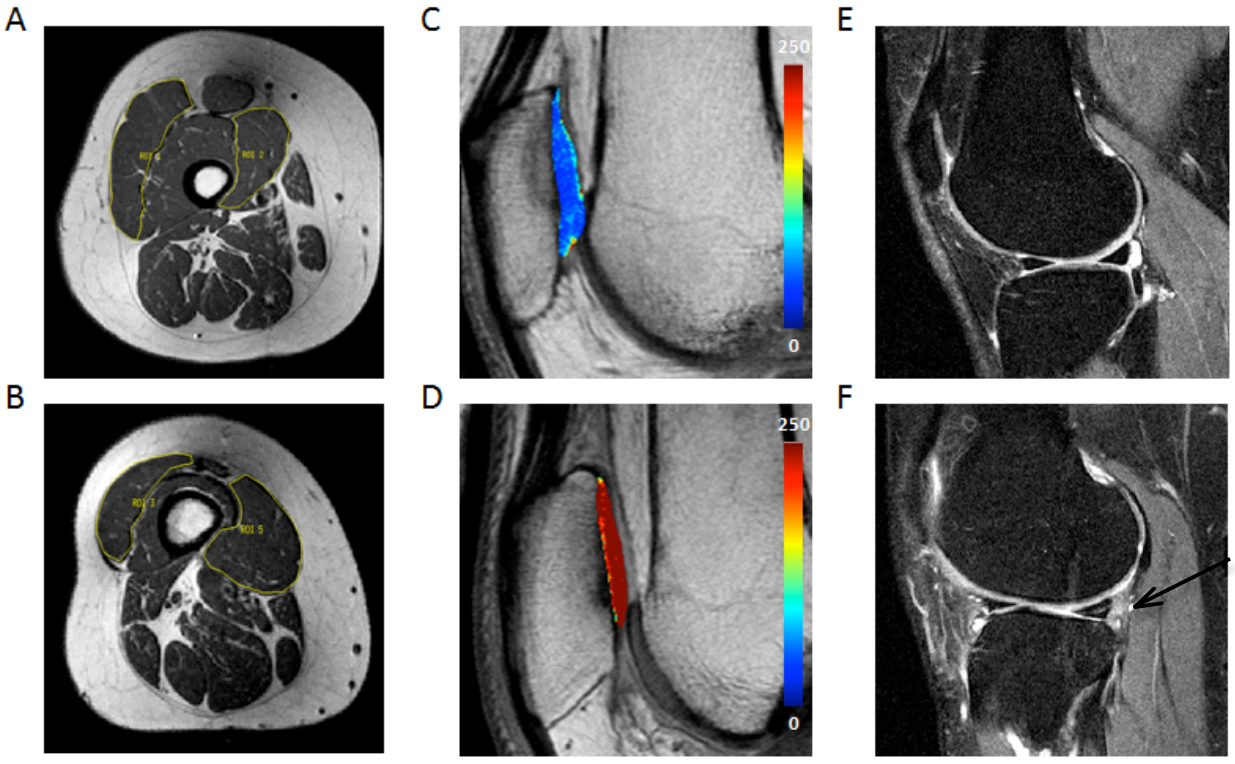


Figure 21: Representative images of subjects with significant difference in vastus lateralis volume/vastus medialis cross-sectional area ratio showing difference in muscle size (A, B), cartilage T2 colour map (C, D), and MR morphological abnormalities (E, F). A, C, and E are taken from a subject with high VL/VM ratio (1.72) whereas B, D, and F are taken from a subject with low VL/VM ratio (0.58). Note that relatively normal morphology is demonstrated in E, whereas a tear of the posterior horn of the lateral meniscus (black arrow) and a full-thickness tear of the lateral femoral condyle cartilage is observed in F. Published in(78).

Since highly significant differences in cartilage T2 values between subjects with lower VL/VM ratio and those with higher VL/VM ratio were found, the differences in MR morphological changes between these two groups were analysed. A significant difference between these two groups was identified in combined WORMS summation scores with the high VL/VM ratio group showing lower morphological abnormality scores (mean 18.68 ± 17.05 vs. 14.12 ± 15.47, p = 0.0316). When individual morphological abnormalities were investigated, significantly lower prevalence of abnormalities in the high VL/VM ratio group for menisci, cartilage, synovial fluid, and loose bodies was found (table 11).

The Recht scoring system was also used to compare cartilage abnormalities and a significantly lower Recht summation score was found in the high VL/VM ratio group. Additionally, males and females were analysed separately for the differences in WORMS scores between subjects with higher VL/VM ratio and those with lower ratio. No significant differences in WORMS scores (summation score and individual component scores) were found in males. In females, however, subjects with high VL/VM ratio showed significantly lower WORMS summation score, and lower WORMS scores for the menisci, cartilage, and joint effusion (figure 22).

	Low VL/VM	**High VL/VM**	***P***
WORMS summation score	18.68 ± 17.05	14.12 ± 15.47	***0.0316****
Menisci	2.07 ± 3.03	1.33 ± 2.45	***0.0411****
Ligaments	0.38 ± 0.87	0.46 ± 1.05	*0.2822*
Cartilage lesion	4.80 ± 4.44	3.39 ± 3.94	***0.0146****
Bone marrow oedema	1.40 ± 1.94	0.99 ± 1.53	*0.0615*
Subarticular cysts	0.11 ± 0.54	0.11 ± 0.38	*0.4637*
Osteophytes	4.89 ± 6.57	3.66 ± 6.63	*0.1125*
Joint effusion	0.51 ± 0.79	0.31 ± 0.66	***0.0396****
Loose bodies	0.08 ± 0.35	0.01 ± 0.11	***0.0416****
Popliteal cysts	0.53 ± 0.91	0.40 ± 0.76	*0.1552*
RECHT cartilage summation score	4.33 ± 3.90	3.05 ± 3.34	***0.0108****

Table 11: Semi-quantitative MR morphological scores (WORMS and RECHT scores) in subjects (males and females combined, n=174) with low and high vastus lateralis/vastus medialis (VL/VM) ratio. Published in(78).

Interestingly, all these results indicate that a higher strength of the vastus lateralis muscle, compared to the vastus medialis, has a protective impact on the joint, represented by lower T2 values and lower WORMS and Recht scores. It should be highlighted that these effects are more prominent in females than in males. Looking at these results, it is to hypothesise that a higher vastus lateralis strenght protects the joint by shifting the body load from the medial cmpartment more into the middle of the joint by changing the mechanical leg axis. Thereby, the medial condyle, which is mostly affected in early stages of OA does not carry the whole body wheight and might not be as much affected. It is to recognise, that not only the tibiofemoral joint is protected but also the patellofemoral joint, when VL has higher strenght. Having a higher VL strenght might cause the patella to slide better inside the trochlea and thereby harm less cartilage depeding on the mechanical leg axis.

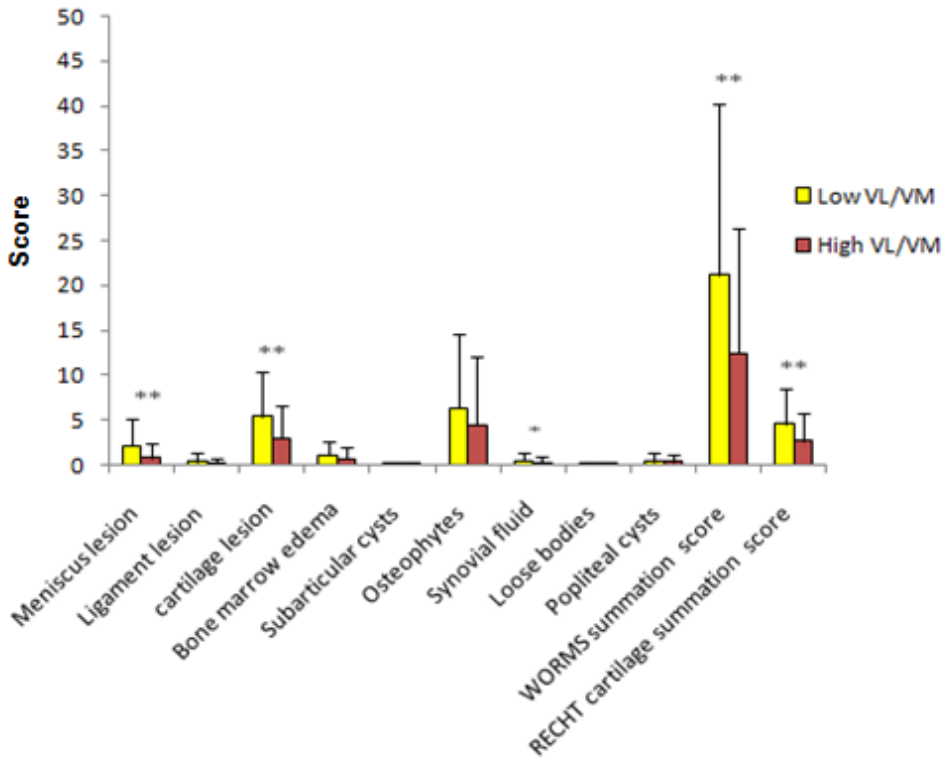


Figure 22: Semi-quantitative analysis of morphological knee abnormalities using WORMS and RECHT scoring systems with female subjects grouped according to their vastus lateralis (VL) volume. Vertical bars represent standard deviation. * $p < 0.05$; ** $p < 0.01$. Published in(78).

DISCUSSION

A number of studies examined OA risk factors in relation to quantitative and qualitative loss of cartilage determined by MRI (20, 60, 85, 107, 108). However, there is a paucity of data analysing cartilage degeneration using MRI in relation to physical activity. As far as it is known there is no study yet that assessed variations in T2 relaxation time over 24 months in correlation to PASE, WORMS and WOMAC scales in such a big cohort. Therefore, the purpose of this study was to determine the prevalence and development of cartilaginous, meniscal and ligamentous damage and of bone marrow oedema pattern as well as the cartilage T2 values in relatively healthy, young subjects. These subjects were taken from the Incidence cohort of the OAI with high and low levels of physical activity and without clinical symptoms of pain over 24 months. Furthermore, it was analysed whether asymptomatic subjects from the OAI with higher cartilage T2 values relaxation time and higher WORMS scores, determined in baseline 3T knee MRI studies, would more likely develop increased pain, limited function, and reduced physical activity after 24 months compared to subjects with lower scores. Additionally, a correlation of parameters with thigh muscle strength was performed to investigate whether muscle strength has an impact on T2-values, PASE, WORMS score or Recht score.

When PASE scores were correlated with T2 relaxation values and WORMS scores, a high correlation was found. At baseline, subjects with higher PASE scores showed higher T2 and subjects with WORMS scores >1 showed a significant decrease in PASE over time (table 3).

Furthermore, it was analysed whether cartilage T2 values at baseline may predict changes in physical activity levels (using the PASE score) and knee symptoms (using WOMAC) over a period of 24 months. Subjects with a higher amount of knee abnormalities and higher T2 values were prone to an increase of knee symptoms and thereby to a decreased physical activity over time. Interestingly, a highly significant change in PASE was found only for subjects with higher T2 values at baseline. On the other hand subjects with cartilage lesions or joint effusions showed a lower PASE scale and higher WORMS score at baseline as well as after 24 months. Then an association between cartilage T2 relaxation time and the prevalence of cartilage lesions was discovered. When cartilage lesions were present, T2 values were elevated. Incident pain changes (WOMAC score) after 24 months highly correlated with higher KL-Scores, cartilage abnormalities and MR-based BMEP, joint effusion and osteophytes at baseline (table 4).

Significant differences in subjects with and without OA indicated that both T2 and morphometric parameters may be useful in quantifying early OA related changes, like collagen matrix changes and hydration of the cartilage.

Cartilage T2 relaxation time measurement is a relatively new quantitative MRI parameter to assess the water content and collagen quality in subjects with evolving cartilage degeneration. It has been used with good results in differentiating healthy subjects from those with asymptomatic early OA(45). Already in 1997, it was postulated that there is a correlation between T2 relaxation time and cartilage alteration caused by changes in water and PG content and that T2 values might therefore be a valid marker for early changes in the cartilage matrix(54). In 1999, Bredella et al.(109) performed a study on 130 patients to compare the accuracy of routine T2-weighted MRI and arthroscopy in detecting cartilage lesions. The patients underwent axial and coronal MR imaging and arthroscopy of the knee where internal derangement was suspected. Also this group pointed out that T2-weighted fast spin-echo MRI with fat saturation was an accurate technique to grade and detect cartilage defects of the knee. Best accuracy was reached in subjects with low grade OA (grade 1, accuracy 86%) becoming less with higher grades of OA (grade 4, accuracy 76%). But they also addressed the fact that cartilage lesions were more often undergraded than overgraded in MR imaging especially in advanced OA stages. It was recently shown that cartilage T2 values of the patella and radiomorphological damage of the cartilage highly correlate with physical activity levels suggesting that higher physical activity may promote cartilage degeneration(91, 110).

In contrast, there were no significant alterations of T2 relaxation times in a one year follow-up study(106) that compared eight patients with early knee OA (KL score 2-3) to ten healthy controls. These diverging results might be due to the shorter observation interval, the smaller cohort and technical factors such as different T2 mapping sequence. Anyway, this underlines the suggestion that OA involving cartilage and joint degeneration is a gently progressing disease.

Concluding, these findings indicate that T2 mapping might be a useful quantitative parameter to assess longitudinal changes in early OA and that higher T2 values might be associated with a higher degree and incidence of morphological cartilage lesions.

Compared with T2 relaxation, T1 relaxation time is relatively insensitive to cartilage degeneration. By using Gd-DTPA^2, it can become specific to molecular cartilage composition, if

measured after contrast agent application(60). Several studies(14, 48, 49) were performed with dGEMRIC and already in 1999(48) in vivo MR images were compared to histological images of the same joint after total knee replacement surgery. The results show that MR-calculated GAG images and the histological assessment of GAG content provided comparable results. In these studies it could be shown that in vivo T1 images of knee cartilage after Gd-DTPA^2 - application correlated with the in vitro images of the same cartilage. Hence, Bashir et al. validated the method for imaging GAG concentration in human cartilage, and for imaging a specific macromolecule non-destructively in vivo. In 2008, a study(111) was published that examined the predictive value of dGEMRIC cartilage imaging concerning future development of knee OA. 17 subjects with knee pain and arthroscopic cartilage changes ranging from superficial fibrillation to fissuring and softening, but with normal radiography, were examined. After six years, nine out of 16 subjects showed radiographic OA changes. Looking at their baseline dGEMRIC index, Owman et al. found a lower index in these subjects. So they suggested that a low dGEMRIC index is associated with an increased risk of radiographic OA changes and may also be predictive for the development of knee OA. Anyhow, as discussed earlier, Gd-DTPA^2 has allergic potential and can cause nephrogenic systemic fibrosis syndrome. Therefore, another T1 relaxation parameter, T1rho became point of interest for further studies.

A small number of studies have used MR imaging to assess the relationship between physical activity and T1rho and T2 values of the knee cartilage (45, 109, 47, 56). Subjects with cartilage abnormalities had significantly higher WOMAC scores, T2 relaxation times(45, 106) and T1rho(47) relaxation times. In addition, physically active, asymptomatic controls with cartilage lesions also had higher T1rho values compared to subjects without knee abnormalities(56). Thereby, Stahl et al.(56) concluded that T1rho is suitable to differentiate early OA patients from healthy subjects and might be even more sensitive than T2 relaxations times. The diagnostic performance of T1rho and T2 relaxation time was also compared in a study on menisci of subjects with mild and severe OA and healthy controls(112). Also in this study both parameters correlated with clinical OA findings and helped to differentiate healthy subjects from those with OA. In detail, T2 had better performance to depict abnormalities in menisci, whereas T1rho was more useful in detecting alterations of the hyaline cartilage.

In conclusion, T2 and T1rho relaxation times are suitable to display cartilage or menisci degeneration. Additionally, there is no need of contrast agent application and they do have a

shorter acquisition time than gradient echo sequences. But for daily clinical routine it should not be ignored that there are also limitations of this technique, such as susceptibility to motion artefacts and the dependence on the manual segmenting technique and thereby the lack of inter– and- intra– personal reproducibility.

An important factor in degeneration of the hyaline cartilage is the change of its water content under physical stress. Therefore, in 2002, Liess et al.(53) investigated water content changes in cartilage in vivo. Twenty healthy volunteers were asked to perform 60 knee bends in order to put stress on their patellar cartilage. It was found that compressing the patellar cartilage at first leads to a decrease of thickness by forcing a small amount of water out of the cartilage. This water leaks out into the joint space and will later be reabsorbed into the cartilage matrix. At two time points (directly after and 45min. after knee bending) MRIs were performed and cartilage thickness and T2 maps were determined. The change of water content and T2 relaxation time in vivo was correlated. Right after the exercise both parameters decreased and after 45 minutes of rest cartilage thickness showed an increase of 4,5% (from 2.94±0.15 mm to 3.10 ± 0.15 mm) coming along with an increase of 2,6% (from 23.1 ± 0.5 ms to 23.7 ± 0.6 ms) in T2 values. There was a significant correlation between cartilage thickness and T2 values ($p < 0.01$). The recovery time of thickness and T2 values, as well as the degree of cartilage deformation varied between both study groups(53). In this study, the impact of physical activity on the cartilage matrix was shown but no correlation was made to thigh muscle strength. Since muscle strength might have had impact on the joint recovery, the present study also concentrated on activity levels, thigh muscle strength, T2 values and WORMS scores.

Initially, the thigh muscle measurements showed a significant gender difference in the total quadriceps and hamstring volume ($p = 0.0001$), meaning that women had less muscle size and cross-sectional volume than men. After correction for body surface area the vastus medialis muscle size still showed a significant inter-gender value difference. Overall, subjects with larger cross-sectional muscle volume demonstrated higher physical activity parameters. Furthermore, the results showed a highly significant difference in mean cartilage T2 ($p = 0.0039$) and morphological abnormality scores ($p = 0.0248$) between subjects with low vastus lateralis/medialis ratio and those with high ratio. Subjects with high VL/VM ratio had significantly less morphological joint abnormalities and lower T2 values. Additionally, subjects

with higher muscle strength had lower WORMS and Recht scores. Surprisingly, these findings were more distinct for women than for men.

Summing up, these results lead to the assumption that higher muscle volume in general, and especially a high strength of vastus lateralis muscle, might be protective for the knee joint. Finally, the hypothesis emerged that muscle strength could have a protective impact on the progression of joint/cartilage degeneration and pain development.

Also in other studies higher quadriceps strength was found to be associated with significantly reduced risk of developing knee OA in women(76). Plus it was found to be protective against cartilage degeneration in the lateral compartment of the patello-femoral joint(77). Amin et al.(77) examined 265 subjects over a period of 30 months who met the American College of Rheumatology criteria for symptomatic knee OA. Subjects with greater quadriceps strength had less pain and better physical function ($p < 0.001$). Furthermore, they were able to show an inverse correlation between quadriceps strength and cartilage loss at the lateral compartment of the patello-femoral joint meaning that subjects with more muscle had less cartilage loss.

Similar results were obtained in studies on rabbits(113). The rabbits' knees were either weakend by botulinum toxine injections into the quadriceps or an anterior cruciate ligament transection was performed. In two animals reddening of tibial joint margins and histological degeneration of cartilage from different areas of the joint were found. These authors suggested that muscle weakness might be an independent risk factor for joint degeneration leading to osteoarthritis. In 2006, Mikesky at al. investigated whether thigh strengthening exercises prevent incident radiographic changes or slow down the progression of knee OA(114). A study on 164 adults older than 55 years was performed over a period of 30 months. The subjects underwent standing anteroposterior radiographic imaging and administration of the WOMAC score and then were separated into groups according to the presence of radiographic evidence of knee OA and knee pain. They were randomised separately into either the strength training (ST) group or the range-of-motion (ROM; attention control) group. During the 30 months the ST group was asked to do leg presses, leg curls, seated chest presses, and seated back rows at least three times a week. The intensity of exercise was based on a clinical determination of the maximum resistance in 3 sets of 8–10 repetitions. The ROM group performed simple movement exercises involving no external loading. The authors were able to show that in the ST group the subjects gained more strength

and exhibited less frequent progressive space joint narrowing than the ROM group(114). These findings are congruent with the present results that subjects with higher VL/VM ratio had less morphological abnormalities of the joint.

In 2010, a longitudinal study(115) was launched based on the data of the Multicentre Osteoarthritis study to investigate the impact of muscle strength on the joint. 3856 knees with an OARSI joint space narrowing score < 3 were included. In a 30 months follow-up, measures included bilateral weight-bearing fixed flexion radiographs, isokinetic concentric quadriceps and hamstring strength, height and weight, and physical activity levels. The results revealed that women with low muscle strength were at elevated risk to develop joint space narrowing in the whole knee, as well as in the tibio-femoral joint, compared to those with higher quadriceps strength. These results are congruent with the findings of the present study that a higher VL/VM ratio in women correlates with lower WORMS score.

LIMITATIONS OF THE STUDY

The group separations into Incident cohort or lower and higher T2 values, as well as into high, mid and low PASE scale groups**,** in the present study might occur artificial regarding the continuum between newly developing and progressive disease, the subjectivity of physical activity or the development of OA over many years. However, there was a need to select a collective and to categorize it. In the chosen MRI segmenting technique the slices thickness was thicker than in former established techniques, so that slight degenerations in between the slices might have been overseen because of the limited slice levels. Nevertheless, this technique was less time consuming and still a reliable technique as Stehling et al.(8) was able to show. Apart from this another limitation was that only T2 mapping was used for the biochemical composition assessment of the cartilage. Unfortunately, in the OAI protocol only T2 mapping sequences and no other quantitative MR sequences were included. Promising new techniques like T1rho and dGEMRIC(14) were not available. Furthermore, not all of the data could be used due to motion artefacts or the data could not be regained after 24 months for the follow-up because of subjects` absence.

Limitations of the muscle data evaluation were that only standardised axial T1W images through the right mid thigh region were used for the segmentation of the thigh muscle groups, which

allowed the evaluation of muscle size in cross-sectional area but not of the muscle volume. Another limitation of this study was that subcutaneous and peripheral fat was excluded during muscle segmentation, whereas fatty infiltration within each muscle group was not evaluated separately. Therefore, variation in intramuscular fat was not accounted for when calculating muscle cross-sectional area. Furthermore, there was no possibility to evaluate the impact of muscle training because there was no 24 months follow-up data launched yet.

CONCLUSION

In conclusion, the present study underlines that T2 mapping is a valid parameter to evaluate changes in cartilage matrix and that T2 values and morphological knee abnormalities were able to predict clinical changes in physical activity and pain over a period of 24 months. These findings suggest that subjects with higher baseline T2 values may be at greater risk for the development of symptomatic knee OA. It is assumed that MRI T2 mapping is a quantitative measurement that has diagnostic impact in the future of OA diagnostics, especially because T2 relaxation time depicts cartilage changes at an early stage of the disease.

Since hyaline cartilage does not regenerate and cartilage loss is irreversible, it is crucial to diagnose degeneration at the earliest stages or before cartilage loss occurs, having in mind the increasing number of patients that develop OA. There does not yet exist an accepted medical treatment that is capable to structurally modify OA. Using T2 mapping as a non-invasive method to detect early changes in cartilage matrix, it may be possible to prevent progression of OA by identifying individuals at risk, who may benefit from a treatment.

With this study it was possible to highlight preliminary findings and to determine that especially sites of abnormal cartilage T2 values are associated with structural cartilage damage and might have prognostic potential for disease progression, for instance by controlling the effects of cartilage tissue modifying drugs.

Because there was no 24 months follow-up in the muscle data group, this study could not investigate whether muscle strength does protect the knee from degeneration. But it could be pointed out that a higher VL/VM ratio leads to lower WORMS and RECHT scores, as well as lower T2 values of the knee cartilage (table10, table 11). Besides this, healthy sportive activity does lead to other benefits including improvement in bone mineral density, decreased risk of falling due to better thigh strength, better balance, and increased stair-climbing ability or walking speed. But as the present study showed, too much activity can also harm the cartilage, which was represented by higher T2 values in the high PASE scale group.

Further studies need to be performed to investigate for example whether the method of muscle mass strengthening (isometric versus isotonic) and muscle balance have an impact on joint protection. Furthermore, other imaging techniques, such as dGEMRIC and T1rho will have to be

compared in bigger cohorts over a longer period of time to evaluate their prognostic impact and also their ability to depict cartilage matrix change/damage at the earliest time point possible.

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GLOSSARY

AC	Articular Cartilage
ANOVA	Analysis of Variance
BMEP	Bone Marrow Oedema
BMI	Body Mass Index
BSA	Body Surface Area
CNRE	Contrast to Noise Ratio
COX2	Cyclooxigenase 2
CV	Coefficient of Variation
DEFT	Driven Equilibrium Fourier Transform
DESS	Double Echo Steady State Sequence
Gd-DTPA^2	Gadopentetate Dimeglumine
dGEMRIC	delayed Gadolinuim-Enhanced Magnetic Resonance Imaging of Cartilage
ECM	Extracellular Matrix
ETL	Echo Time Length
FLASH	Fast Low Angle Shot
FS	Fat Suppression
FSE	Fast Spin-Echo
GAG	Glycosaminoglycan
HA	Hyaluronic Acid
IDL	Interactive Display Language

ICC	Interclass Correlation Coefficient
KL	Kellgren Lawrence Scale
KOOS	Knee Injury and Osteoarthritis Outcome Score
ME	Multi Echo
MSME	Multi Slice Multi Echo
MOST	Multicentre Osteoarthritis Study
MRI	Magnetic Resonance Imaging
NSAID	Nonsteroidal Antiinflammatory Drugs
OA	Osteoarthritis
OAI	Osteoarthritis Initiative
OARSI	Osteoarthritis Research Society International
PACS	Picture Archiving Communication System
PASE	Physical Activity Scale for Elderly
PD	Proton Density
PG	Proteoglycan
ROI	Regions of Interest
ROM	Range of Motion
SE	Spin Echo
SPGR	Spoiled Gradient Echo
SSFP	Steady-state Free Precision
ST	Strength Training
TE	Echo Time

TR	Relaxation Time
T1W	T1 weighted
VL	Vastus Lateralis
VM	Vastus Medialis
WE	Water Excitation
WOMAC	Western Ontario Mc Master Osteoarthritis Index
WORMS	Whole Organ Magnetic Resonance Imaging Score

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APPENDIX

Menisci

Location(s) within menisci

1 = medial anterior

2 = medial body

3 = medial posterior

4 = lateral anterior

5 = lateral body

6 = lateral posterior

Visualisation

0 = no lesion

1 = questionable depiction of lesion

2 = lesion likely present

3 = lesion definitely present

Type of menisci lesion(s)

1 = intrasubstance abnormalities

2 = non-displaced tear

3= displaced or complex tear without deformity

4 = maceration of the meniscus

Other pathology of the menisci

1 = vertical tear

2 = horizontal tear

3 = flap

4 = bucket handle

5 = meniscocapsular separation

6 = meniscocapsular tear

7 = root tear anterior medial (i.e. 9a)

8 = posterior medial

9 = anterior lateral

10 = posterior lateral

11 = discoid meniscus

12 = meniscal cysts

13 = extrusion

Ligaments and Tendons

Location(s)

1 = ACL

2 = PCL

3 = MCL

4 = LCL

5 = popliteus

6 = patellar ligament

Ligament lesion grade

0 = no lesion

1 = grade 1 sprain

2 = grade 2 sprain

3 = grade 3 sprain

Location of lesions

1 = patella

2 = trochlea

3 = femoral condyle medial

4 = femoral condyle lateral

5 = tibia medial

6 = tibia lateral

Cartilage:

WORMS-Score:

0 = normal thickness and signal

1 = normal thickness but increased signal on T2 swelling

2.0 = partial thickness focal defect < 1 cm in greatest width

2.5 = full thickness focal defect < 1 cm in greatest width

3 = multiple areas partial-thickness (grade 2.0)

4 = diffuse (≥75% of the region) partial thickness loss

5 = multiple areas of full-thickness loss (grade 2.5) or a grade 2.5 lesion wider than 1 cm but <75% of the region

6 = diffuse (≥75% of the region) full-thickness loss

Recht-Score:

0 = normal thickness and signal

1 = swelling and increased signal on T2

2 = thickness loss < 50%

3 = thickness loss > 50%

4 = full-thickness loss

Bone marrow oedema

WORMS and Mink:

0 = normal

1 = minimal (minimal diameter < 5mm)

2 = moderate (diameter 5mm-20mm)

3 = severe (diameter > 20mm)

Signal Intensity

0= none

1 = mild (on fat-sat images)

2 = moderate

3 = as joint fluid

Additional morphological findings

0 = none

1 = subchondral fractures

2 = fracture lines

Flattening or depression of articular surfaces

Signal intensity grading:

0 = normal

1 = mild

2 = moderate

3 = severe

Subarticular cysts

Grading:

0 = normal

1 = minimal (<3mm)

2 = moderate (3-5mm)

3 = severe (>20mm)

Osteophytes (WORMS):

0 = none

1 = equivocal

2 = small

3 = small – moderate

4 = moderate

5 = moderate to large

6 = large

7 = very large

Synovial thickening + effusion (WORMS)

0 = normal

1 = <33% of maximum potential distention

2 = 33%-66% of maximum potential distention

3 = >66% of maximum potential distention

Loose bodies (WORMS)

0 = none

1 = 1 loose body

2 = 2 loose bodies

3 = 3 or more loose bodies

Popliteal cysts (WORMS)

0 = normal

1 = minimal

2 = moderate

3 = severe