TECHNISCHE UNIVERSITÄT MÜNCHEN

Institut für Röntgendiagnostik der Technischen Universität München
Univ.-Prof. Dr. E. J. Rummeny

Meniscal Measurements of $T_{1\rho}$ and T_2 at MR Imaging in Healthy Subjects and Patients with Osteoarthritis

Isabel Rauscher

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List of abbreviations

A_z	area under curve (receiver operating characteristic)
BME	bone marrow edema
BMI	body mass index
CI	confidence interval
CV	coefficient of variation
dGEMRIC	delayed gadolinium-enhanced magnetic resonance imaging
FOV	field of view
Gd-DTPA2-	gadopentate dimeglumine
GAG	glycosaminoglycan
HIPAA	Health Insurance Portability and Accountability Act
KL	Kellgren Lawrence
MRI	magnetic resonance imaging
OA	osteoarthritis
PG	proteoglycan
ROC Analysis	receiver-operating-characteristics-analysis
SPGR	spoiled gradient echo
TE	echo time
TI	repetition time
TSL	time of spin-lock
T_{rec}	time of recovery
VPS	views per segment
WOMAC	Western Ontario and McMaster Osteoarthritis
WORMS	whole-organ MR imaging score

1. Introduction

Osteoarthritis (OA) is a multifactorial degenerative joint disease and the most common form of arthritis, apart from other common rheumatic conditions including gout, fibromyalgia and rheumatoid arthritis. OA is characterized by joint degeneration, loss of cartilage, alterations of subchondral bone and damage to the extra-cellular matrix. Overall OA affects 12.1% of adults aged 25 - 74 and an estimated 27 million adults in the US have osteoarthritis [30], with majority being older.

The population of people age over 65 years increases fast and health issues including the integrity of diarthrodial synovial joints and pain-free movement become a more and more important issue. OA is the leading cause of disability [11], and associated with substantial activity limitation, work disability, reduced quality of life, and high health-care costs [12, 44]. As the population ages, arthritis is expected to affect an estimated 67 million adults in the United States by 2030 [26].

The knee is the most common site affected, with an incidence of 240 cases per 100,000 individuals a year. The incidences of hand OA (100 cases per 100,000 individuals annually) and hip OA (88 cases per 100,000 individuals annually) follow [50].

Previous studies have shown that OA leads to progressive cartilage loss, which can be evaluated with magnetic resonance (MR) imaging. MR sequences to evaluate cartilage qualitatively [23, 29, 36, 54] and quantify cartilage volume [19, 51] have been developed. OA is characterized by the progressive and irreversible loss of hyaline articular cartilage; however, the cartilage loss and clinical symptoms are preceded significantly by damage to the collagen-proteoglycan (PG) matrix and elevation of cartilage water content [40]. Therefore, a sensitive technology for detecting these structural and functional changes during the early stages of OA could

be valuable tool not only for the early diagnosis and preventing the progression of the disease and long-term consequences but also for therapeutic monitoring.

Recent studies have shown the potential of MR imaging examinations to reveal changes in the biochemical composition of hyaline cartilage with early OA. These techniques include T_2 [16, 47] and $T_{1\rho}$ (T_1 relaxation time in the rotating frame) quantifications [32, 56], diffusion-weighted imaging [45] and delayed gadolinium enhanced MR imaging of cartilage (dGEMRIC) [4, 9]. Although these techniques have shown promise for characterizing the cartilage matrix composition, the segmentation of hyaline cartilage required for quantitative analysis is a cumbersome procedure that may take several hours per knee.

In addition, OA is a multisystemic disease and not merely a disease of cartilage. Recent studies show that the origin and progression of OA are not attributable to disease in only one tissue, such as articular cartilage, but rather to disease in any tissues of the affected joint, including the subchondral bone, synovium, capsule, periarticular muscles, sensory nerve endings and meniscus [8]. Thus, attention has also been focused on the meniscus because the structure of the meniscus is very similar to the one of the hyaline cartilage. Both contain mainly water, collagen and proteoglycans. Additionally, the segmentation of the meniscus is substantially less challenging.

2. Aims

The aims of this study were (i) to characterize the matrix of the meniscus with $T_{1\rho}$ and T_2 measurements and evaluate differences in $T_{1\rho}$ and T_2 values in patients with varying degrees of osteoarthritis (OA) and healthy controls, (ii) to determine the reproducibility of the meniscal measurements and (iii) to correlate meniscal $T_{1\rho}$ and T_2 values with other quantitative and qualitative parameters obtained from knee MR studies, such as cartilage $T_{1\rho}$ and T_2 values, age, BMI and WORMS score. Additionally, (iv) the WOMAC score was used to detect correlation with clinical findings.

3. Background

3.1. Anatomy of the meniscus

For some synovial joints that are not congruent in shape as the weight bearing knee joint, the meniscus exists to help distribute the load and maintain stability. The menisci are semilunar in shape and are situated between the femoral condyles and the tibial plateau of the knee (Figure 1).

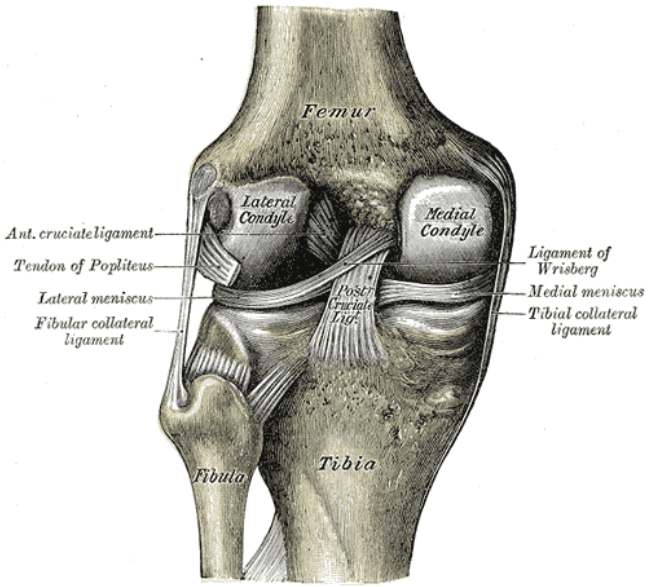


Figure 1: Anatomy of the knee joint

(Henry Gray, Anatomy of the Human Body, 20th edition, New York: Bartleby.com, 2000)

The C-shaped medial and the U-shaped lateral meniscus provide structural integrity to the knee when it undergoes tension and torsion (Figure 2). They reduce friction during movement and disperse the weight of the body.

Since the condyles of the femur and tibia meet at one point they spread the load of the body's weight. Since 70% of the body's load is on the medial meniscus during

activity, the medial meniscus is of higher importance than the lateral meniscus and may indicate why there are more often tears in the medial meniscus.

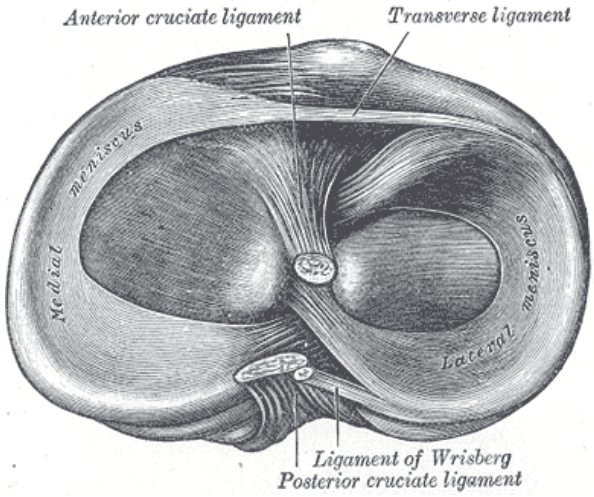


Figure 2: Anatomy of the meniscus

(Henry Gray, Anatomy of the Human Body, 20th edition, New York: Bartleby.com, 2000)

The peripheral border of each meniscus is thick, convex, and attached to the inside capsule of the joint; the opposite border tapers to a thin, free edge. The inner 2/3 of the meniscus are nutritioned by diffusion of the synovial liquid, whereas the outer 1/3, the basis of the meniscus is vasculated from the membrana fibrosa.

Tissue	Water	Collagen	Proteoglycan
Articular cartilage	68 - 85%	10 - 20% (type2)	5 - 10%
Meniscus	60 - 70%	15 - 25% (type1)	1 - 2%

Table 1: Composition of articular cartilage and meniscus

Tissues like the meniscus are often mistakenly viewed as a tantamount to hyaline cartilage but there are some important differences. First of all, the meniscus and hyaline cartilage differ in their content of water, collagen and proteoglycans (Table 1). Whereas the articular cartilage has a slightly higher concentration of water and proteoglycan than the meniscus, the meniscus has a higher collagen concentration [61].

Apart from composition, hyaline articular cartilage is exclusively composed of chondrocytes that produce primarly type 2 collagen, whereas the meniscus of the knee has a mixed cell population of fibroblasts and cells similar to chondrocytes, which predominantly secrete type 1 collagen.

Additionally, fibrocartilaginous tissues have a low glycosaminoglycan content, a low compressive modulus, and a high tensile modulus when compared to hyaline cartilage [2].

3.2. Pathophysiology of osteoarthritis

Osteoarthritis is a heterogeneous and multi-factorial disease. It affects approximately 14% of the adult population [21] and is the second most common cause of permanent disability among subjects over the age of fifty [53].

It can be classified in idiopathic (localized or generalized) or secondary (traumatic, congenital, metabolic/endocrine/neuropathic and other medical causes).

Men under age 55 are more likely to have OA than women under 55. After age 55, women are more commonly affected; and, overall, more women have OA than men. It is thought that his is because the broader female hips put more long-term stress on the knees.

Primary OA is mostly related to ageing because the water content of the cartilage increases and the protein makeup of cartilage degenerates. Conditions that lead to secondary OA include obesity, repeated trauma or surgery to the joint structure, abnormal joints at birth, muscle weakness, gout, diabetes and other hormone disorders.

Clinical Symptoms include pain after overuse or after long periods of inactivity, joint swelling and joint fluid accumulation, warmth, and creaking in the affected joint after repetitive use. Pain and stiffness of the joints can also occur after long periods of inactivity.

In severe osteoarthritis, complete loss of cartilage cushion causes friction between bones, causing pain at rest or pain with limited motion.

The most common course of OA is an intermittent, progressive worsening of symptoms over time, although in some patients the disease stabilizes.

There are several factors that increase a person’s chances of developing osteoarthritis, these include heredity, obesity, injury or joint overuse. Factors associated with

progression of OA in the knee include high body mass index and varus or valgus knee deformity.

Radiography is still standard for assessment of the progression of OA, and the Kellgren-Lawrence (KL) scale [27] is used most frequently by physicians. Additionally, clinical symptoms such as pain, stiffness and limited function confirm the diagnosis.

One of the most well established scores is the Western Ontario and MC Master University (WOMAC) osteoarthritis index, a multidimensional health status instrument [5, 14] that quantifies pain, stiffness, and limited function in patients with osteoarthritis of the knee and hip. Concerning treatment, the process of clinically detectable osteoarthritis is irreversible, and typical treatment consists of medication or other interventions (e.g. application of heat) that can reduce the pain of OA and thereby improve the function of the joint.

OA accounts for 55% of all arthritis-related hospitalizations; 409,000 hospitalizations for OA as principal diagnosis in 1997 [31]. From 1990 to 2000 the age-adjusted rate of total knee replacements in Wisconsin increased 81.5 %. 7.9 billion dollars estimated cost of knee and hip replacement in 1997. Job-related OA costs 3.4 to 13.2 billion dollars per year. OA accounts for 55% of all arthritis-related hospitalizations; 409,000 hospitalizations for OA as principal diagnosis in 1997 [31].

3.3 Traditional Diagnosis of OA and new parameters for the quantification of the cartilage

Traditionally, OA diagnosis is done through x-rays characterized by the progressive loss of hyaline articular cartilage and the development of altered joint congruency which you can see in the x ray pretty late only as an indirect sign with narrowing of the joint space between the articulating bones. Secondary changes of OA such as subchondral sclerosis, intraosseus cysts, and osteophytes can be seen but x-ray does not image cartilage directly. It remains an open question whether the initial changes take place in cartilage or bone or other articular tissues, and, more importantly, what the causal relationship between these changes is.

Conventional x-ray alone is insensitive of early biochemical changes and can just show indirect signs of OA. The only accepted standard for monitoring cartilage damage and repair directly is arthroscopy. Arthroscopy is very invasive and expensive and since MR imaging is an excellent soft tissue contrast, research focuses now on MRI methods.

Since early OA is associated with loss of proteoglycan which you can't see with x-ray or arthroscopy, MR imaging techniques which can quantify the biochemical composition of the cartilage are increasingly important, apart from morphologic parameters such as cartilage volume and thickness.

Cartilage is mainly composed of water, collagen and proteoglycans. There exist several new methods quantifying these components including $T_{1\rho}$, T_2, dGEMRIC and diffusion-weighted imaging.

$T_{1\rho}$ measurements

One biochemical marker which has been proposed to measure cartilage composition is $T_{1\rho}$. $T_{1\rho}$ describes the spin-lattice relaxation in the rotating frame and reflects the

interactions between motionally restricted water molecules and their local macromolecular environment. Changes to the extracellular matrix, such as proteoglycan loss, may be reflected in measurements of $T_{1\rho}$. Since the loss of PG has been shown to be an initiating event in early stages of OA, $T_{1\rho}$ mapping may be a promising diagnostic tool for early OA evaluation [17]. $T_{1\rho}$ relaxation time has been shown to increase with decreasing PG content in ex vivo bovine patellae [18] and has been proposed as a more specific indicator of PG content than T_2 relaxation in trypsinized cartilage [57]. In vivo studies have also shown increased cartilage $T_{1\rho}$ values for patients with OA [17, 56]. However, the relationship between $T_{1\rho}$ and the PG/collagen matrix remains controversial in the literature [42, 46].

T_2 relaxation time measurements

Quantitative T_2 relaxation time is a non-invasive marker of cartilage degeneration and it's sensitive to tissue hydration and biochemical composition. Loss of collagen and proteoglycan in degenerating cartilage increases the mobility of water and therefore the signal intensity on T_2-weighted images.

In articular cartilage, the T_2 relaxation time has a linear correlation with the water content of tissue [38], is sensitive to loss of collagen content [49]and to the orientation of collagen fibers [63] in the extracellular matrix.

In vitro imaging studies have evaluated the relationship between biochemistry of content remains controversial in literature.

A study of Watrin-Pinzano [62] found significantly increased global T_2 with proteoglycan loss in rat patellar cartilage induced by hyaluronidase degeneration which does not alter the collagen network, whereas other studies showed minimal association between the depletion of proteoglycan and T_2 [7, 46, 60].

In summary, these in-vitro studies show that the biochemical changes associated with cartilage degeneration are related to increased T_2 but that the effects of proteoglycan concentration on T_2 need further investigation.

Both $T_{1\rho}$ and T_2 reflect changes associated with proteoglycan, collagen content and hydration.

$T_{1\rho}$ has a larger dynamic range than T_2 [55], indicating that it may be more sensitive to degenerative changes occurring in cartilage OA.

A recent study by Majumdar et al investigated the differences between T_2 and $T_{1\rho}$ values between OA patients and healthy controls. OA patients had a significantly increased cartilage $T_{1\rho}$ value compared to healthy controls, while the increase in T_2 was insignificant [39].

Delayed gadolinium-enhanced magnetic MRI of the meniscus

Although T_1 is relatively insensitive to cartilage degeneration, it can become a very sensitive and specific marker after the application of the clinically approved contrast agent MRI contrast agent GdDTPA2-.

Delayed gadolinium-enhanced magnetic resonance imaging (dGEMRIC) images the glycosaminoglycan content of articular cartilage with the premise that the negatively charged MRI contrast agent gadopentate dimeglumine (Gd-DTPA2-) would distribute in inverse relation to the negatively charged glycosaminoglycan.

Krishnan et al [28] analyzed the T_1 of gadolinium-based contrast material in the meniscus and the relationship between this parameter and the T_1 of gadolinium-based contrast material in the articular cartilage at gadolinium-enhanced MR imaging of cartilage data sets. Their study results showed that the T_1 in the meniscus correlated significantly with that in the articular cartilage, potentially demonstrating associated degenerative processes in the knee joint.

4. Material and methods

4.1. Subjects and clinical assessment

The study was performed in accordance with the rules and regulations of the University of California Committee for Human Research and was Health Insurance Portability and Accountability Act (HIPAA) compliant. Written informed consent was obtained from all subjects.

For this study, 27 patients with mild OA (13 male, 14 female), 10 patients with severe OA (3 male, 7 female) and 23 healthy controls (12 male, 11 female) (Table 2) were recruited from February 2006 to April 2007.

Characteristic	Healthy Subjects	Active Subjects	Mild OA	Severe OA
No. of patients	10	13	27	10
Male/Female	6/4	6/7	13/14	3/7
Mean age	36.0	32.7	52.5	61.6
Mean BMI	22.9	23.3	25.6	29.9
Mean WOMAC	7.1	0.6	24.2	49.3

Table 2: Characteristics of the study population

Inclusion criteria for all subjects were good health according to medical history, physical examination, and clinical laboratory data as well as the absence of contraindications to MR imaging.

Inclusion criteria for the patients specifically were mild radiographic signs of OA without joint space narrowing (grade 1 or 2 based on the Kellgren-Lawrence (KL) OA classification system) [27] or severe radiographic signs of OA with joint space narrowing (Kellgren-Lawrence grade 3 or 4). For inclusion, subjects also had to have clinical symptoms of knee OA, such as frequent or chronic knee pain and limited

function as assessed by using medical history and physical examination [3]. Control subjects were included if they had no clinical evidence of knee OA, were examined by a sports medicine physician and found to have intact joint function with full strength, and had no history of chronic or frequent knee pain. Exclusion criteria were inflammatory arthritis and knee OA secondary to other causes (acute or chronic infection, metabolic abnormalities, previous surgery or previous fracture).

The control subjects were classified into a physically 'sedentary' control group and into a physically 'active' control group by use of the Tegner score [59]. The Tegner activity level score is a quantitative grading method, which was originally developed to document activity levels of patients with anterior cruciate ligament insufficiency. It reflects the amount of biochemical loading on the knee joint. The amount of physical activity is rated numerically on a scale from 0 to 10. Lowest values are assigned to subjects who are disabled (score 0) or only able to perform sedentary work (score 1) because of knee problems. Participation in national or international contact sport yields the highest score of 10. Seven subjects were assigned to the 'sedentary' group (Tegner score 1-3, 35.43 ± 10.66 years, 4 male 3 female); the remaining 13 subjects formed the 'active' group (Tegner score 4-7, 32.69 ± 9.02 years, 6 male, 7 female, performing recreational sports like long-distance running, biking, skiing, hiking). No information could be obtained from the remaining 3 subjects.

All patients completed a standardized clinical WOMAC questionnaire (Western Ontario and McMaster Universities Pain, Stiffness, and Physical Function scales) for measuring the degree of pain, functional impairment and stiffness in all subjects through a five-point scale (none, slight, moderate, severe and extreme) before undergoing MR imaging [5]. The WOMAC score was used to correlate the $T_{1\rho}$ and T_2 value with the degree of pain, functional impairment and stiffness. The separate pain, stiffness and function score was combined to a total WOMAC score.

4.2. Imaging techniques

We obtained anteroposterior radiographs of the knee in standing position in all patients with OA to determine the Kellgren-Lawrence grade. MR imaging of the most severely affected knee joint in the patients with OA and of the dominant knee joint in the control subjects was performed by using a 3.0 Tesla system (Figure 3) (Signa, GE Medical Systems, Waukesha, WI) and a dedicated knee coil (Clinical MR Solutions, Brookfield, WI, USA). The dominant knee was identified by asking the control subject which leg he or she would use to kick a ball.

The morphology of the cartilage and other knee structures and the integrity of the meniscus were assessed by using a sagittal fat-saturated intermediate-weighted fast spin-echo sequence (4300/51 [repetition time msec/echo time msec], echo train length of nine, two acquired signals, acquisition time of 12 minutes 42 seconds, 45 sections, 16-cm field of view, 512 × 256 matrix, in-plane spatial resolution of 0.293 × 0.293 mm, 2-mm section thickness, 0.5-mm intersection gap) and a sagittal T_1-weighted three-dimensional high-spatial-resolution volumetric fat-suppressed spoiled gradient-echo (SPGR) sequence (20/7.5, 12˚ flip angle, 512 × 512 matrix, 0.293 × 0.293 mm in-plane spatial resolution, 16-cm field of view, 0.75 acquired signal, acquisition time of 7 minutes 37 seconds, 1-mm section thickness).

Sagittal $T_{1\rho}$ and T_2 mapping sequences were used to assess the meniscal matrix. Three-dimensional $T_{1\rho}$-weighted images were obtained by using spin-lock techniques and an SPGR image acquisition, as previously described in detail by Li et al [33]. The sagittal three-dimensional $T_{1\rho}$-weighted imaging sequence consisted of two parts: magnetization preparation for the imparting $T_{1\rho}$ contrast, and an elliptically-centered segmented three-dimensional SPGR acquisition immediately after the $T_{1\rho}$ preparation during transient signal evolution. The duration of the spin-lock pulse was defined as time of spin-lock (TSL), and the strength of the spin-lock pulse was defined as spin-lock frequency (FSL). The number of pulses after each $T_{1\rho}$ magnetization preparation was defined as views per segment (VPS).

There was a relatively long delay (time of recovery, T_{rec}) between each magnetization preparation to allow enough and equal recovery of the magnetization before each $T_{1\rho}$ preparation. The main parameters used for this sequence were as follows: 9.3/3.7, 14-cm field of view, 256 × 192 matrix, 3-mm section thickness, receiver bandwidth of 31.25 kHz, VPS of 48, T_{rec} of 1.5 seconds, TSL of 0/10/40/80, and spin-lock frequency of 500 Hz.

The total acquisition time was 12 minutes 42 seconds. Sagittal three-dimensional T_2 maps were acquired by adding a nonselective T_2 preparation imaging sequence to the SPGR sequence used for $T_{1\rho}$ mapping and using a repetition time of 2000 msec and echo times of 4.1, 14.5, 25.0, and 45.9 msec. All other prescription parameters for the T_2-weighted sequence were identical to those used for the $T_{1\rho}$ sequence, and the total acquisition time was 10 minutes 36 seconds.

With use of the model introduced by Collins et al [13] , the estimated average specific absorption rate achieved with the parameters used in this study was 2.06 W/kg, which is substantially lower than the Food and Drug Administration, mandated maximal specific absorption rate of 12 W/kg in 1g of tissue in the extremities averaged over five minutes.

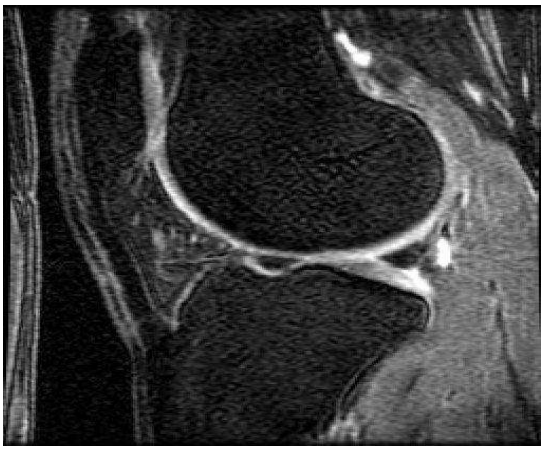


Figure 3: An example of a sagittal $T_{1\rho}$ sequence at 3 Tesla

4.3. Image analysis: $T_{1\rho}$ and T_2 measurements in the menisci

Meniscus segmentation was performed by using in-house software [10] developed with Matlab (Mathworks, Natick, Mass) and a semiautomatic technique based on Bezier splines and edge detection.

In each medial and lateral meniscus, distinct regions were defined: the anterior, posterior and body part of the medial and lateral meniscus. The above-mentioned regions were combined to larger units: the medial and lateral meniscus and both menisci together as "whole". Segmentation was performed in sagittal three-dimensional SPGR images as they had a high spatial resolution.

The meniscal body was defined mesially as the first section where the anterior and posterior parts of the meniscus were connected and peripherally as the last section showing the meniscus without partial volume effects, which were characterized by a change in the signal intensity of the meniscus compared with the signal intensity of the adjacent sections. The posterior border of the posterior horn of the lateral meniscus was defined by the hiatus popliteus. The fascicles were not included in the analysis. The mesial and peripheral borders separating the meniscus from the roots and capsular ligaments were identified on the basis of partial volume effects and signal intensity changes: Only those areas that had the same signal intensity as the more central aspects of the menisci were segmented. The vascular pedicle was not excluded from the analysis because it could not be consistently visualized or segmented.

After segmentation, the meniscus was transformed into a three-dimensional binary mask with isotropic voxels by using shape-based interpolation with distance fields. The $T_{1\rho}$ maps were reconstructed by fitting the image intensity pixel-by-pixel to the equation below using a Levenberg-Marquardt mono-exponential fitting algorithm developed in-house [32]

$$S(TSL) \propto \exp(-TSL/T_{1\rho})$$

The T_2 maps were reconstructed by fitting the image intensity pixel-by-pixel to the equation:

$$S(TE) \propto \exp(-TE/T_2)$$

Both $T_{1\rho}$ and T_2 maps were automatically registered to the $T_{1\rho}$ and T_2 images with a rigid-body registration technique to reduce effects of knee movement. Meniscus segmentations were then resampled and superimposed on the $T_{1\rho}$ and T_2 maps to define the regions of interest for $T_{1\rho}$ and T_2 assessment. Areas of partial volume effects due to fluid were manually excluded from the respective maps. One observer (I.R.) performed the segmentations and analyses after undergoing 1 week of training with experienced investigators (X.L., J.C.) and under the supervision of an experienced musculoskeletal radiologist (T.M.L., 20 years experience in musculoskeletal radiology). The segmentation and analysis required about 30 minutes. None of the menisci were excluded. Figure 4 shows a segmented medial meniscus on an SPGR image.

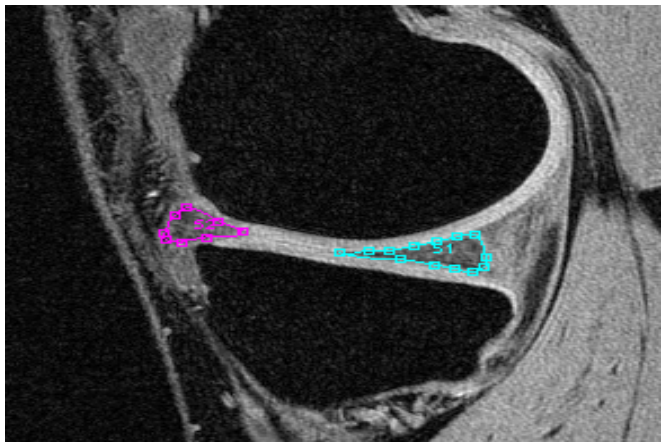


Figure 4: SPGR MR image shows segmented anterior and posterior horns of the medial meniscus

Reproducibility measurements

Coefficients of variation (CVs) were calculated to determine the reproducibility of measurement in the entire menisci (medial and lateral meniscus combined) and in the meniscal subregions. Three subjects were randomly selected, and their menisci were segmented three times by the same investigator. Note that the reproducibility assessment performed accounted for the variation in image analysis findings only and not for the variable error in data acquisitions.

Cartilage $T_{1\rho}$ and T_2 measurements

In addition to the menisci, hyaline articular cartilage was segmented in the control subjects and patients with mild OA by using the same software and semiautomatic technique [10]. The articular cartilage was segmented in six regions: medial and lateral femora, medial and lateral tibiae, patella, and trochlea. These regions were combined into larger units - namely, the femoropatellar joint (trochlea and patella) and the medial and lateral femorotibial joints. Coregistration was performed as in the meniscus.

Whole-organ MR imaging scores

Two experienced radiologists (T.M.L., R.S., 20 and 4 years experience, respectively) analyzed and scored the MR imaging findings in the knee joint in consensus by using a modified semiquantitative whole-organ MR imaging score (WORMS) [52]. The WORMS was developed to semiquantitatively analyze OA by separately grading the following entities: 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 or effusion, intraarticular loose

bodies, and periarticular cysts or bursitis [52]. Seven compartments were analyzed: medial and lateral tibiae, trochlea, medial and lateral femora, and medial and lateral patellae. These compartments were combined into larger units - namely, the femur, lateral-medial compartment, tibia, patellofemoral compartment, all.

We used the WORMS [52] to semiquantitatively grade cartilage abnormalities in terms of morphology and size and to semiquantitatively grade the bone marrow edema pattern in terms of size. Meniscal lesions were graded morphologically by differentiating between intrasubstance degeneration (grade 1), nondisplaced tears without deformity (grade 2), displaced tears (grade 3) and severe destruction or maceration of the meniscus (grade 4).

4.4. Statistical analysis

All statistical testing was performed with JMP, version 6, software (SAS institute, Cary, NC). Descriptive statistical evaluation was performed, and differences in age between the male and female study subjects, in body mass index, and in WOMAC scores were compared by using standard t tests. After evaluating the mean $T_{1\rho}$ and T_2 values (with standard deviations) for the segmented menisci, we performed analysis of variance with post hoc t-tests and adjusted the data for multiple comparisons by using Bonferroni corrections. Differences were deemed to be significant at $P<0.05$. To account for parameters that were significantly different between the three groups, such as age, we performed multivariate analysis with stepwise forward linear regression.

Receiver operating characteristic analysis [43] was performed to better assess the diagnostic performance of $T_{1\rho}$ and T_2 measurements in the differentiation of the healthy versus mild OA groups because these are the most clinically relevant populations and patients with severe OA can be easily identified on the basis of their cartilage morphology and meniscal abnormalities. The binomial model was fitted by using logistic regression; the discriminatory power of the model was analyzed by calculating the areas under the receiver operating characteristic curves (A_z), with corresponding 95% confidence intervals.

The correlations between changes in $T_{1\rho}$ and T_2 measurements and both age and body mass index (expressed as R^2 values) in the healthy subjects and the correlations between $T_{1\rho}$ and T_2 values derived from cartilage and those derived from menisci in all subject groups were calculated by using linear regression analysis. R^2 values were also calculated for correlations between meniscal $T_{1\rho}$ and T_2 values and WORMS and WOMAC scores. In addition to P-values, 95% confidence intervals of the correlation coefficients were generated with Fisher r to z transformation [20].

5. Results

5.1. Correlation between sedentary and active subjects

The mean $T_{1\rho}$ and T_2 values of healthy active and healthy sedentary controls in the medial and lateral meniscus are shown in Table 3. Both the $T_{1\rho}$ and the T_2 values in active controls were mildly higher compared to the sedentary control group. However, the mean $T_{1\rho}$ and T_2 values did not show significant differences between sedentary and active controls ($P > 0.05$).

	Sedentary controls	Active controls	P-value
Lateral Meniscus $T_{1\rho}$	13.7	14.6	0.3
Lateral Meniscus T_2	10.5	11.1	0.3
Medial Meniscus $T_{1\rho}$	14.1	15.9	0.1
Medial Meniscus T_2	11.7	12.0	0.6

Table 3: Mean $T_{1\rho}$ and T_2 values in the medial and lateral meniscus in sedentary and active controls and their P-values

In Table 4 the comparison of meniscal P-values is shown by dividing the patient population into 4 groups: a sedentary control group, an active control group, a mild OA patient group, and a severe OA patient group. There is a significantly correlation ($P<0.05$) in the $T_{1\rho}$ and T_2 value in both the medial and the lateral meniscus by comparing sedentary subjects with mild OA patients and severe OA patients. Compared to active subjects there was no significant difference in $T_{1\rho}$ and T_2 values of the medial and lateral meniscus ($P>0.05$).

Comparison of meniscal P-value Parameter	Medial Meniscus $T_{1\rho}$	Medial Meniscus T_2	Lateral Meniscus $T_{1\rho}$	Lateral Meniscus T_2
sedentary subjects vs				
(i) active subjects	0.1351	0.7873	0.3424	0.4973
(ii) patients with mild OA	0.0605	0.0100*	0.0073*	0.0012*
(iii) patients with severe OA	< 0.001*	< 0.001*	< 0.001*	< 0.001*

Table 4: comparison of meniscal P-values in the medial and lateral meniscus of sedentary subjects vs (i) active subjects, (ii) patients with mild OA, and (iii) patients with severe OA

Additionally, the following figures (Figure 5-9) demonstrate the differences in the $T_{1\rho}$ and T_2 values in sedentary controls, active controls, mild OA and severe OA patients for the medial and lateral meniscus and their subregions.

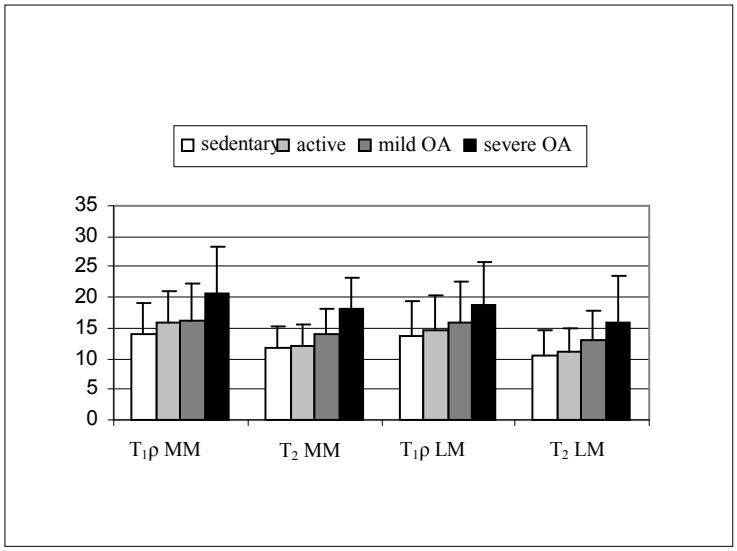
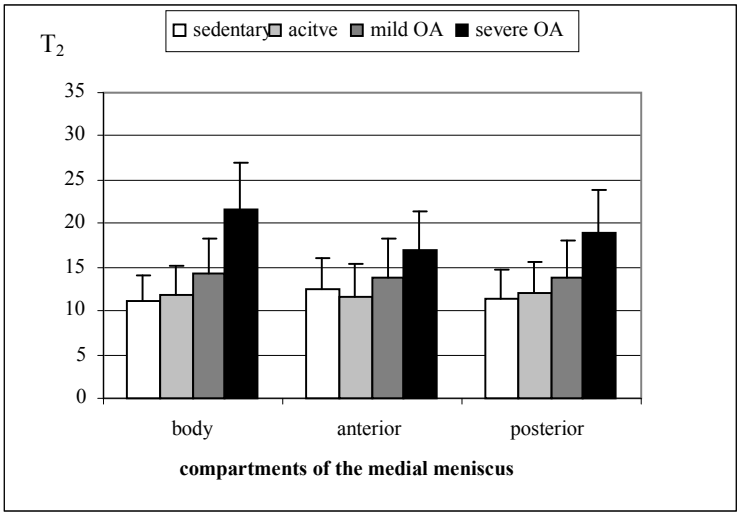
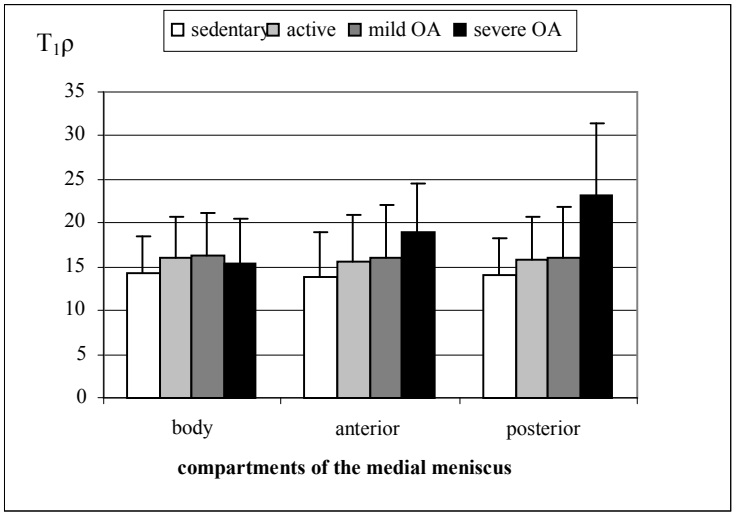
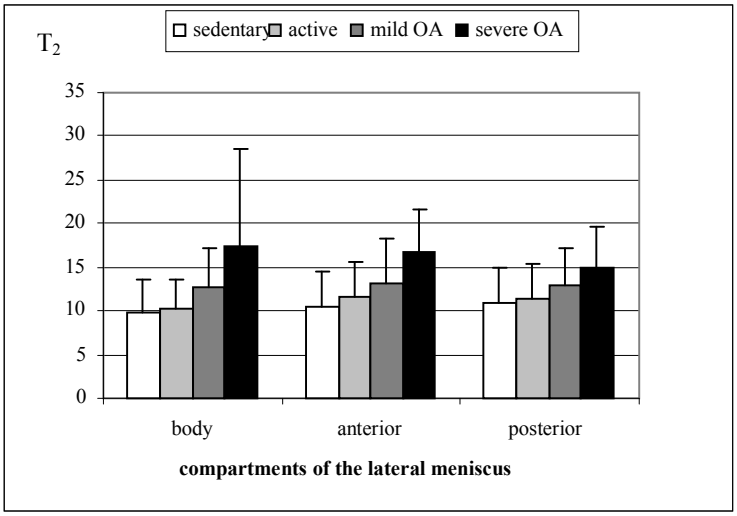


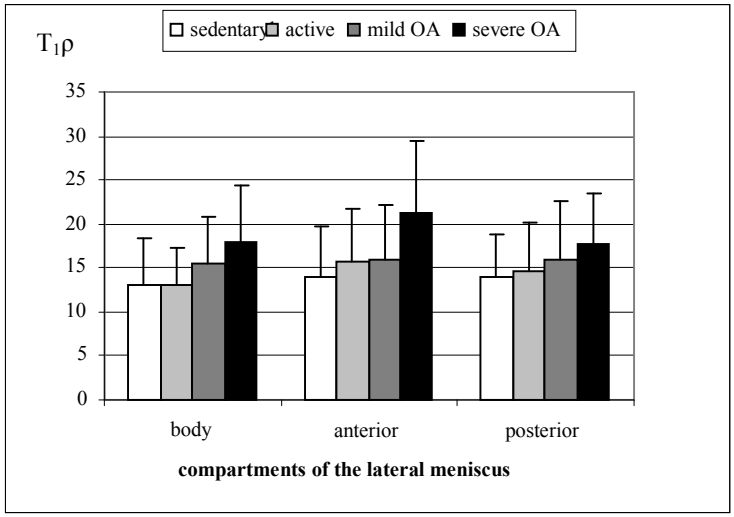
Figure 5: comparison of the means and standard deviation of the medial meniscus (MM) and the lateral meniscus (LM) in sedentary controls, active controls, patients with mild OA and severe OA with $T_{1\rho}$ and T_2 parameters





Figures 6 and 7: comparison of the means and standard deviation of the body, anterior and posterior horn of the medial meniscus in sedentary controls, active controls, patients with mild OA and severe OA with T_2 and $T_{1\rho}$ parameters





Figures 8 and 9: comparison of the means and standard deviation of the body, anterior and posterior horn of the lateral meniscus in sedentary controls, active controls, patients with mild OA and severe OA with T_2 and $T_{1\rho}$ parameters

The sedentary group and the active group, both healthy, were combined to a larger "control" group because there were no significant differences ($p > 0.05$) in meniscal $T_{1\rho}$ and T_2 values and in order to get a more representable control group to compare to the mild and severe OA group.

5.2. Differences between control group and different stages of osteoarthritis

5.2.1. Mean and standard deviation of $T_{1\rho}$ measurements

Means and Standard deviations (STDEV) of $T_{1\rho}$ measurements in controls, mild and severe OA patients in the entire (both menisci combined), the lateral and medial meniscus are shown in Table 5. $T_{1\rho}$ values increased from healthy to diseased subjects and with the degree of osteoarthritis.

		Control	Mild OA	Severe OA
$T_{1\rho}$	Entire Meniscus	14.7 ± 5.5	16.1 ± 6.6	19.3 ± 7.6
$T_{1\rho}$	Lateral Meniscus	14.1 ± 5.6	16.0 ± 6.6	18.7 ± 7.1
	Anterior Part	14.9 ± 5.8	16.0 ± 6.2	21.3 ± 8.2
	Body Part	13.1 ± 4.7	15.4 ± 5.4	18.0 ± 6.4
	Posterior Part	14.2 ± 5.3	15.9 ± 6.7	17.8 ± 5.7
$T_{1\rho}$	Medial Meniscus	15.0 ± 5.0	16.1 ± 6.0	20.7 ± 7.6
	Anterior Part	14.7 ± 5.1	16.0 ± 6.1	18.9 ± 5.6
	Body Part	15.2 ± 4.4	16.3 ± 4.9	15.4 ± 5.1
	Posterior Part	14.9 ± 4.5	16.2 ± 5.6	23.2 ± 8.3

Table 5: Mean and standard deviation (STDEV) of controls, mild and severe OA patients in the meniscus with $T_{1\rho}$ measurements

5.2.2. Mean and standard deviation of T_2 measurements

Means and standard deviations (STDEV) of T_2 measurements in controls, mild and severe OA patients in the entire, the lateral and medial meniscus are shown in Table 6. T_2 values increased from healthy to diseased subjects and with the degree of osteoarthritis; note that differences between the three groups were more pronounced than for the $T_{1\rho}$ values.

		Control	Mild OA	Severe OA
T_2	Entire Meniscus	11.4 ± 3.9	13.5 ± 4.7	16.6 ± 8.2
T_2	Lateral Meniscus	10.8 ± 4.1	13.0 ± 4.8	15.9 ± 7.5
	Anterior Part	11.0 ± 4.1	13.2 ± 5.0	16.6 ± 5.0
	Body Part	10.0 ± 3.6	12.7 ± 4.5	17.3 ±11.2
	Posterior Part	11.1 ± 4.1	12.9 ± 4.4	15.0 ± 4.6
T_2	Medial Meniscus	11.8 ± 3.5	13.9 ± 4.3	18.0 ± 5.3
	Anterior Part	12.0 ± 3.7	13.9 ± 4.4	16.9 ± 4.6
	Body Part	11.5 ± 3.2	14.3 ± 4.0	21.6 ± 5.4
	Posterior Part	11.7 ± 3.4	13.9 ± 4.2	18.9 ± 4.9

Table 6: mean and standard deviation (STDEV) of controls, mild and severe OA patients in the meniscus with T_2 measurements

5.2.3. P-values for Intergroup Comparisons of $T_{1\rho}$ and T_2 Values

Differences in $T_{1\rho}$ and T_2 values among the three groups were significant ($P<0.05$) as shown in Table 7-9, the only exception being the difference in medial meniscus $T_{1\rho}$ between the control subjects and the patient wild mild OA. Differences in T_2 values between the three groups were more significant than differences in $T_{1\rho}$ values. After adjustments for age in the multivariate regression model, differences in T_2 values were significant ($P<0.05$) for comparisons in the entire meniscus (both menisci combined), medial meniscus, and anterior horns of medial and lateral menisci, but differences in $T_{1\rho}$ values were not. BMI and WOMAC scores were found to have no significant contribution in the multivariate regression model.

	Medial Meniscus		Lateral Meniscus		Entire Meniscus	
	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2
Comparison						
(i) Control subjects vs patients with mild OA	0.2290	0.0018*	0.0063*	0.0003*	0.0278*	0.0002*
(ii) Control subjects vs patients with severe OA	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*	<0.0001*
(iii) Patients with mild OA vs patients with severe OA	0.0005*	<0.0001*	0.0014*	0.0001*	0.0005*	0.0002*

Table 7: P-values for Intergroup Comparisons of meniscal $T_{1\rho}$ and T_2 values in the medial, lateral and the combined entire meniscus

* indicates a significant difference ($P<0.05$)

	Medial Meniscus					
	Anterior		Body		Posterior	
	$T_{1\rho}$	T_2	$T_{1\rho}$	$T_{1\rho}$	$T_{1\rho}$	T_2
Comparison						
(i) Control subjects vs patients with mild OA						
	0.1569	0.0032*	0.4312	0.0009*	0.3534	0.0130*
(ii) Control subjects vs patients with severe OA						
	0.0019*	<0.0001*	0.9939	0.0001*	<0.0001*	<0.0001*
(iii) Patients with mild OA vs patients with severe OA						
	0.0213*	0.0025*	0.8058	0.0036*	0.0001*	0.0001*

Table 8: P-values for Intergroup Comparisons of meniscal $T_{1\rho}$ and T_2 values in the anterior, body and posterior part of the medial meniscus

* indicates a significant difference (P<0.05)

	Lateral Meniscus					
	Anterior		Body		Posterior	
	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2
Comparison						
(i) Control subjects vs patients with mild OA						
	0.1910	0.0028*	0.0052*	0.0010*	0.0203*	0.0025*
(ii) Control subjects vs patients with severe OA						
	<0.0001*	<0.0001*	0.0003*	<0.0001*	0.0003*	<0.0001*
(iii) Patients with mild OA vs patients with severe OA						
	<0.0001*	0.0003*	0.0452*	0.0002*	0.0424*	0.0037*

Table 9: P-Values for Intergroup Comparisons of meniscal $T_{1\rho}$ and T_2 values in the anterior, body and posterior part of the lateral meniscus

* indicates a significant difference (P<0.05)

In the following figures (Figure 6-11) differences in the $T_{1\rho}$ and T_2 values are shown in controls, mild OA and severe OA patients for the lateral and the medial meniscus and the combined entire meniscus. The following figures show the values for each

single subject in the healthy or mild/severe OA group, gives an overview of the main distribution of the values and the overlapping or not overlapping circles show whether there is a significant difference between the groups.

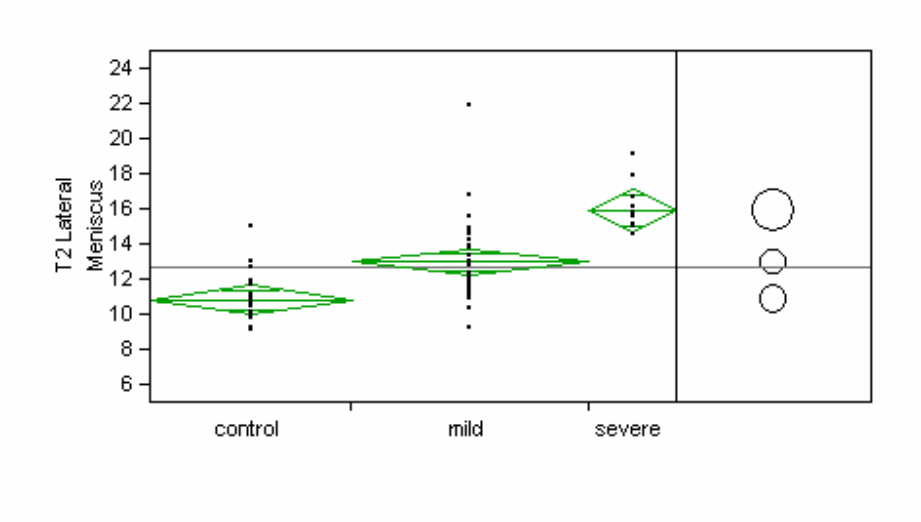


Figure 6: Oneway Analysis of the single values in each group (control group, mild OA patients and severe OA patients) in the lateral meniscus with T_2 measurements

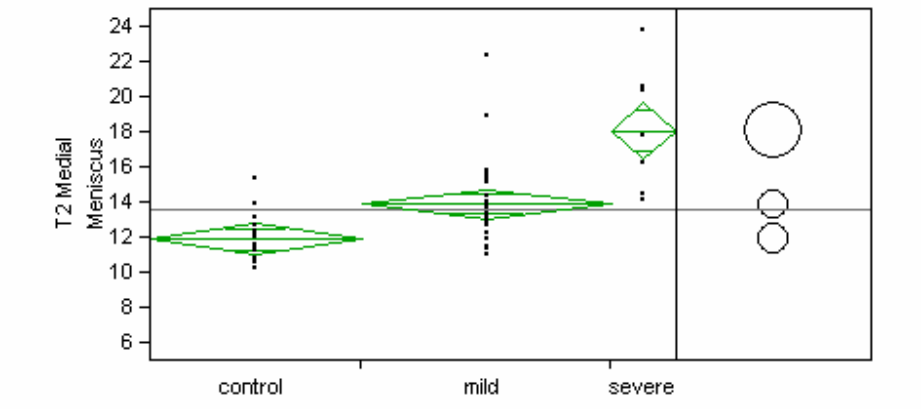


Figure 7: Oneway Analysis of the single values in each group (control group, mild OA patients and severe OA patients) in the medial meniscus with T_2 measurements

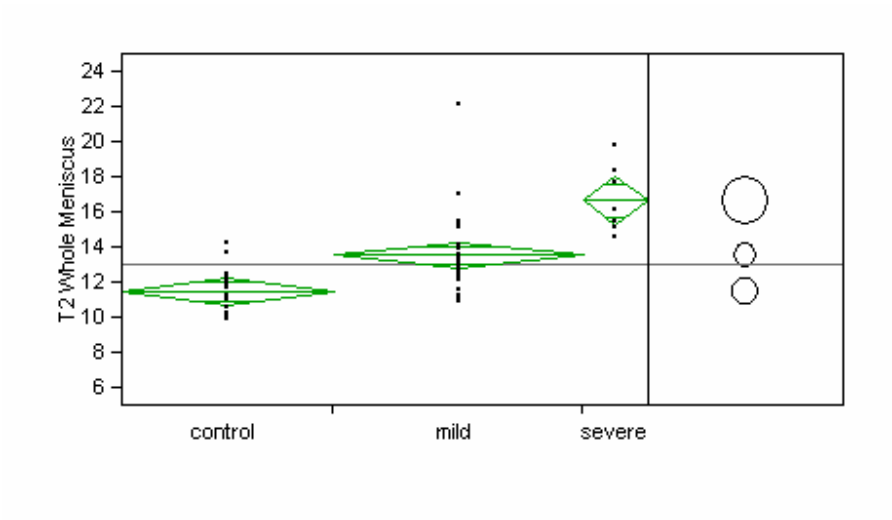


Figure 8: Oneway Analysis of the single values in each group (control group, mild OA patients and severe OA patients) in the whole meniscus with T_2 measurements

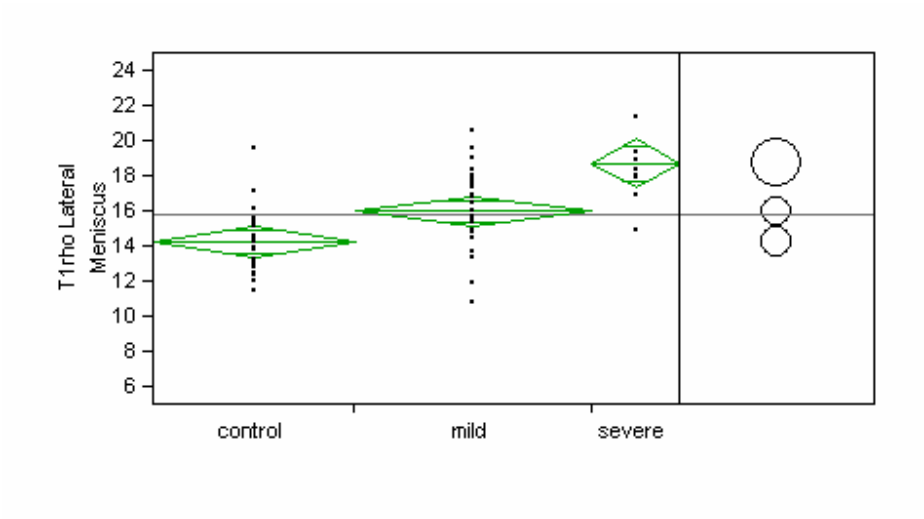


Figure 9: Oneway Analysis of the single values in each group (control group, mild OA patients and severe OA patients) in the lateral meniscus with $T_{1\rho}$ measurements

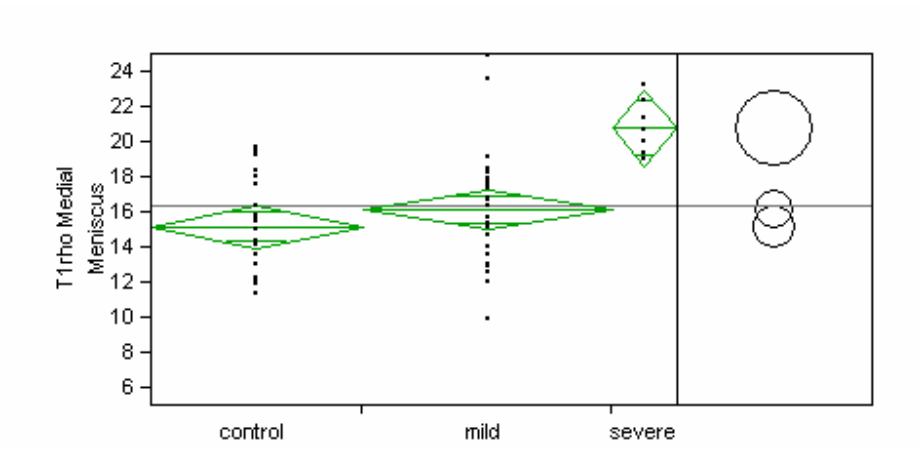


Figure 10: Oneway Analysis of the single values in each group (control group, mild OA patients and severe OA patients) in the medial meniscus with $T_{1\rho}$ measurements

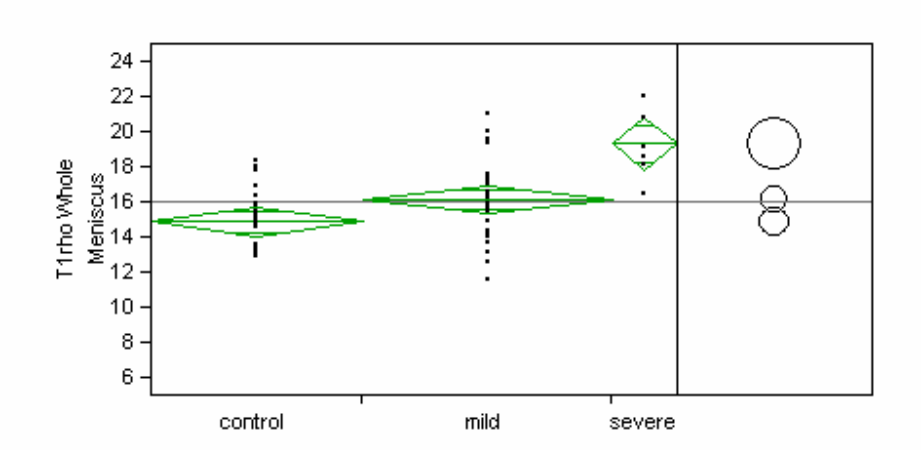


Figure 11: Oneway Analysis of the single values in each group (control group, mild OA patients and severe OA patients) in the whole meniscus with $T_{1\rho}$ measurements

Figure 12 shows representative fat-saturated intermediate-weighted FSE images and $T_{1\rho}$ and T_2 maps obtained in subjects from each group.

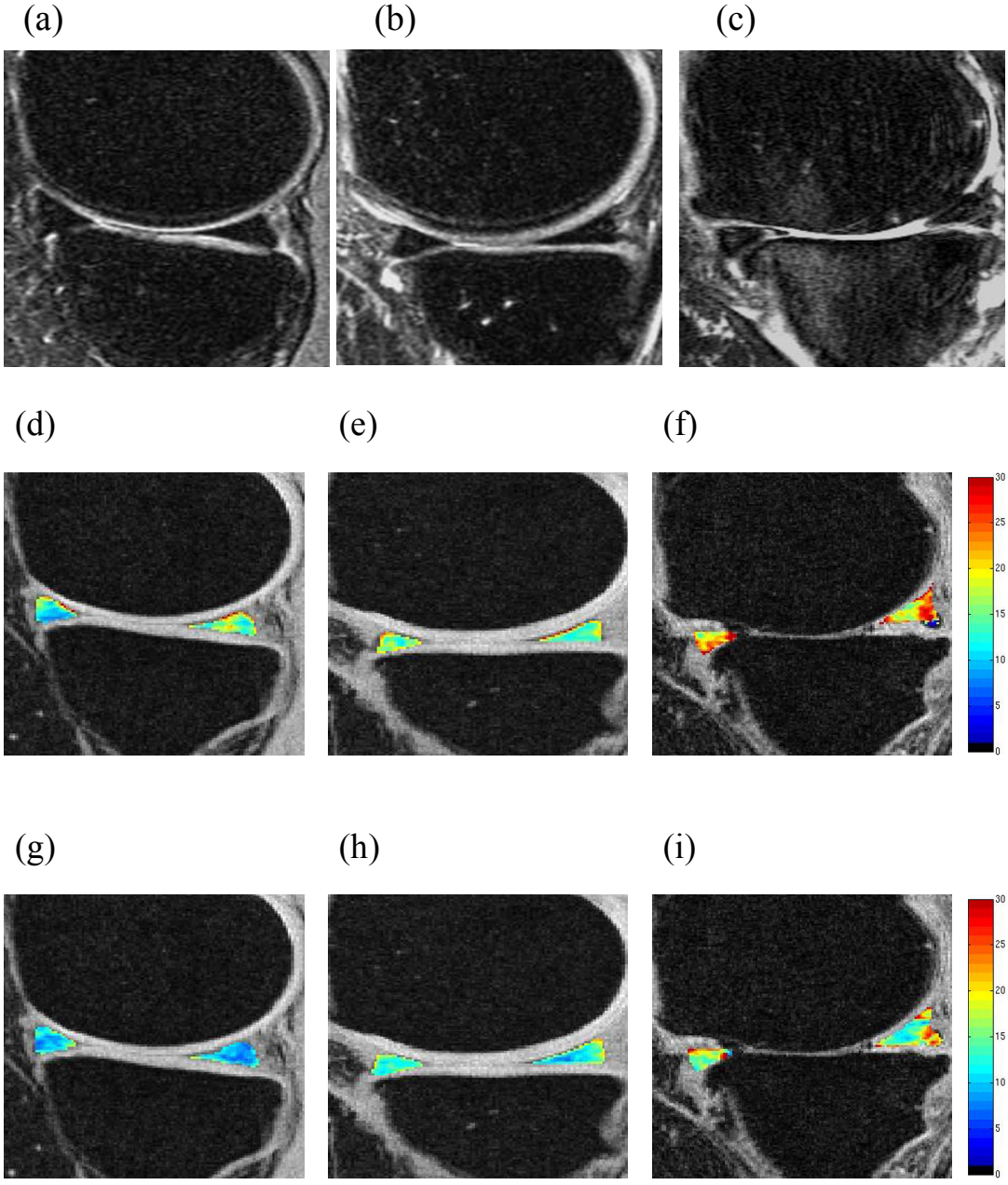
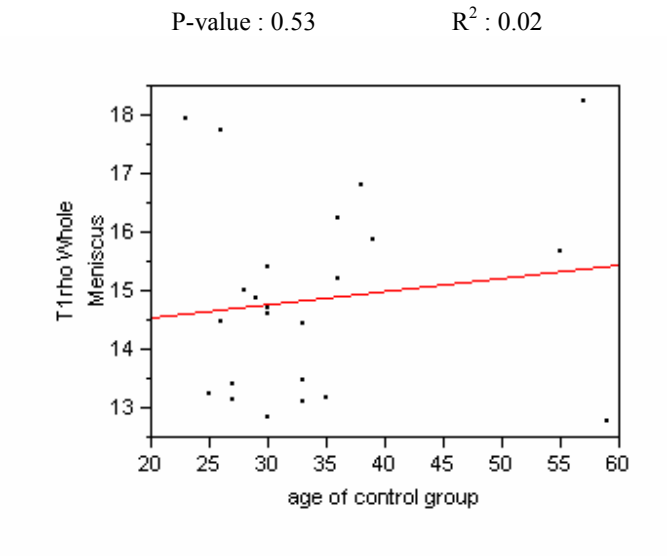


Figure 12: Representative MR images show the medial meniscus in (a, d, g) a healthy subject, (b, e, h) a patient with mild OA, and (c, f, i) a patient with severe OA. (a-c) Fast spin-echo images show morphology of the menisci. In a and b, the meniscus appears normal, but c shows a tear in the anterior and posterior horns of the medial meniscus. Corresponding (d-f) $T_1\rho$ (in milliseconds) and (g-i) T_2 (in milliseconds) color maps clearly show differences in the meniscal matrix among the three subjects.

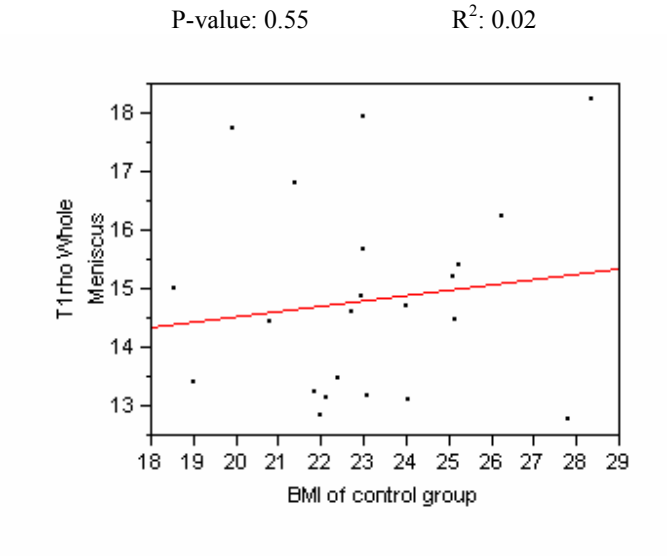
5.3. Correlation with age and BMI

5.3.1. Correlation of $T_{1\rho}$ measurements

Figure 13 shows the correlation between meniscal $T_{1\rho}$ values and age and Figure 14 the correlation between meniscal $T_{1\rho}$ values and BMI. The correlations were only obtained for the control group and not the diseased subjects. The correlations were nonsignificant for both age (P-value 0.53, R^2 0.02) and BMI (P-value 0.55, R^2 0.02). Correlations between $T_{1\rho}$ values calculated separately for medial and lateral meniscus were in the same range.



Figures 13: correlation of age with meniscal $T_{1\rho}$ values within the control group

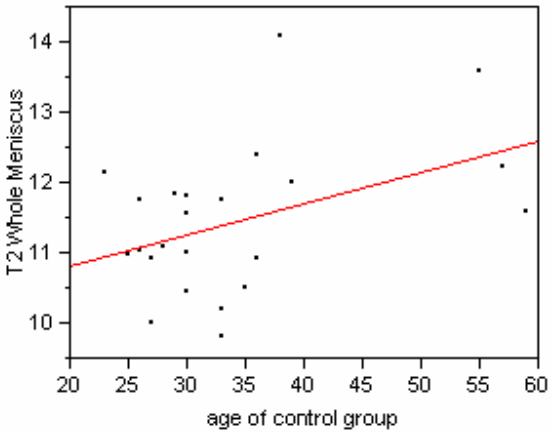


Figures 14: correlation of Body Mass Index (BMI) with meniscal $T_{1\rho}$ values within the control group

5.3.2. Correlation of T_2 measurements

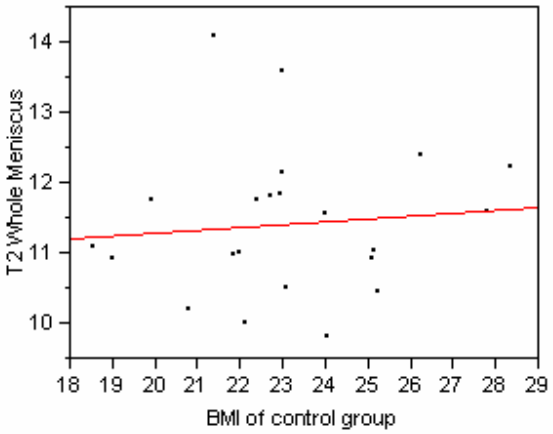
Figure 15 shows the correlation between meniscal T_2 values and age and Figure 16 the correlation between meniscal T_2 values and BMI. The correlations were only obtained for the control group and not the diseased subjects. Only the correlation between T_2 for the entire meniscus and age was found to be significant (P-value 0.0429, R^2 0.18). The correlations were nonsignificant for the correlation between BMI and T_2 (P-value 0.68, R^2 0.009). Correlations between T_2 values calculated separately for medial and lateral meniscus were in the same range.

P-value: 0.0429* R^2: 0.18



Figures 15: correlation of age with meniscal T_2 values within the control group

P-value: 0.68 R^2: 0.009



Figures 16: correlation of Body Mass Index (BMI) with meniscal T_2 values within the control group

5.4. Correlation with WOMAC score

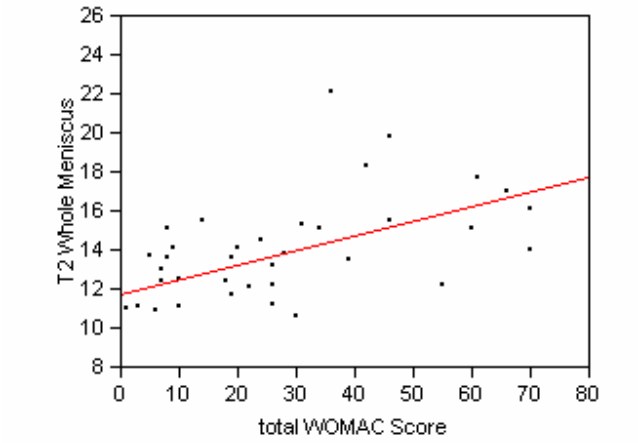
WOMAC scores were correlated with $T_{1\rho}$ and T_2 measurements as seen in Table 10. The highest correlations observed were those between T_2 values in the lateral meniscus/both menisci combined and the WOMAC parameter stiffness ($P < 0.05$). Significant correlations were also observed between T_2 in the lateral meniscus/both menisci combined and the total WOMAC score. Correlations with T_2 measurements were consistently higher than correlations with $T_{1\rho}$ measurements. However, no significant correlations between articular cartilage $T_{1\rho}$ and T_2 measurements and WOMAC scores were demonstrated.

WOMAC Parameter		Entire Meniscus		Lateral Meniscus		Medial Meniscus	
		$T_{1\rho}$	T_2	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2
Total score	R^2	0.21	0.40	0.30	0.41	0.13	0.34
	P-value	0.0006	<0.0001	<0.0001	<0.0001	0.0083	<0.0001
Pain	R^2	0.18	0.37	0.22	0.36	0.15	0.35
	P-value	0.0011	<0.0001	0.0002	<0.0001	0.0033	<0.0001
Stiffness	R^2	0.22	0.42	0.32	0.45	0.14	0.36
	P-value	0.0004	<0.0001	<0.0001	<0.0001	0.0052	<0.0001
Function	R^2	0.19	0.38	0.29	0.38	0.11	0.31
	P-value	0.008	<0.0001	<0.0001	<0.0001	0.0135	<0.0001

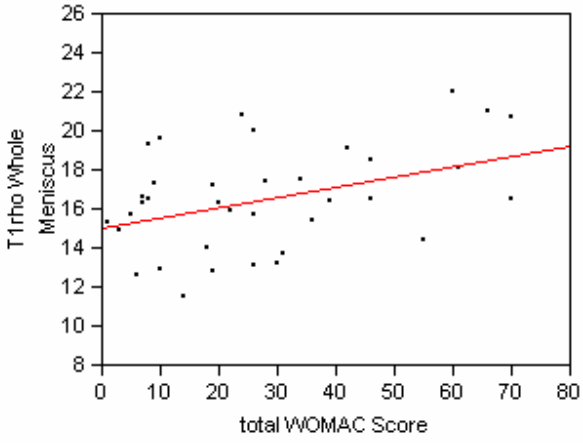
Table 10: Correlations of meniscal $T_{1\rho}$ and T_2 measurements with total and individual-parameter WOMAC scores

In Figure 17 and 18 the correlation between the total WOMAC score and the whole meniscus with $T_{1\rho}$ and T_2 measurements is shown. The P-value was used to describe a significant difference between the WOMAC Score and the $T_{1\rho}$ and T_2 values, the coefficient of determination (R^2) parameter demonstrated their correlation.

P-value: <0.0001* R^2: 0.401



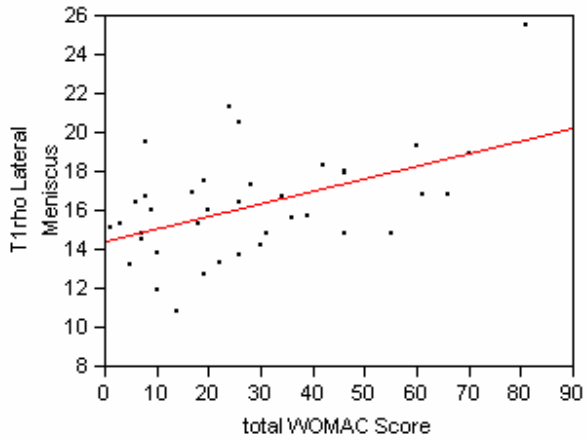
P-value:0.0006* R^2: 0.21



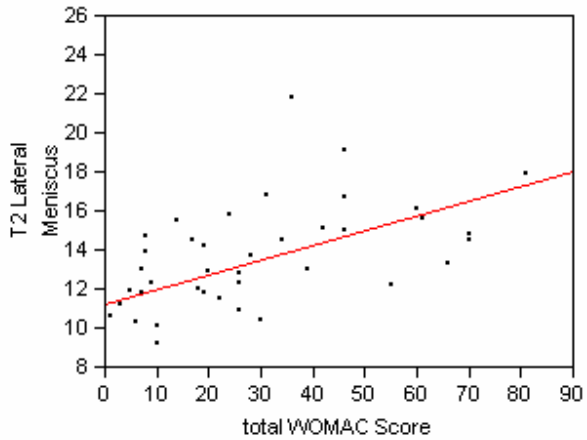
Figures 17 and 18: correlation between the total WOMAC score and the whole meniscus with $T_{1\rho}$ and T_2 measurements

To see possible differences within the meniscus the medial and lateral meniscus were evaluated separately (Figure 19-22).

P-value: <0.0001* R^2: 0.30

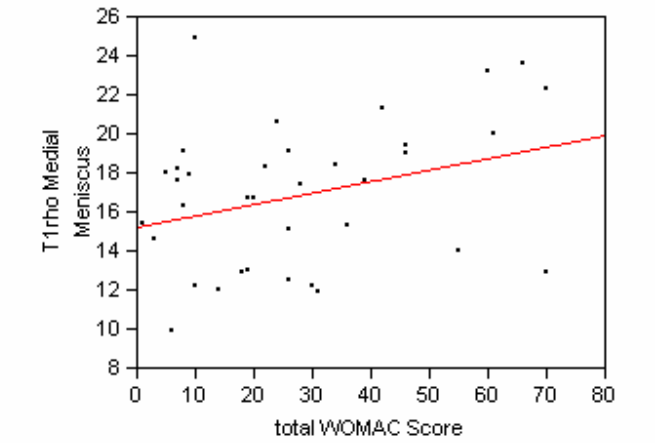


P-value: <0.0001* R^2: 0.41

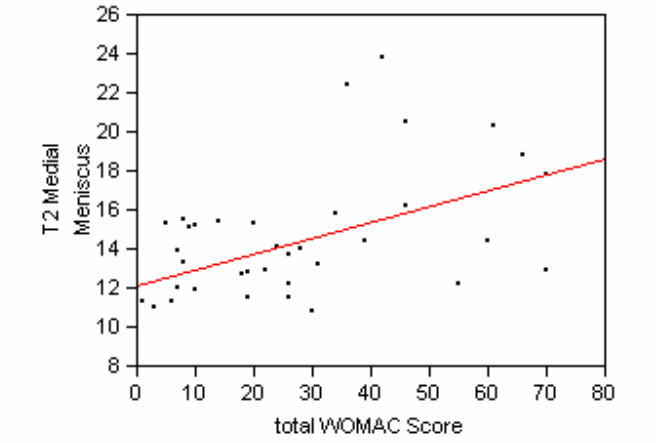


Figures 19 and 20: correlation between the total WOMAC score and the lateral meniscus with $T_{1\rho}$ and T_2 measurements

P-value: 0.0083* R^2: 0.13



P-value: 0.0001* R^2: 0.34



Figures 21 and 22: correlation between the total WOMAC score and the medial meniscus with $T_{1\rho}$ and T_2 measurements

5.5. Correlation with WORMS score

For correlation with WORMS score, the meniscal $T_{1\rho}$ and T_2 values were correlated separately with the cartilage WORMS score, the BME WORMS score and the meniscal WORMS score in the entire meniscus (Table 11) and in the medial and lateral meniscus (Table 12).

Comparisons of WORMS with meniscal $T_{1\rho}$ and T_2 revealed the most significant correlations with meniscal abnormality: The R^2 was 0.53 for the correlation of WORMS with medial meniscal T_2 and R^2 was 0.37 for the correlation of WORMS with medial meniscal $T_{1\rho}$. Correlations with lateral meniscal values were substantially lower but still significant ($p<0.05$). In the healthy group of 23 subjects, only two individuals had meniscal lesions: One subject had a grade 1 lesion at the medial meniscus, and one had a grade 2 lesion at the lateral meniscus. In the mild OA group of 27 patients, seven medial meniscus abnormalities were detected: two grade 3, two grade 2, and three grade 1 lesions. All 10 patients with severe OA had meniscal lesions of grades higher than 1.

There were no significant differences in $T_{1\rho}$ and T_2 values between the patients with mild OA who had meniscal lesions and the patients in this group who did not have these lesions. However, the two healthy subjects with meniscal lesions had higher $T_{1\rho}$ and T_2 values compared with the other healthy subjects. We observed significant correlations between the WORMS for medial joint compartment cartilage and the $T_{1\rho}$ ($R^2 = 0.38$) and T_2 ($R^2 = 0.20$) values in the medial meniscus ($p<0.05$) and between lateral joint compartment cartilage WORMS and lateral meniscal T_2 ($R^2 = 0.15$, $P<0.05$). In addition, the WORMS for bone marrow edema pattern correlated mildly but significantly with T_2 ($R^2 = 0.30$) and $T_{1\rho}$ ($R^2 = 0.11$) values in both menisci combined ($p<0.05$).

WORMS Parameter	$T_{1\rho}$ entire meniscus R^2	T_2 entire meniscus R^2
Cartilage	0,03	0.19*
BME	0.11*	0.3*
Lateral Meniscus	0,01	0,05
Medial Meniscus	0.3*	0.37*

* indicates a significant difference (P<0.05) between the two groups

Table 11: correlation of $T_{1\rho}$ and T_2 values of the whole meniscus with cartilage, BME and meniscal WORMS score

	Lateral Meniscus		Medial Meniscus	
	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2
WORMS Parameter	R^2	R^2	R^2	R^2
Cartilage Medial Femur and Tibia	X	x	0.2*	0.38*
Cartilage Lateral Femur and Tibia	0,08	0.15*	x	x
BME Medial Femur and Tibia	X	x	0.08	0.18*
BME Lateral Femur and Tibia	0.09	0.10	x	x
Lateral Meniscus	0.12*	0.11*	x	x
Medial Meniscus	X	x	0.37*	0.53*

* indicates a significant difference (P<0.05) between the two groups

Table 12: correlation of $T_{1\rho}$ and T_2 values of the medial and lateral meniscus with cartilage, BME and meniscal WORMS score

5.6. Cartilage $T_{1\rho}$ and T_2 values and their correlation with meniscal $T_{1\rho}$ and T_2 measurements

The mean cartilage $T_{1\rho}$ values of controls and patients with mild OA are shown in Table 13. Cartilage $T_{1\rho}$ values in patients with mild OA were significantly ($P<0.05$) higher compared to values in the control group in the femoral and femoropatellar compartment, but not in the tibia compartment. Differences in femoropatellar $T_{1\rho}$ between the control and the mild OA group were highest.

		Mean $T_{1\rho}$ in msec		
		Controls	Mild OA	P-value
Femur	medial	39.09	41.76	0.0172*
	lateral	39.94	42.43	0.0054*
Tibia	medial	36.15	35.53	0.6290
	lateral	38.03	36.94	0.3879
Femoropatellar		38.78	42.85	0.0011*
All compartments		38.83	41.17	0.0072*

* indicates a significant difference ($P<0.05$) between the two groups

Table 13: Mean hyaline cartilage $T_{1\rho}$ in different knee compartments in control subjects and patients with mild OA

The mean cartilage T_2 values of controls and patients with mild OA are shown in Table 14. The T_2 values in the mild OA group were mildly higher compared to the control group. However, the mean T_2 values did not show significant differences between controls and mild OA patients ($P>0.05$), the only exception being the difference in medial femur T_2 between the control subjects and the mild OA patients.

		Mean T_2 in msec		
		Controls	Mild OA	P-value
Femur	medial	30.79	33.34	0.0010*
	lateral	31.15	32.51	0.1146
Tibia	medial	26.57	27.52	0.3123
	lateral	27.52	27.86	0.7662
Femoropatellar		31.11	33.07	0.1060
All compartments		30.23	31.68	0.0894

* indicates a significant difference ($P<0.05$) between the two groups

Table 14: Mean hyaline cartilage T_2 in different knee compartments in control subjects and patients with mild OA

The $T_{1\rho}$ and T_2 values of the femoral and tibial cartilage were correlated with the meniscal $T_{1\rho}$ and T_2 values in different subregions. Femoral cartilage $T_{1\rho}$ and T_2 values (Table 15 and 16) correlated significantly with medial and lateral meniscal $T_{1\rho}$ and T_2 values ($R^2 = 0.22\text{-}0.29$, $P< 0.05$) in the control subjects and patients with mild OA. However, tibial cartilage $T_{1\rho}$ and T_2 values did not show significant correlations with meniscal values.

	Entire meniscus	
	$T_{1\rho}$	T_2
Cartilage Parameter	R^2	R^2
$T_{1\rho}$ Femur	0.22*	0.29*
T_2 Femur	0.24*	0.28*
$T_{1\rho}$ Tibia	0,05	0,02
T_2 Tibia	0,03	0,06

* indicates a significant difference (P<0.05) between cartilage and meniscal $T_{1\rho}$ and T_2 values

Table 15: correlation (R^2) of $T_{1\rho}$ and T_2 values of the entire meniscus with $T_{1\rho}$ and T_2 values of the femoral and tibial cartilage

	Lateral Meniscus		Medial Meniscus	
	$T_{1\rho}$	T_2	$T_{1\rho}$	T_2
Cartilage Parameter	R^2	R^2	R^2	R^2
$T_{1\rho}$ Femur	0.15*	x	0.09	x
T_2 Femur	x	0.18*	x	0.19*
$T_{1\rho}$ Tibia	0.0002	x	0.06	x
T_2 Tibia	x	0.07	x	0.02

* indicates a significant difference (P<0.05) between cartilage and meniscal $T_{1\rho}$ and T_2 values

Table 16: correlation (R^2) of $T_{1\rho}$ and T_2 values of the lateral and medial meniscus with $T_{1\rho}$ and T_2 values of the femoral and tibial cartilage

5.7. Reproducibility test

The reproducibility test based on the coefficient of variation (CV) was calculated for each part of the meniscus. CVs were higher for T_2 measurements than for $T_{1\rho}$ measurements (Table 17), indicating that T_2 measurements may be less reproducible. For measurement reproducibility in the anterior and posterior horns of the menisci, CVs ranged from 3.88 (medial posterior horn $T_{1\rho}$) to 10.57 (lateral posterior horn T_2). The highest CVs were found in the bodies of the lateral and medial menisci, consistent with limited segmentation due to partial volume effects in these areas.

			CV in %
both menisci		$T_{1\rho}$	3.61
		T_2	4.73
lateral meniscus		$T_{1\rho}$	4.99
		T_2	7.83
medial meniscus		$T_{1\rho}$	3.71
		T_2	4.55
lateral	anterior	$T_{1\rho}$	5.23
		T_2	8.91
	body	$T_{1\rho}$	13.36
		T_2	6.45
	posterior	$T_{1\rho}$	7.43
		T_2	10.57
medial	anterior	$T_{1\rho}$	6.08
		T_2	7.44
	body	$T_{1\rho}$	5.96
		T_2	13.71
	posterior	$T_{1\rho}$	3.88
		T_2	9.35

Table 17: coefficient of variation (CVs) for reproducibility of $T_{1\rho}$ and T_2 measurements in menisci and meniscal subregions

5.8. Coefficient of variance

Table 18 shows the A_z values for meniscal.$T_{1\rho}$ and T_2 measurements. The T_2 in the entire meniscus (lateral and medial meniscus combined) had the highest diagnostic performance in differentiation control subjects from patients with mild OA (A_z = 0.842), and T_2 values in the medial and lateral menisci were similar as shown in Table 18. Compared with the A_z values for T_2 differentiation performance, the A_z values for $T_{1\rho}$ differentiation performance were lower in every meniscal compartment, and $T_{1\rho}$ A_z values at the lateral meniscus were notably higher than those at the medial meniscus.

Measurement Area	$T_{1\rho}$	T_2
Both menisci	0.677 (0.524, 0.830)	0.842 (0.730, 0.954)
Lateral Meniscus	0.758 (0.620, 0.897)	0.820 (0.699, 0.940)
Anterior Horn	0.640 (0.480, 0.800)	0.766 (0.631, 0.901)
Body	0.767 (0.625, 0.910)	0.802 (0.674, 0.931)
Posterior Horn	0.741 (0.596, 0.886)	0.760 (0.627, 0.893)
Medial Meniscus	0.579 (0.419, 0.741)	0.813 (0.693, 0.933)
Anterior Horn	0.601 (0.442, 0.759)	0.784 (0.654, 0.915)
Body	0.549 (0.371, 0.726)	0.804 (0.662, 0.947)
Posterior Horn	0.547 (0.381, 0.711)	0.763 (0.624, 0.903)

Table 18: A_z values for differentiation between control subjects and patients with mild OA based on meniscal $T_{1\rho}$ and T_2 measurements including 95% confidence intervals in parentheses

The range of A_z values for the differentiation between hyaline cartilage $T_{1\rho}$ and T_2 values in healthy subjects and those in patients with mild OA were similar to those calculated for the menisci: The highest A_z values were 0.86 for femoropatellar cartilage $T_{1\rho}$ and 0.81 for medial femoral condyle cartilage T_2. However, while in the menisci T_2 had a better performance in the differentiation of the two groups, in the hyaline cartilage $T_{1\rho}$ had a better differentiation performance.

6. Discussion

Our study results indicate significant differences in meniscal $T_{1\rho}$ and T_2 values between healthy subjects, patients with mild OA, and patients with severe OA. These differences most likely reflect degeneration within the matrix of the menisci. An interesting finding was that in the menisci, T_2 values were more useful than $T_{1\rho}$ values for differentiating the subject groups, but in the articular cartilage, $T_{1\rho}$ values were more useful for this differentiation. These meniscal matrix measurements correlated significantly with the clinical findings determined by using WOMAC scores.

To our knowledge, only one study of MR-based meniscal matrix measurements has been published previously: Krishnan et al [28] analyzed the T_1 of gadolinium-based contrast material in the meniscus and the relationship between this parameter and the T_1 of gadolinium-based contrast material in the articular cartilage at gadolinium-enhanced MR imaging of cartilage data sets. Their study results showed that the T_1 in the meniscus correlated significantly with that in the articular cartilage, potentially demonstrating associated degenerative processes in the knee joint.

Mild yet significant correlations between meniscal and cartilage $T_{1\rho}$ and T_2 values were also observed in our study. Corresponding T_1 (Gd) values in the meniscus and in the cartilage were in the same range. In our study the meniscal $T_{1\rho}$ and T_2 values were correlated with articular cartilage $T_{1\rho}$ and T_2 values and only mild, yet significant, correlations between meniscal and cartilage $T_{1\rho}$ and T_2 values were found. However, the range of meniscal $T_{1\rho}$ and T_2 values ($T_{1\rho}$ values 12.5 - 20.9, T_2 values 9.8 - 16.9) was different from those of the cartilage ($T_{1\rho}$ values 30.8 - 47.8, T_2 values 22.9 - 39.6). Correlations between meniscal and articular cartilage $T_{1\rho}$ and T_2 values were in the same order as those described for dGEMRIC by Krishnan et al [28].

The physical basis of $T_{1\rho}$ and T_2 measurements in the meniscus is complex: it is known that cartilage has a proteoglycan concentration of 5 - 10%, while the meniscal proteoglycan (PG) concentration is comparatively low with 1 - 2% [41]. PG consists of a central protein core with a large number of negatively charged glycosaminoglycans (GAG) side chains covalently attached. It was shown that $T_{1\rho}$ correlates highly with the PG content of cartilage [1] and since loss of PG is meant to be the initiating event in early OA, while neither the content nor the type of collagen is modified in the cartilage of early OA [15], the $T_{1\rho}$ parameter seems to be well suited to differentiate early OA patients from healthy controls. If GAG and therefore PG is the dominating factor in $T_{1\rho}$ measurements, lower $T_{1\rho}$ values in the meniscus than in the articular cartilage are expected. This could be an explanation for the lower $T_{1\rho}$ values calculated for the meniscus in this study.

On the other hand, T_2 is sensitive to interactions between water molecules and the macromolecular concentration and structure of the extracellular matrix [22, 24, 35, 38, 42, 46], especially such interactions based on the content, orientation, and anisotropy of collagen [25, 64]. The correlation of T_2 with PG, however, remains controversial. Although Watrin-Pinzano et al. [62] found significantly increased T_2 with hyaluronidase-induced PG degeneration, in other studies, the depletion of PG had little influence on T_2 [7, 46, 60]. Compared with articular cartilage, which has a type 2 collagen concentration of 10% - 20%, the meniscus has a higher type 1 collagen concentration: 15% - 25% [61]. The higher collagen concentration in the meniscus may in part also explain the lower meniscal T_2 values compared with the cartilage T_2 values. Given the increased water content of the articular cartilage and the dense collagen network in the menisci this may be an explanation why lower T_2 values were calculated for the menisci. The factors that contribute to $T_{1\rho}$ changes in the meniscus are not clear and need further investigation. In cartilage, changes in collagen and hydration may affect $T_{1\rho}$. However, even with the current spin-lock frequency (500 Hz) of clinical MR imagers, $T_{1\rho}$ values are approximately 30% higher

than T_2 values in cartilage and approximately 20% higher in the menisci. Spin locking reduces dipolar interaction, which dominates T_2 relaxation. Previous study findings have suggested that chemical exchanges between bulk water and the OH and NH groups of PG may be important relaxation mechanisms for $T_{1\rho}$ in articular cartilage. Studies have also shown that $T_{1\rho}$ is more sensitive to PG changes than is T_2 in degenerated cartilage.

Previous study investigators have quantified $T_{1\rho}$ and T_2 measurements in the articular cartilage of control subjects and patients with OA and reported higher $T_{1\rho}$ [17, 32, 34, 56] and T_2 [6, 16, 58] in the cartilage of patients with OA. A previous study in which $T_{1\rho}$ and T_2 measurement techniques were compared revealed better results with $T_{1\rho}$ measurements [39]. However, in our study of the meniscus, T_2 measurements yielded better results. This might be explained by differences in the biochemical composition of these tissues.

The changes in meniscal $T_{1\rho}$ and T_2 values with increasing OA severity were supported by significant correlations with the WOMAC scores. The highest such correlation observed was that with combined T_2 measurements for both menisci. We find it interesting that previous studies of the correlations of WOMAC scores with focal cartilage abnormalities, meniscal abnormalities, and T_2 measurements have revealed lower R^2 values [37, 58]. This is a complex issue, and it has been hypothesized that patients with more advanced disease, characterized my morphologic cartilage lesions and meniscal and ligamentous abnormalities, could be treated with pain medications and might be able to adapt to more advance disease.

Regarding MR matrix measurements of the hyaline cartilage and meniscus, it should be noted that an abnormal matrix pattern is seen in early disease and that, to our knowledge, the results of only smaller-scale studies of the relationships between T_2 and $T_{1\rho}$ in the hyaline cartilage and clinical findings are available. Clearly, larger-scale studies are required.

Because there were gaps in age between the subject groups studied, we used multivariate regression analysis to study the effects of age. Interestingly, T_2 values were still significant at this analysis, whereas no $T_{1\rho}$ values were. It appears that $T_{1\rho}$ measurements are substantially affected by age. Similar findings for the hyaline cartilage were reported in a previous study. Therefore, it is not entirely clear whether $T_{1\rho}$ measurements are related to the aging process, regardless of the presence of OA; however, it is difficult to separate these issues because degeneration is also age related.

Receiver operating characteristic analysis to assess the diagnostic performance of $T_{1\rho}$ and T_2 in the differentiation between healthy and mild OA-affected subjects revealed similar A_Z values for the menisci and articular cartilage. Given the time-consuming segmentation of the articular cartilage - it may take 2 to 4 hours for a whole knee joint -, meniscal matrix characterization, which involves a segmentation time of about 20 minutes, has the potential to serve as an alternative technique. However, given the limited sample size and the lack of hypothesis testing of equivalence in this study, further investigation is required.

In our study we analyzed the entire meniscus without considering zonal variations. This may have been a limitation, and future cadaver studies will be required to analyze $T_{1\rho}$ and T_2 values in the anatomic subregions of the menisci. In addition, the CVs in our study were relatively high and thus consistent with limited reproducibility. Only a small number of subjects were examined, and CVs were obtained for image analysis and not after the subjects had undergone another imaging examination. The high CVs obtained suggest that the reproducibility was not adequate for longitudinal studies. Clearly, more automated segmentation that improves the precision of this technique will need to be developed.

The fat-saturated intermediate-weighted spin echo sequence used for morphologic imaging in our study represents a compromise approach applied to achieve good visualization of the cartilage morphology, bone marrow, ligaments, and menisci. The

use of additional proton density-weighted sequences has been suggested for visualization of meniscal abnormalities, but owing to time constraints, only one morphologic sequence was possible.

However, we did use a section thickness of 2 mm and had an increased signal-to-noise ratio with 3.0-T imaging (as opposed to the signal-to-noise ratio at routine 1.5-T imaging), potentially improving the visualization of meniscal abnormalities compared with the visualization at standard MR imaging.

There also may be concern that the identification of a correlation of meniscal $T_{1\rho}$ and T_2 measurements with early OA does not mean that these measurements represents a more sensitive indicator of OA than currently used indicators. However, our findings show that this is a feasible technique. The fact that meniscal measurements correlated with WOMAC scores - although this has not been shown previously for morphologic markers of OA or for cartilage $T_{1\rho}$ and T_2 measurements - suggests that this technique may be suited for enabling a better understanding of the clinical symptoms related to OA.

In rheumatologic studies, the established reference standards for identifying and grading findings in patients with OA are clinical findings and Kellgren-Lawrence grades. In time, these may be replaced by semiquantitative and quantitative MR-based biomarkers.

This study is a first step in an ongoing investigation of the relationship between OA progression and $T_{1\rho}$ and T_2 measurements. Before these measurements are implemented clinically they need to be validated, and one of the steps in the validation process is to show that different measurements are obtained in subjects with different grades of OA. The long-term goal is to be able to identify early matrix changes of the menisci and cartilage that indicate increased risk for OA in these subjects and monitor new therapies that prevent OA. Thus, these measurements may have a substantial effect on OA prevention.

In a previous study Nakano et al [48] found significant regional variations of GAG content in porcine and bovine menisci (higher in the inner zones and lower in the outer regions), which could not be considered in our study, but needs further investigation.

In addition CV values in our study were relatively high consistent with limited reproducibility. However, this study had an explorative and feasibility character and more automated segmentation improving precision of this technique will have to be developed in the future.

In conclusion, the results of this study demonstrate that meniscal matrix measurements, T_2 values in particular, may be used to differentiate healthy subjects from individuals with early OA. Matrix parameters increased consistently with higher OA grade. In addition, significant correlations between matrix measurements in the meniscus and clinical scores were found; however, these correlations involving the same parameters were not significant in the hyaline cartilage.

7. Summary

Purpose: To prospectively evaluate differences in $T_{1\rho}$ (T_1 relaxation time in the rotating frame) and T_2 values in the meniscus at magnetic resonance (MR) imaging in both patients with varying degrees of osteoarthritis (OA) and healthy control subjects.

Materials and Methods: The study was institutional review board approved and HIPAA compliant. Written informed consent was obtained from all subjects. $T_{1\rho}$ and T_2 measurements were performed at 3.0-T MR imaging in 60 subjects categorized as healthy sedentary controls (n= 10, 6 male, 4 female, mean age 36.0), healthy active controls (n=13, 6 male, 7 female, mean age 32.7), mild OA (n= 27, 13 male, 14 female, mean age 52.5) and severe OA patients (n= 10, 3 male, 7 female, mean age 61.6).

Semiautomatic segmentation was performed to generate $T_{1\rho}$ and T_2 maps of the menisci. Clinical findings were assessed by using WOMAC questionnaires. Differences in $T_{1\rho}$ and T_2 values between the groups were calculated by using two-tailed t tests (with $P < 0.05$ indicating significance), and receiver operating characteristic analyses (ROC) were performed. Correlations of meniscal $T_{1\rho}$ and T_2 values with age, BMI, cartilage derived $T_{1\rho}$ and T_2 parameters, and WOMAC and WORMS scores were calculated.

Results: Significant differences between following subject groups were found: Mean $T_{1\rho}$ values were 14.7 msec ± 5.5, 16.1 msec ± 6.6, and 19.3 msec ± 7.6 for the healthy controls, mild OA, and severe OA groups. Mean T_2 values were 11.4 ms ± 3.9, 13.5 msec ± 4.7, and 16.6 msec ± 8.2 for the healthy controls, mild OA, and severe OA groups. Correlations of meniscal $T_{1\rho}$ and T_2 values with subject age (R^2 = 0.18, for correlation with T_2 only), cartilage-derived parameters (R^2 = 0.11 – 0.45) were significant.

Conclusion: Meniscal $T_{1\rho}$ and T_2 values correlate with clinical findings of OA and can be used to differentiate healthy subjects from patients with mild or severe OA.

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