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Quantitative evaluation of hyaline articular cartilage T2 maps of knee and determine the relationship of cartilage T2 values with age, gender, articular changes

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Abstract. – OBJECTIVE: To identify changes in knee joint cartilage transverse relaxation values depending on the patient's age and gender and to investigate the relationship between knee joint pathologies and the transverse relaxation time.

PATIENTS AND METHODS: Knee MRI images of 107 symptomatic patients with various pathologic knee conditions were analyzed retrospectively. T2 values were measured at patellar cartilage, posteromedial and posterolateral femoral cartilage adjacent to the central horn of posterior meniscus. 963 measurements were done for 107 knees MRI. Relationship of T2 values with seven features including subarticular bone marrow edema, subarticular cysts, marginal osteophytes, anterior-posterior cruciate and collateral ligament tears, posterior medial and posterior lateral meniscal tears, synovial thickening and effusion were analyzed. T2 values in all three compartments were evaluated according to age and gender.

RESULTS: A T2 value increase correlated with age was present in all three compartments measured in the subgroup with no knee joint pathology and in all patient groups. According to the ROC curve, an increase showing a statistically significant difference was present in the patient group aged over 40 compared to the patient group aged 40 and below in all patient groups. There is a statistically difference at T2 values with and without subarticular cysts, marginal osteophytes, synovial thickening and effusion. T2 relaxation time showed a statistically significant increase in the patients with a medial meniscus tear compared to those without a tear and no statistically significant difference was found in T2 relaxation times of patients with and without a posterior lateral meniscus tear.

CONCLUSIONS: T2 cartilage mapping on MRI provides opportunity to exhibit biochemical and structural changes related with cartilage extracellular matrix without using invasive diagnostic methods.

Key Words:
T2 mapping, Femoral cartilage, T2 relaxation time.

Introduction

Cartilage is a very special connective tissue of our body with its hypocellular, aneural and alymphatic features and limited regeneration ability. Its main function is to ensure equal load distribution during joint function and to protect the joint sliding mechanism. The organization of chondrocytes, which are metabolically very active despite having a hypocellular structure, collagen fibrils and matrix in a zonal character, enables cartilage to function for a long time.

Magnetic resonance imaging (MRI) provides direct visualization of articular cartilage and is expected to provide useful information on cartilage aging. Current MRI techniques enable evaluation of morphological changes such as focal and superficial cartilage lesion[1]. The defined techniques to evaluate spatially localized quantitative maps of MRI relaxation times can identify and localize specific biochemical and structural changes of the cartilage extracellular matrix[2].

Transverse relaxation time (T2) is a measurable temporal MRI value that is sensitive to the molecular motions in protons. The T2 relaxation time in the articular cartilage is associated with the organization of the collagen fibers with the tissue water-collagen content. The sensitivity of cartilage T2 values to the structural changes in the collagen matrix has made it an important imaging method in age-related cartilage changes and early-stage osteoarthritis.

Some studies on the age- and sex-related changes in T2 cartilage values in humans and their relationship with meniscal pathologies have been performed. Studies examining the age- and sex-related T2 cartilage changes have been conducted in asymptomatic patient groups. The primary aim of our study was to evaluate the

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change of age- and sex-related T2 cartilage values in patient groups with and without MRI findings related to knee joint pathology. The second aim was to investigate the relationship between knee joint pathologies (subarticular bone marrow edema; subarticular cysts; marginal osteophytes; anterior-posterior cruciate and collateral ligament tears; posterior medial and posterior lateral meniscal tears; synovial thickening and effusion) and T2 cartilage values.

Patients and Methods

Patient Selection

A total of 107 consecutive patients (mean age 38.2 ± 12 years, age range 12-63 years) who presented to the Ankara University Faculty of Medicine, Avicenna Hospital between October 2010 and April 2012 with knee joint symptoms were included in our study. There were 47 (45%) males and 60 (55%) females.

Magnetic Resonance Imaging

All 107 knee MR examinations were performed on a 3 Tesla MR device (Siemens, Orlando, FL, USA) by using a knee coil that can be commercially obtained. Routine settings on the 3 Tesla MRI device were as follows: T1 Weighted (TSE 450/17, TF in the coronal plane: 3, FOV: 16 cm, 3 mm/0.6 mm, 307 × 384, A: 2) and STIR (Saturation Invertion Recovery) (TIRM 4000/16, TF: 12, FOV: 16 cm, 3 mm/0.6 mm, 256 × 320, A: 2); Proton Density (PD) (TSE 3800/19, TF sagittal plane: 12, FOV: 16 cm, 3 mm/0.6 mm, 358x448, A: 2), fat-saturated PD (TSE 3800/19, TF: 12, FOV: 16 cm, 3 mm/0.6 mm, 358 × 448, A: 2), T2 STAR (GRE 424/18, FOV: 16 cm, 3 mm/0.6 mm, 283 × 384, A: 1) and FLASH (MERGE 971/4.36-11.9-19.44-29.98-34.52, FOV: 16 cm, 3 mm/0.6 mm, 384 × 384, A: 1); on the axial plane, fat-saturated PD (TSE 3000/19, TF: 6, FOV: 16 cm, 3 mm/0.3 mm, 272 × 320, A: 2).

MR images were evaluated on the workstation. T2 cartilage maps were created automatically by the device with the FLASH multi-echo (5 echo) sequence, using the licensed MAPLT software.

Measurements

Cartilage T2 relaxation time measurements were performed from three different regions including the patellar cartilage and the femoral cartilage sections adjacent to the medial and lateral meniscus posterior horn central section. The measurements were taken from three consecutive sagittal sections by using a 1 mm^2 examination area (ROI, region of interest) and the mean values were recorded. A total of 963 measurements were taken from the 107 knee MRI (Figures 1, A-C).

Seven accompanying characteristics were evaluated in the three compartments where T2 values had been measured to identify the relationship of cartilage T2 values with pathologies involving the knee joint. These were subarticular bone marrow edema; subarticular cysts; marginal osteophytes; anterior-posterior cruciate and collateral ligament tears; posterior medial and lateral meniscal tears; synovial thickening; and effusion.

Subarticular bone marrow edema and cysts were evaluated in the patellofemoral, posteromedial femorotibial and posterolateral femorotibial compartments in the knee joints with fat-saturated PD-weighted TSE images.

The patients were divided into two groups as with and without osteophytes to identify the relationship between the osteophyte formations and cartilage T2 values.

Anterior (ACL) and posterior (PCL) cruciate ligaments were evaluated on sagittal PD-weighted FSE images, and the medial (MCL) and lateral (LCL) collateral ligaments were evaluated on coronal images. Patients were divided into two groups as with and without tears (complete or partial).

The patients were divided into two groups: one of the groups was composed of those who were found to have tears in the medial and lateral meniscus posterior horn, and the other group was composed of the ones who were not found to have a meniscal pathology signal change to identify the relationship of medial and lateral meniscal posterior tears with T2 values.

Two groups were identified as with and without synovial thickening and effusion to identify the relationship of synovial thickening and effusion in the knee joint with T2 values.

Statistical Analysis

The homogeneity tests of the distribution were performed on the SPSS 15.0 program. The effect of patient age on the knee joint cartilage transverse relaxation value changes in all three regions was investigated with regression analysis in the form of curve estimation. The homogenous distribution of the predictive value and residues were also tested in regression analysis and the homogenous distribution of all values

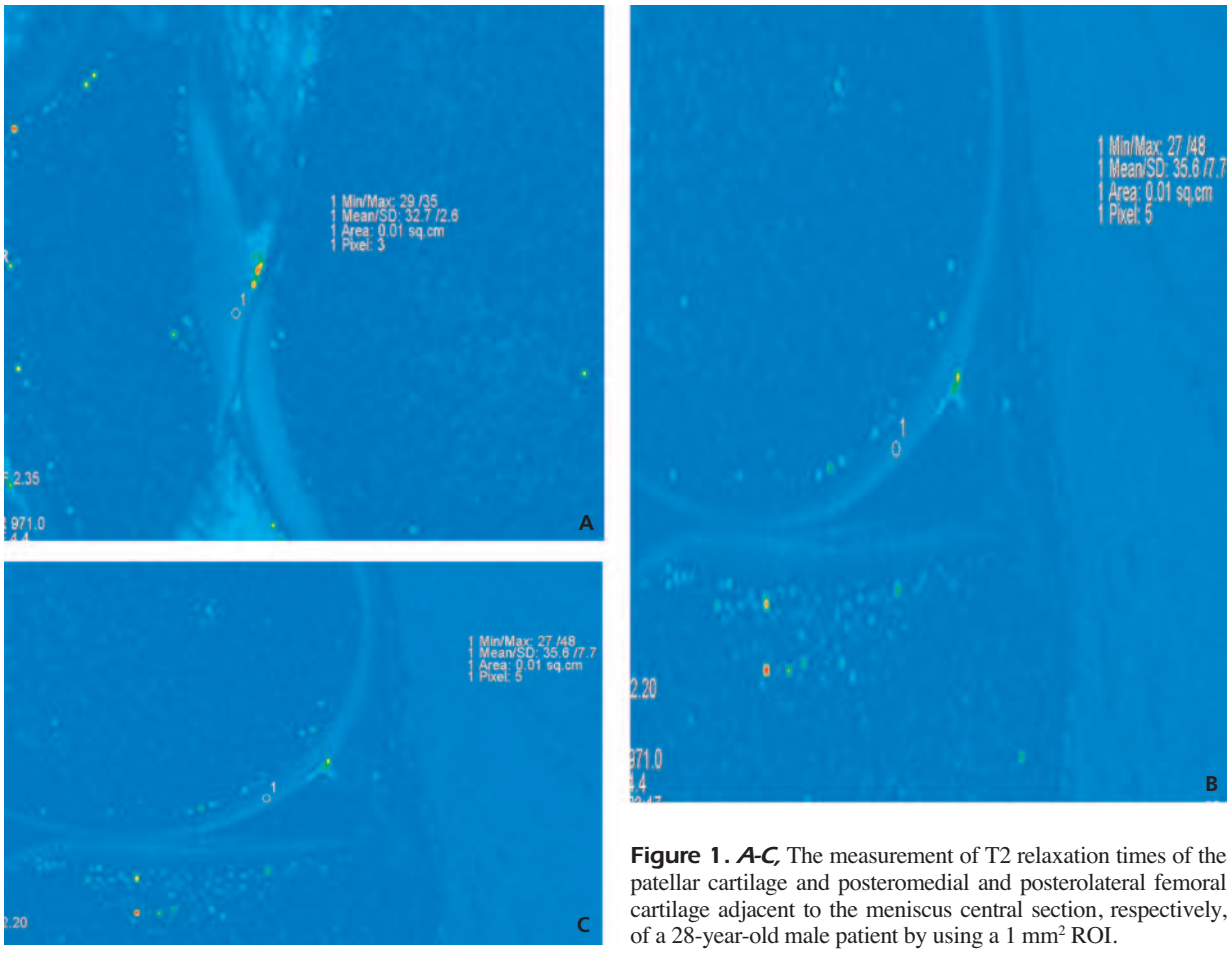

Figure 1. ***A-C,*** The measurement of T2 relaxation times of the patellar cartilage and posteromedial and posterolateral femoral cartilage adjacent to the meniscus central section, respectively, of a 28-year-old male patient by using a 1 mm^2 ROI.

together with age-T2 values was checked. The presence of linear correlation was investigated with Pearson's correlation test. Gender and presence of joint pathology were investigated as covariants and partial regression analysis was conducted. Regression analyses were performed for the age-T2 values of the male and female subgroups in the normal group. The lesion-T2 relationship in patient subgroups was investigated with Student's *t*-test. $p < 0.05$ was considered statistically significant.

Results

There were 60 females and 47 males with an age range of 12-63 years. The mean age was 38.2±12 years. There was no knee joint pathology on MRI in 19 female patients aged 12 to 45 years and 24 male patients aged 16 to 60 years. At least one knee joint space pathology (subarticular bone marrow edema; subarticular cysts; marginal osteophytes; anterior-posterior cruciate and collateral ligament tears; posterior medial and posterior lateral meniscal tears, synovial thickening and effusion) was found in 64 patients (Table I).

The mean T2 relaxation time was 34.9 ± 5.4 ms for the patellar cartilage (PC T2), 34.8 ± 4.9 ms for the posteromedial femoral cartilage (PMFC T2) and 35.3 ± 5.9 ms for the posterolateral femoral cartilage (PLFC T2) in patients without knee joint pathology. A T2 value increase correlated with age was present in all three compartments measured in the subgroup with no knee joint pathology and in the total patient group. According to the ROC curve, an increase showing a statistically significant difference was present in the patient group aged over 40 compared to the patient group aged 40 and below in the total patient group.

No statistically significant difference was found between the female and male cartilage T2 relaxation times in the subgroup with no knee joint pathology and in the total group in all three compartments where a measurement was performed.

Table I. Mean T2 values in the total patient group aged over and below 40.

Age group	N	Mean	Std. Deviation	Std. Error Mean
PCT2 ≤ 40	57	33.4464	5.13165	0.68575
PCT2 > 40	50	41.8720	4.34873	0.61500
PLFCT2 ≤ 40	57	33.3218	4.89984	0.66069
PLFCT2 > 40	50	43.5700	5.00429	0.70771
PMFCT2 ≤ 40	57	33.76316	4.396575	0.582341
PMFCT2 > 40	50	42.36600	4.295447	0.607468

A meniscal tear finding was observed on the medial and lateral meniscus posterior horns of 39 of 107 patients. A tear was seen on the medial meniscus posterior horn of 29 patients and the lateral meniscus posterior horn of 10 patients. The mean PMFC T2 relaxation time was 41.5 ± 5.1 ms in patients with a medial meniscal tear and 36.3 ± 5.8 ms without one. The T2 relaxation time showed a statistically significant increase in the patients with a tear compared to those without a tear ($p < 0.001$).

No statistically significant difference was found in T2 relaxation times of patients with and without a posterior lateral meniscus tear.

A ligament tear was identified in 18 of 107 patients as 3 MCL, 1 LCL and 14 ACL tears. No statistically significant difference was found in patellar cartilage T2 relaxation time between those with and without a ligament tear ($p = 0.171$). The mean PMFC T2 relaxation time was 37 ± 6.1 ms in those without a ligament tear and 41.4 ± 4.2 ms ($p = 0.004$) in those with one while the mean PLFC T2 relaxation time was 37.4 ± 6.9 ms in those without a ligament tear and 41.8 ± 6.8 ms ($p = 0.019$) in those with a tear, with the difference being statistically significant.

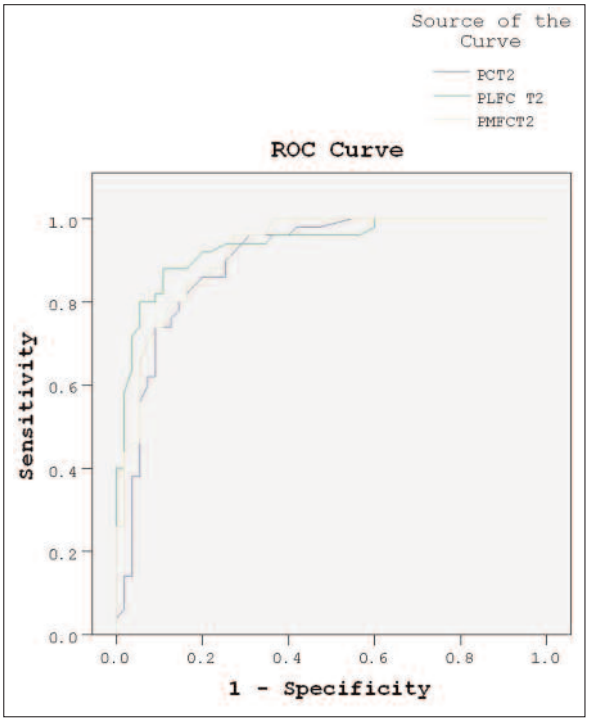

Figure 2. The Age-T2 value ROC curve AUC values in the total patient group: PCT2: 0.901, PLFCT2: 0.937, PMFCT2: 0.922.

Effusion was seen in the knee joint of 28 and an appearance consistent with synovial thickening in 15 of the 107 patients. Subchondral cyst formations were observed in 28 of the 107 knees. Subchondral cyst formation was present in the patellofemoral compartment in 20 knees, in the posteromedial femorotibial compartment in 17 knees, in the posterolateral femorotibial compartment in 11 knees, in both posteromedial femorotibial and patellofemoral compartments in 4 knees and in all three compartments in 8 knees.

Osteophyte formations were seen in 21 of 107 knees. Osteophyte formations were seen in the medial femorotibial compartment in 21 knees and in all three compartments in 15 knees.

Table II presents the mean T2 values in patients with and without an osteophyte, subchondral cyst, synovial thickening and effusion in the knee joint. The p values were under 0.05 in all 3 compartments where measurement was performed when the subgroups with pathology were compared to those without the pathology.

Subarticular bone marrow edema was present in 23 of 107 knees. Subarticular bone marrow edema was found in the patellofemoral compartment in 8 patients, the posteromedial femorotibial compartment in 14 patients, the posterolateral femorotibial compartment in 7 patients, and in both posteromedial and posterolateral femorotibial compartment in 3 patients. No statistically significant difference was found in any of the three compartments with and without subarticular bone marrow edema ($p > 0.05$).

Table II. Mean T2 values in patients with and without an osteophyte, subchondral cyst, synovial thickening and effusion in the knee joint.

	Mean PCT2	Mean PMFCT2	Mean PLFCT2
Osteophyte (+)	41.7 ± 7.1	42.8 ± 4.8	36.9 ± 5.9
Osteophyte (–)	36.7 ± 5.9	37.4 ± 7	36.9 ± 5.9
Effusion (+)	40.9 ± 6	40.8 ± 6	41.3 ± 7.6
Effusion (–)	36.1 ± 6	36.7 ± 6	37 ± 6.5
Synovial thickening (+)	40.8 ± 6.6	40.6 ± 5.1	41.7 ± 8.9
Synovial thickening (–)	36.8 ± 6.1	37.3 ± 6.1	37.6 ± 6.1
Subchondral cyst (+)	42.1 ± 6.8	42.6 ± 5.6	43.9 ± 7.7
Subchondral cyst (–)	36.3 ± 5.7	36.9 ± 5.8	37.4 ± 6.7

Discussion

We observed a statistically significant increase in the patellar, posterolateral and posteromedial femoral cartilage T2 relaxation times in patients over the age of 40 in this study. Biochemical studies have shown a number of changes in the structure and content of the cartilage with age. A decrease in water content and increase in proteoglycan concentration are seen as age increases[3,4]. The age-related increase in the cartilage T2 value is not due to the decrease in water content, as the T2 value increases in proportion to the water content. Studies have also shown that the T2 value is not sensitive to changes in the proteoglycan concentration only[5]. This suggests that the main cause of the increased T2 with age is the changes in the cartilage proteoglycan content or structure.

Some studies have reported strong evidence that the increases in the T2 value may be secondary to structural changes in the type 2 collagen matrix[6]. The limited water movements and collagen matrix anisotropy result in a short T2 time. The bipolar interaction between the collagen fibrils and the water in the cartilage suggests that the T2 values change due to the effect of the collagen matrix fibers in the magnetic field[7,8].

Both previous studies on age-related changes of T2 cartilage values belong to Mosher et al[9,10]. Mosher et al[9] compared patellar cartilage T2 values in asymptomatic female patients aged 22 to 86 years and found an elevation of patellar cartilage T2 values in asymptomatic women aged 46 years and older compared with young asymptomatic volunteers. In another study, Mosher et al[10] found an age-dependent elevation in superficial cartilage T2 values in asymptomatic men aged 46-65 years compared to men aged 18-30 years.

Unlike other studies, we evaluated symptomatic patients who had presented to our clinic due to various reasons instead of asymptomatic volunteer subjects in our study. We also evaluated the patient population with no pathology in the knee joint on MRI separately as a subgroup. There was an increase correlated with age in the patellar cartilage, posteromedial and posterolateral femoral cartilage T2 relaxation time in the patient group without knee joint pathology and in the total patient group. We found a statistically significant increase in the patient group aged over 40 compared to the patient group aged 40 or less in the total patient group.

Biochemical studies have shown sex hormones play a role in the pathogenesis of osteoarthritis with their effects on cartilage metabolism[11,12]. Estrogen receptors were found in the cartilage in monkeys with surgically induced menopause and an increase in proteoglycan synthesis by chondrocytes was reported with estrogen replacement therapy[11]. A significant increase was found in the proteoglycan and collagen concentration of male mice compared to female mice in other studies. Mouritzen et al[13] found age, sex, and menopausal status to be effective on the destruction of cartilage type II collagen. Mosher et al[14] compared the gender-dependent changes in the patellar, femoral and tibial cartilage T2 relaxation times of 17 asymptomatic young volunteers and found no statistically significant difference. We found no statistically significant difference between males and females for cartilage T2 relaxation times of all three regions. The lack of a statistically significant gender-dependent difference in cartilage T2 relaxation times indicates that similar results will be obtained with other parametric MRI cartilage techniques. The MRI T2 relaxation time is primarily sensitive to the collagen concentration and fiber orientation and less sensitive to the water content and proteoglycan content. Considering the increasing effect of estrogen on proteoglycan synthesis, MR examinations such

as dGEMRIC (delayed gadolinium enhanced MRI of cartilage), T1rho mapping and Na MRI that are more sensitive to the proteoglycan concentration may be useful in the identification of the gender-related cartilage changes[15-17].

Menisci have load distributing, stability increasing and lubrication providing effects. A strong relationship was found between meniscus damage and cartilage loss at the medial tibiofemoral compartment[18]. The degree of the risk formed by lateral meniscus damage on the tibiofemoral joint was found to be less than the degree of the risk formed by medial meniscus damage[18]. Kai et al[19] reported a statistically significant increase in medial and lateral tibial cartilage T2 relaxation times in patients with an ipsilateral meniscus tear compared to patients without a tear. However, no significant difference was found to be between medial and lateral femoral cartilage measurements. Biswal et al[20] found a strong relationship between meniscal damage and cartilage loss in the medial tibiofemoral joint. The degree of cartilage loss risk created by lateral meniscus damage on the lateral tibiofemoral joint was found less than the degree of cartilage loss risk formed by medial meniscus damage on the medial tibiofemoral joint.

A statistically significant increase was found in the posteromedial femoral cartilage T2 relaxation time in patients observed to have a tear in the medial meniscus posterior horn compared to the patients without a tear. There was no significant difference in the posterolateral cartilage T2 relaxation time in patients with a lateral meniscus posterior horn tear compared to the patients without a tear. Our results partially support the findings of study conducted by Biswal et al[20].

Ligament dysfunction is also a cause of meniscal tear, cartilage loss and osteoarthritis development[21]. Link et al[22] found ACL and collateral ligament lesions together with advanced osteoarthritis in a study on 50 knees. The etiology and the significance of incidental ACL tears in degenerative joint diseases are not known. The presence of a complete ACL tear has been reported to be a risk factor for cartilage loss in the medial tibiofemoral compartment of the knee. However, a complete ACL tear was found to have no effect on cartilage loss when medial meniscus tears were also included[23]. We found no significant relationship between the T2 relaxation time and ligament tears in the measurements performed on patellar cartilage in our study. However, a statistically significant increase was present in the posterolateral and posteromedial femoral cartilage T2 relaxation times in the group with ligament tears.

MRI can show hyperintense areas with undefined borders in the subarticular bone marrow. The described areas are similar to the pathological signal changes observed in trauma, infection, inflammation and acute ischemic necrosis, and are therefore mostly described as "bone marrow edema"[22]. However, these changes have been reported not to be histologically consistent with edema[24]. Subarticular bone marrow edema has been suggested to have a high predictive value for cartilage loss. Kijowski et al[25] found a significant relationship between the degree of the cartilage defect and subchondral bone marrow edema prevalence in their study. There is no previous study on the relationship between T2 relaxation time and bone marrow edema. We observed subchondral bone marrow edema most frequently in the posteromedial femorotibial compartment in our study. There was an increase in T2 relaxation times in patients with bone marrow edema compared with those without for all three compartments, but this was not statistically significant.

Subarticular bone cysts are essential components of degenerative joint diseases[24]. MRI detection is markedly superior to x-ray film in identification of subarticular cysts. A subarticular cyst was present in 36% of our cases. Subarticular bone cysts were most commonly located in the patellofemoral compartment and least in the posterolateral femorotibial compartment. A statistically significant difference was found in T2 relaxation times when all patients with and without a subchondal cyst in the three compartments were compared.

MRI provides the opportunity of accurate evaluation of synovial thickening and joint effusion in three planes. Whether the synovial thickening observed in degenerative joint diseases causes articular cartilage damage directly or is a reaction against the disconnected particles after cartilage damage for another reason is controversial. Link et al[22] found effusion in 76% of the 50 osteoarthritic knees. Peterfy et al[21] found joint fluid and distention in 75% of the cases in their study. We found effusion in 28 patients and an appearance consistent with synovial thickening in 15 patients. A statistically significant difference was found in cartilage T2 relaxation time between patients with and without effusion and synovial thickening in the three compartments where measurements were performed.

Osteophyte formations are frequently reported in patients with advanced osteoarthritis[22]. Osteophytes can be clearly shown with MRI. The localization of osteophytes can be correctly evaluated as an image can be obtained in three planes. Osteophyte formation can be seen in 20% of the knees included in the study. Osteophytes are known to be a significant characteristic of osteoarthritis together with cartilage loss[22]. A statistically significant increase was found in the cartilage T2 relaxation time in all 3 compartments in patients with osteophytes compared to those without osteophytes in our study.

We would like to underline that 40% of the group of patients with bone marrow edema was under the age of 40 and some also had accompanying disorders consistent with degenerative joint processes. When we consider that the bone marrow edema observed in this age group can be secondary to processes such as trauma and infection, the lack of change in the cartilage structure and T2 relaxation time could be normal. Moreover we did not divide the female patient group into premenopausal and postmenopausal or consider the age distribution and perform statistical analysis accordingly. Evaluation of cartilage T2 values in the female patient group by taking into account the effect of estrogen on cartilage will be another source of research.

Conclusions

MRI enables visualization of the articular cartilage and provides information on cartilage age and lesions.Biochemical and structural changes due to the changes in cartilage extracellular matrix can be identified with T2 cartilage mapping on MR. Cartilage T2 values are increased over the age of 40 due to the accompanying osseous, synovial and meniscal lesions.

Conflict of Interest

The Authors declare that there are no conflicts of interest.

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