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Impact of T2* MR Cartigraphy in Knee Joint Osteoarthritis

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Abstract: ***Background: MRI allows direct visualization of all tissues involved in osteoarthritis disease process including articular cartilage. In addition to morphologic assessment, MRI-based techniques have been developed that allow characterization and quantification of biochemical composition of cartilage. We have focussed on T2* mapping in our study. Objective: To study and grade changes in knee joint cartilage in various stages of osteoarthritis and to evaluate role of MR cartigraphy in early diagnosis of osteoarthritis. Methods: A retrospective and prospective observational study of 45 patients at a tertiary care centre referred for knee pain who presented during period of July 2020 to January 2023 using Philips 3T Ingenia MRI machine. Results: All patients in our study with Kellgren-Lawrence (KL) grade 0 and 1 (n=5) had raised T2* value (p value <0.001). T2* values increase with higher grade of osteoarthritis. Conclusion: T2* mapping helps in detecting early cartilage degeneration, even when grey scale MRI yields normal results. Clinical Impact: In order to start treatment early and track course of disease in osteoarthritis, it is crucial to diagnose cartilage damage before it is detected by conventional sequences that find morphological cartilage lesions when cartilage has already irreversibly damaged. This can be achieved with T2* mapping.***

Keywords: Cartigraphy - Knee joint - MRI - Osteoarthritis - T2* mapping

1. Introduction

Osteoarthritis (OA) is a type of joint disease that results from breakdown of joint cartilage and underlying bone. The most common symptoms are joint pain and stiffness. One of the hallmark features of OA from a structural perspective is cartilage degeneration, which has a progressive, irreversible course and is closely interrelated with pathology of other joint tissues, including the subchondral bone, meniscus, synovium and others.

The structural diagnosis of OA is based on the presence of a definite osteophyte on an anterior-posterior radiograph. Joint space narrowing (JSN) is considered to be a surrogate for cartilage loss although it is well established that meniscal damage and particularly extrusion contribute to JSN [1]. Although radiography is not sensitive to progression of cartilage loss, JSN on radiographs is recommended by regulatory agencies including the United States Food and Drug Administration (FDA) as the primary imaging endpoint to establish the effectiveness of disease-modifying OA drugs [2].

Magnetic resonance imaging (MRI) allows direct visualization of all tissues involved in the OA disease process including articular cartilage. In addition to qualitative or quantitative morphologic assessment, MRI-based techniques have been developed that allow characterization and quantification of the biochemical composition of cartilage. These include relaxometry measurements (T2, T2*, T1rho mapping and T1), sodium imaging, delayed gadolinium-enhanced MRI of cartilage (dGEMRIC), glycosaminoglycan specific chemical exchange saturation transfer (gagCEST), diffusion weighted imaging (DWI), and diffusion tensor imaging (DTI). These compositional MRI techniques may have the potential to serve as quantitative, reproducible, non-invasive and objective endpoints for OA research, particularly in early and pre-radiographic stages of the disease [3].

2. Literature Survey

Basic principles of compositional MRI techniques and application of compositional MRI techniques in osteoarthritis research [4]

Articular cartilage is responsible for resistance to compressive forces, distribution of load, and together with synovial fluid, frictionless movement of the articular joint components. It consists of approximately 70–80% fluid and 20–30% solid extracellular matrix (ECM) with a sparse distribution (about 2%) of chondrocytes. Chondrocytes are presumed to be responsible for any homeostatic and repair processes that modulate the composition of the fluid-like macromolecular network of cartilage. The ECM is made up

of a network of collagen fibrils and proteoglycan molecules. Collagen, a fibrillar macromolecule, is by far the most abundant macromolecule, accounting for about 20% of cartilage volume by weight. Physiologically, the collagen network is highly organized and serves as the tissue's structural framework and is principal source of tensile and shear strength. Although the collagen network becomes disrupted in OA and there is a net loss in total collagen content, its concentration is not appreciably affected in disease states. A proteoglycan unit includes a protein core and covalently attached glycosaminoglycans (GAGs). The negatively charged GAGs contribute to the majority of the fixed charge density in the ECM and are neutralized by mobile cations, usually sodium (^{23}Na) being the most abundant physiologically.

Initial histological and biochemical changes of cartilage degeneration involve disruption of the collagen network, decrease in proteoglycan content and increase in permeability to water. Compositional MRI techniques enable detection of these biochemical changes in the cartilage ECM before morphological change occurs. Because of well-documented importance of collagen and GAG to the functional and structural integrity of cartilage, efforts toward developing MRI techniques to interrogate cartilage macromolecules have focused on collagen and GAG.

T2* mapping

Compared with other biochemically sensitive MRI techniques, T2* mapping has unique features including speed of imaging, high image resolution, and the ability to carry out isotropic three-dimensional (3D) cartilage evaluation [5]. It is also easy to implement on clinical MRI systems, as pulse sequences and inline processing software for generating quantitative T2* maps are available commercially. In addition, there is no need for contrast media administration or special hardware

T2* relaxation is unique for gradient echo (GRE) imaging because it requires a de-phasing effect that is eliminated in spin-echo MRI. GRE sequences are more time-efficient than spin-echo sequences, but are also more prone to local field inhomogeneities and susceptibility. In common with T2 mapping, T2* mapping enables assessment of water content, collagen fiber network, and zonal variation reflecting biochemical composition of cartilage. As for T2 measurements, a decrease in T2* is noted toward the deep cartilage zones in normal cartilage and the T2* values are higher in diseased cartilage. Despite these similarities, there are significant differences between the two imaging modalities that have led to diverging T2 and T2* values in various grades of cartilage degeneration. T2 mapping spin-echo sequences utilize echo times of ~ 10–100 ms. Therefore, T2 mapping techniques capture T2 relaxation, which to a large extent is related to bulk water, while they are rather insensitive to T2 signals that decay more rapidly (T2 relaxation < 10 ms). T2* mapping, in contrast, includes shorter echo times and as such reflects a wider range of T2 relaxation occurring in cartilage tissue. Notably, because of the absent 180° refocusing pulse, T2* relaxation is less sensitive to stimulated echoes and magnetization transfer.

We have used **Kellgren and Lawrence system for classification of osteoarthritis.** Its grades are as follows:

Grade 0 (none): definite absence of x-ray changes of osteoarthritis

Grade 1 (doubtful): doubtful joint space narrowing and possible osteophytic lipping

Grade 2 (minimal): definite osteophytes and possible joint space narrowing

Grade 3 (moderate): moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends

Grade 4 (severe): large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends

Aims & Objectives of the study:

- To evaluate the role of MR cartigraphy in early diagnosis of osteoarthritis.
- To study the changes in joint cartilage in various stages of osteoarthritis and to grade cartilage degeneration.

3. Methods

The study is a retrospective and prospective evaluation of 45 patients at a tertiary care centre referred for knee pain who presented during the period of July 2020 to January 2023.

The patients were selected via convenience sampling (non-probability sampling). Patients who gave valid consent and fulfilled the below mentioned inclusion and exclusion criteria were subjected to MRI of the affected knee.

The MRI was performed on 3 Tesla Philips Ingenia MRI machine.

Inclusion Criteria: All adult patients >30 year of age with history of knee joint pain.

Exclusion Criteria:

- Patient with history of trauma/operative history.
- Pregnant females
- Patient with history of claustrophobia
- Patients with history of cardiac pacemakers, metallic foreign bodies and cochlear implant and other contraindications for MRI.

Study Protocol:

Patient Data Collection

a) Demographic details – Age, gender, height, weight, address, contact number.
b) History – Symptomatology, duration of symptoms, duration of disease (in diagnosed cases), treatment taken.
c) Clinical examination.
d) Investigations.

All the patients were subjected to MRI evaluation of the affected knee joint.

Imaging was done on 3 Tesla Philips Ingenia MRI machine.

Patient's position- Routine knee MRI positioning.

- Feet first supine.
- Knee positioned in knee coil and immobilised with cushion.
- Position of slight flexion and internal rotation.

MRI protocol- The following sequences of the affected knee were taken

- PD coronal and sagittal
- PD SPAIR axial
- T2Cal (T2*) sequence for cartilage imaging

Parameters of Scanning are described in Table 1.

Table 1: MRI Protocol for evaluation of knee

Image plane	Acquisition scheme	Slice thickness (mm)	TR (ms)	TE (ms)	FOV (mm)	Matrix	Flip angle
PD CORONAL	Turbo Spin Echo	3	2700	30	160	260 x 219	90
PD SAGITTAL	Turbo Spin Echo	3	2700	30	160	260 x 219	90
PD SPAIR AXIAL	Turbo Spin Echo	4	2900	30	160	292 x 224	90
T2 CAL (T2*)	Turbo Spin Echo	2.5	2000	13	160	384 x 315	90

Image analysis:
T2* values were calculated using mono-exponential fitting algorithm.

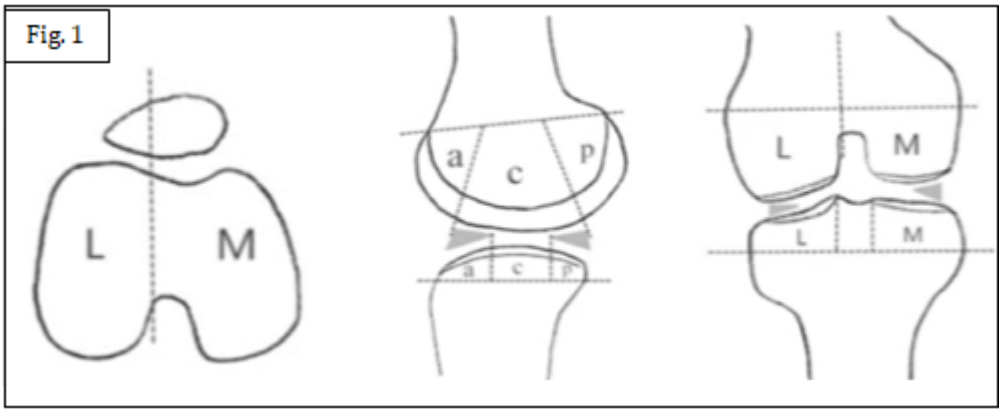

Figure 1: The femur (F) was divided into medial (M) with the trochlear groove and lateral (L) regions. The femur was further divided into anterior (a), central/ weight bearing (c) and posterior (p) regions. The central/ weight bearing femur referred to the region extending from the anterior edge of the anterior horn to the posterior edge of the posterior horn of the meniscus.

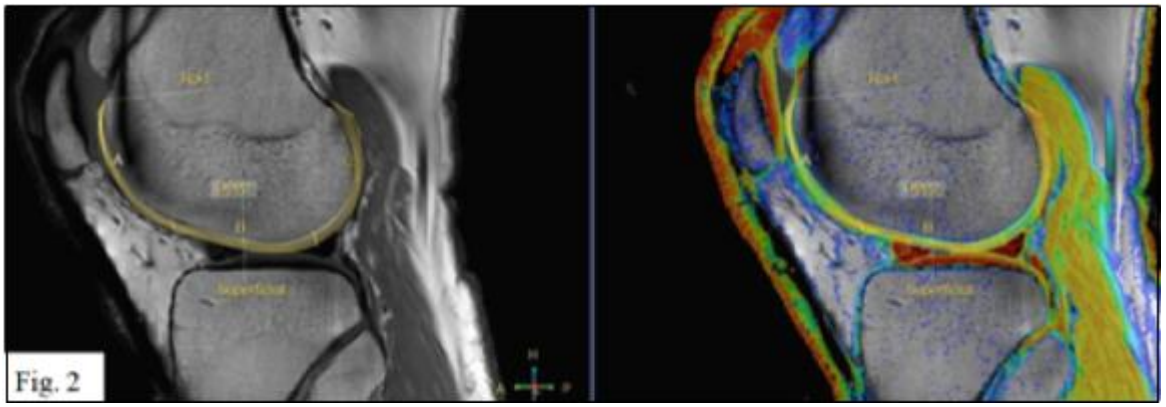

Figure 2: Each region was again equally divided into superficial (s), intermediate (i) and deep (d) layers according to the thickness of cartilage. The superficial area is from the articular surface to the middle of the cartilage and the deep area is from the middle of the cartilage to the bone-cartilage interface, intermediate area is in between them. Thus 9 zones are present in each femoral condyle.

Data analysis:
We took following T2* values as cut-off, above which articular cartilage degradation was considered degraded. The normal articular cartilage has a lower T2* value in deep layer than the superficial layer (97).

Zone of articular cartilage	T2* relaxation time cutoff (millisecond)
Deep	40
Intermediate	43
Superficial	45

All the T2* values of 9 zones for each femoral condyle were added and mean value was derived for medial and lateral femoral condyle and patellar cartilage separately. Average T2* value cut-off was taken as 45 msec.

Colour map of T2* value (Figure 3):

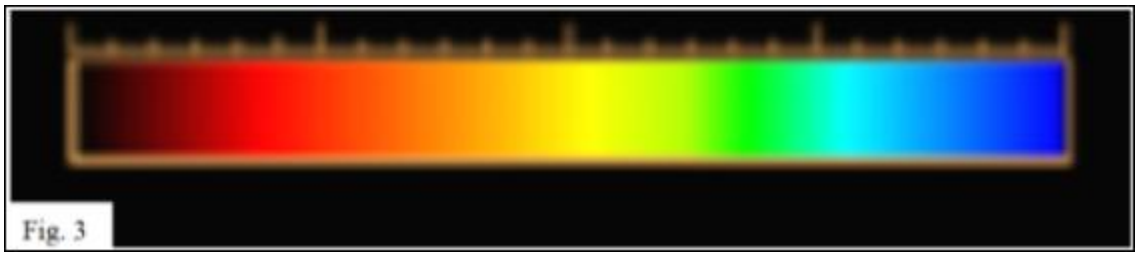

Fig. 3

T2* values (in milliseconds): 1-20 --- 21-40 --- 41-60 --- 61-80
Colour map: Red --- Yellow --- Green --- Blue

Statistics:
Sample size of the study was determined using SAS 9.2 package. Comparison of means of 2 groups was carried out by Student's unpaired t test for numerical normal data and by Mann Whitney U test for abnormal data. Fisher Exact Probability tests were applied to compare percentages for categorical data between 2 groups. Chi square test was applied to compare percentages of more than 2 groups. Sensitivity, Specificity, and negative and positive predictive values and Accuracy of MR was calculated and presented as percentages and 95% Confidence Intervals. Alpha (α) Level of Significance was taken as P<0.05.

4. Results

Adult patients> 30 yrs old were enrolled in the study. Maximum patients (n = 16) were found in the age group of 41-50 and 51-60 years and the least number of patients were found in the age group of <=40 years (n = 5). The youngest patient was 36 years old; the oldest patient was 64 years old. The mean age of our study group was 51.6 years with a standard deviation of ±8.15 years.

Out of 45 patients, 19 (42.2%) were males and 26 (57.8%) were females.

MRI findings were as follows: Out of 45 patients, 40 patients (88.9 %) had cartilage thinning, 7 patients (15.6%) had cartilage fissuring, 17 patients (37.8%) had patellar cartilage involvement.

Out of 45 patients, 5 patients (11.1%) had grade 0, 5 patients (11.1%) had grade 1, 11 patients (24.4%) had grade 2, 15 patients (33.3%) had grade 3 and 9 patients (20%) had grade 4 osteoarthritis based on Kellgren Lawrence (KL) grading on grey scale MRI. **(Table 2)**

Table 2: Distribution of Study Subjects according to the Kellgren Lawrence Grading of Osteoarthritis (N=45)

KL Grading	No.	Percent
0	5	11.1
1	5	11.1
2	11	24.4
3	15	33.3
4	9	20.0

Out of 45 patients, 45 patients (100%) had increased T2* relaxation time of medial femoral condyle cartilage and 11 patients (24.4%) had increased relaxation time of lateral femoral condyle cartilage.

For medial femoral condylar cartilage: In the ≤ 40 year age group, all patients had T2* value between 46-55. In 41-50 year age group, maximum no. of patients (n=12) had T2* value between 46-55. In 51-60 and >60 year age group, maximum no. of patients (n=6 and 4 respectively) had T2* value between 76-85. In ≤ 40 and 41-50 year age groups, none of the patients had T2* value between 66-85. For these observations, p value was 0.002* (significant) **(Table 3).**

Table 3: Association between Age and Medial Femoral Condyle Cartilage (N=45)

Medial Femoral Condyle Cartilage T2* value	Age (Years)				P Value
	≤ 40	41-50	51-60	>60	
46-55	5 (100.0)	12 (75.0)	3 (18.8)	1 (12.5)	0.002*
56-65		4 (25.0)	3 (18.8)	1 (12.5)	
66-75			4 (25.0)	2 (25.0)	
76-85			6 (37.5)	4 (50.0)	

For lateral femoral condylar cartilage: In the ≤ 40 year age group, all patients had T2* value between ≤ 45. In 41-50, 51-60 and >60 year age groups, maximum no. of patients (n=15, 10 and 4 respectively) had T2* value between ≤ 45. In ≤ 40 and 41-50 year age groups, none of the patients had T2* value between 56-65. For these observations, p value was 0.141 (not significant) **(Table 4).**

Table 4: Association between Age and Lateral Femoral Condyle Cartilage (N=45)

Lateral Femoral Condyle Cartilage T2* value	Age (Years)				P Value
	≤ 40	41-50	51-60	>60	
≤ 45	5 (100.0)	15 (93.8)	10 (62.5)	4 (50.0)	0.141
46-55		1 (6.3)	4 (25.0)	2 (25.0)	
56-65			2 (12.5)	2 (25.0)	

For medial femoral condyle cartilage: All patients with KL grade 0 and 1 had T2* value between 46-55. Maximum no. of patients (n=10) with KL grade 2 had T2* value between 46-55. Maximum no. of patients (n=7) with KL grade 3 had T2* value between 56-65. All patients with KL grade 4 had T2* value between 76-85. For these observations, p value was <0.001* (significant) **(Table 5).**

Table 5: Association between T2* values of Medial Femoral Condyle Cartilage and KL Grading (N=45)

Medial Femoral Condyle Cartilage T2* value	KL Grading					P Value
	0	1	2	3	4	
46-55	5 (100.0)	5 (100.0)	10 (90.9)	1 (6.7)		<0.001*
56-65			1 (9.1)	7 (46.7)		
66-75				6 (40.0)		
76-85				1 (6.7)	9 (100.0)	

5. Discussion

Osteoarthritis is a non-inflammatory degenerative joint condition. It is characterized by articular cartilage degeneration and new bone (osteophytes) formation. It is classified into two types, Primary and secondary. Primary type is more common. It occurs in elderly, without any previous local joint pathology. It is mainly due to wear and tear changes in cartilage because of ageing. Secondary OA is due to a pre disposing cause like injury, infection, rheumatoid arthritis, hyperthyroidism, etc. Sitting cross legged and squatting are some of the reasons of increased prevalence of OA in India. In addition to changes in articular cartilage, OA also causes changes in ligaments and muscles. Due to low grade chronic inflammation, ligaments can undergo fibrous degeneration and muscles can undergo atrophy.

T2* mapping does not rely on spatial resolution to detect the cartilage damage. It depicts the areas of increased water content and altered collagen matrix in the degenerated cartilage. Thus T2* mapping helps in detection of changes in cartilage composition and three-dimensional ultrastructure of cartilage, before the morphological changes occur, thereby helping in early initiation of treatment.

In our study of 45 patients, for medial femoral condyle cartilage: All patients with KL grade 0 and 1 had T2* value between 46-55. Maximum no. of patients (n=10) with KL grade 2 had T2* value between 46-55. Maximum no. of patients (n=7) with KL grade 3 had T2* value between 56-65. All patients with KL grade 4 had T2* value between 76-85. For these observations, p value was <0.001* (significant).

Thus T2* mapping helps in detecting early cartilage degradation even in patients with Kellgren-Lawrence grade 0 **(Figure 4)**. Also, with increasing KL grade, T2* value increases.

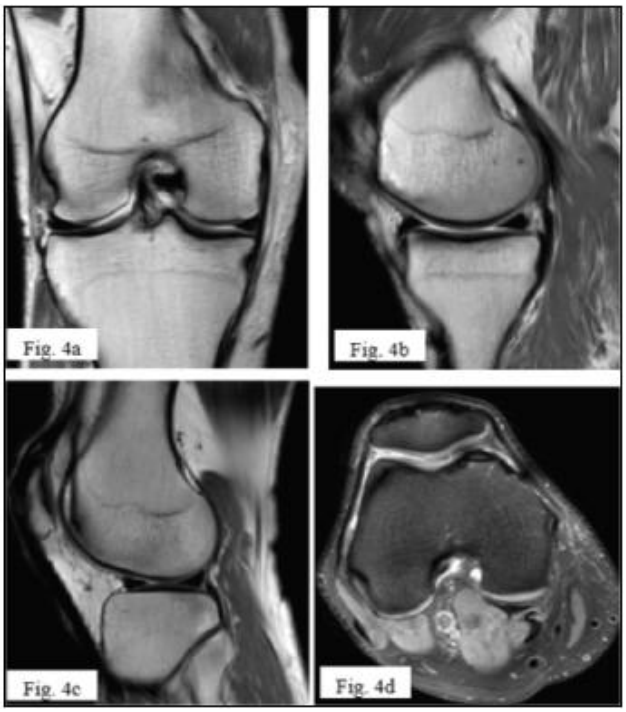

Figure 4a-d: A 49 year old male patient presented with complaint of right knee pain since 1 month. MRI of the knee: 4a- PD coronal, 4b- PD sagittal showing medial femoral condyle, 4c- PD sagittal showing lateral femoral condyle, 4d- PD SPAIR axial. Both medial and lateral compartment appear smooth in outline and show normal signal intensity. Articular and patellar cartilage appears smooth in outline and shows maintained thickness.

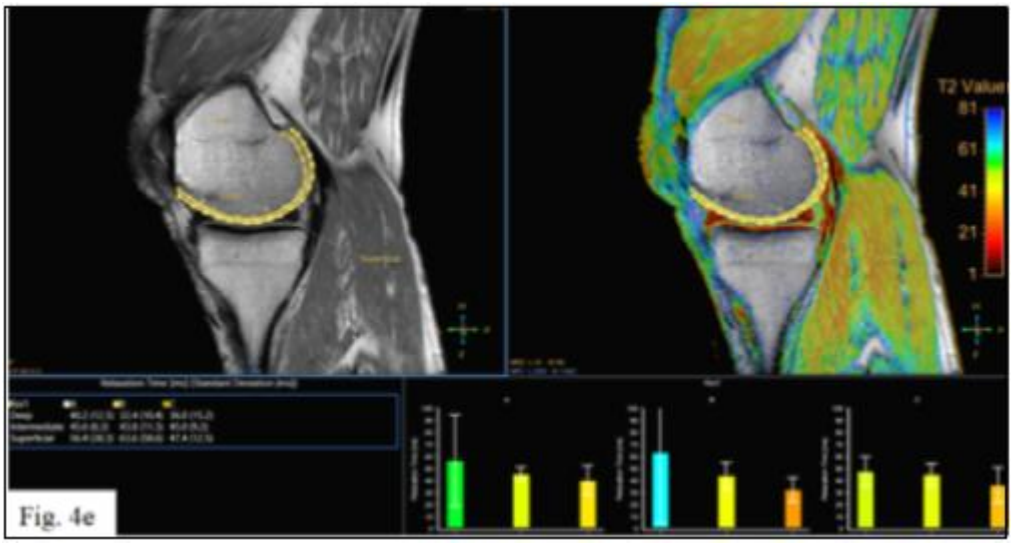

Figure 4e: T2* cartigraphy of medial femoral condyle of same patient shows increased relaxation time of superficial zone of anterior, weight bearing and posterior condyle cartilage. Rest of the zones show normal relaxation times.

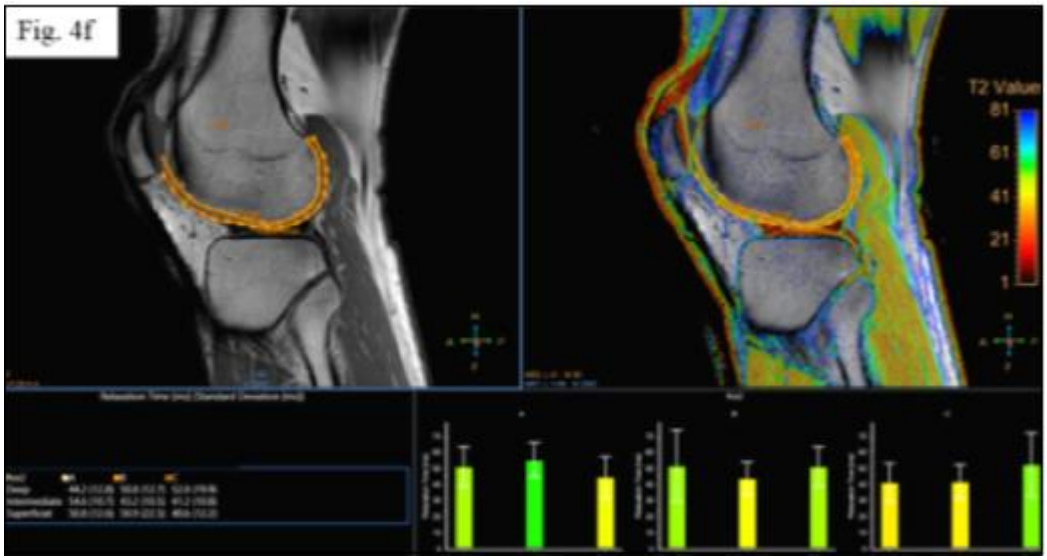

Figure 4f: T2* cartigraphy of lateral femoral condyle of same patient shows increased T2 relaxation time of intermediate and deep zones of anterior lateral femoral condyle cartilage. Increased T2 relaxation time of deep and superficial zone of weight bearing lateral femoral condyle cartilage. Increased T2 relaxation time of deep zone of posterior lateral femoral condyle cartilage.

In a study conducted by **Newbould et al.** (5), a deep to superficial increase in T2* was demonstrated in the femoral condyles of normal-appearing cartilage, as noted in our study. Also, T2* mapping is a repeatable process that showed differences between the OA subject and control groups. Thus these results confirmed that increased T2* value in articular cartilage can be used as an indicator of cartilage degeneration in OA.

In a study conducted by **Tsai, Ping-Huei, et al.** (6), T2* values were significantly greater in the OA group for the medial femoral cartilage, medial tibial cartilage and lateral femoral cartilage relative to those of controls.
Also, age-related increases in T2* values were found in both the medial and lateral compartments of the femoral and tibial cartilages suggesting possible associations between MR T2* values and age.

In a study conducted by **Yang, Lv-Lin, et al.** (7), it was found that the articular cartilage T2* values increased with the severity of the lesions and were negatively correlated with the γ-glutamyl carboxylase (GGCX) content in the cartilage detected by Western blot and immunohistochemistry (IHC). Consequently, it was also found that MRI T2-star mapping for the quantitative analysis of cartilage promotes the early diagnosis of OA.

These findings are similar to our study.
Our study has some advantages over some of the other compositional imaging techniques:

- Shorter imaging time: dGEMRIC, sodium MR imaging, T1 mapping which require a long waiting time (delay after contrast injection in dGEMRIC technique)
- No use of intravenous contrast (required in T1 mapping and dGEMRIC technique).
- No requirement of special coil (required in sodium MR imaging).

- Our study was done on a 3 Tesla MRI scanner as it offers increased SNR and increased resolution than other low field strength scanners.

Our study also had some limitations, few of which are:

- Patients in our study could not be followed up for surgical or arthroscopic correlation of cartilage lesions. Arthroscopy is the reference standard for evaluating articular cartilage. So the exact diagnostic performance of T2* mapping could not be assessed.
- T2* relaxation values are susceptible to the magic angle effect. T2* values will be inaccurate in those areas of the cartilage where collagen fibres are oriented at certain orientations to the external magnetic field.
- Loss of proteoglycans occur prior to degradation of the collagen matrix in OA, therefore T2* mapping may not detect changes as early as techniques sensitive to GAG and PG content, like dGEMRIC or T1rho mapping.
- Ours is a single centre institutional study, a multi-centre study on similar lines in future would support and fortify the findings observed in our study.
- The sample size of our study (n=45) may not be enough to extrapolate the results to a wider population.

6. Conclusion:

Overall, our study concludes that –

- T2* mapping aids in early detection of knee joint osteoarthritis.
- Age is the single most significant factor affecting cartilage degeneration.
- There is increase in cartilage degeneration with increase in age of patient.
- Medial compartment of knee is more frequently affected by osteoarthritis as compared to left side, as it is weight bearing.
- Grade 0 KL staging can have cartilage degradation. Hence T2*cartilage mapping should/ can be recommended in patients with risk factors for osteoarthritis for early management.

Our study has demonstrated that T2* mapping is a non-invasive imaging method that may enhance our capacity to identify early cartilage matrix degeneration at the earliest stage of osteoarthritis pathogenesis, i.e., collagen network alteration. In order to start treatment early and track the course of the disease in OA, it is crucial to diagnose cartilage damage before it is detected by conventional sequences that find morphological cartilage lesions at a time when the cartilage has already irreversibly damaged.

7. Future Scope

The addition of T2* mapping sequence to a routine MR imaging protocol can improve the sensitivity for detecting cartilage lesions. T2* mapping sequence can be used as a valuable tool to evaluate the articular cartilage, to detect cartilage lesions at an earlier stage in osteoarthritis which will be useful in planning the treatment strategies, thereby reducing and preventing the morbidity of osteoarthritis in the elderly.

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