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MRI T2 mapping and quantitative ultrasound shear wave elastography in cartilage integrity assessment for juvenile idiopathic arthritis patients

Wessam Abdelrahman Elzayat¹, Moustafa Hussein Abdelrahman^{1*} , Hend Mohamed Abu Shady² and Hadeel Mohamed Seif¹

Abstract

Background Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease in childhood that can lead to irreversible cartilage damage, with associated disability and decreased life quality. Shear wave elastography and quantitative MRI mapping can be used to identify early cartilage affection.

Purpose To evaluate diagnostic utility of distal femoral cartilage shear wave elastography and MRI T2 mapping in patients with symptomatic knee and investigate their potential clinical significance.

Material and methods Twenty patients with knee affection (study group) and 20 volunteers with the same demographic characteristics but without symptomatic knee pain (control group) were included in the study. A total of 80 knee joints of 40 individuals were evaluated. At the medial, intercondylar, and lateral condylar levels, distal femoral cartilage thickness was measured by B-mode ultrasonography and MRI, stiffness was assessed by shear wave elastography, and T2 relaxation time was measured by MRI.

Results The medial, intercondylar, and lateral cartilage thickness measurements were similar between the two groups and no statistically significant difference was observed while measured by US (P value 0.653, 0.702, 0.607) and MRI (P value 0.414, 0.4187, 0.3903). The shear wave velocity values in the study group were significantly higher than in the control group (P value 0.0202). There was a statistically significant difference between the average T2 relaxation time values for the distal femoral cartilage in the study and the control groups (P value 0.0027). SWE results were statistically significant in moderate and high disease activity while T2* revealed statistically significant p values in low as well as moderate and high disease activity; we found the best cutoff values for detection of cases using shear wave elastography velocity ratio (m/sec) about 4.445 with significant p value = 0.02, sensitivity 59.3% and specificity = 70.45%.

Conclusion Shear wave elastography and MRI T2 mapping are reliable, non-invasive, and acceptable methods for the assessment of pathologic cartilage. Better diagnostic information of hyaline cartilage can be obtained by adding up an extra sequence called T2 mapping to the routine MRI protocol of knee.

Keywords T2 mapping, SWE, JIA

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The background section

Juvenile idiopathic arthritis (JIA) represents an assemblage of biologically definite, Incompletely apprehended forms of chronic inflammatory arthritis starting in childhood [1].

Cartilaginous damage originates in the synovial membrane by the autoimmune-mediated inflammation which may extend to the cartilage and result not only in cartilaginous damage but in bone matrix degradation as well. The osteochondral damage is supposedly irreversible and may be a cause of associated disability decreasing life quality [2].

US imaging and conventional MRI can reliably detect architectural bone damage and synovial inflammation but cannot assess cartilaginous microstructural damage [3].

The rapidly evolving advances in therapeutic agents that can be disease modifying tools preventing long-term disability in Juvenile idiopathic arthritis patients, warrants early detection of joint-centered inflammation which cannot rely solely on conventional imaging tools and sometimes may not be evident clinically [4].

Quantitative MRI mapping translates MRI relaxation times into quantitative values that may be able to show early changes in cartilage composition even before structural changes evolve [5].

Elastography is a non-invasive tool that can quantitatively assess tissue mechanics based on its elastic properties. Current ultrasound-based elastography methods have displayed the ability to measure mechano-acoustic properties of cartilage which may reflect early tissue degradation [6].

The aim of this study is to investigate the use of an extra sequence; T2 mapping in routine MRI examination of the knees and to compare its added value to the shear wave elastography.

Patients and methods

Study population

We included 20 patients [4 males, 16 females] who are admitted to the rheumatology outpatient clinical with knee affection on physical examination in terms of joint swelling, tenderness, pain, restricted motion as well as elevated erythrocyte sedimentation rate and C-reactive protein lasting longer than six weeks after exclusion of other causes of arthritis; we excluded those who had previous knee trauma, surgery or septic arthritis. The control group consisted of 20 volunteers (4 males, 16 females) with the same demographic characteristics but without symptomatic knee pain performing other radiological examination unrelated to musculoskeletal (MSK) pathologies.

Methods

Clinical examination

Patients were diagnosed to have JIA according to the International League Association for Rheumatology (ILAR) proposed criteria [7].

Assessment of disease activity was achieved by measuring Juvenile Arthritis Disease Activity Score (JADAS10) [8] including the following four measures:

- Clinician's comprehensive assessment of disease activity measured on a 0–10 visual rating scale where 0 = no activity and 10 = maximum activity
- Parent/patient global assessment of well-fare and comfort measured on a 0–10 visual analog scale (VAS) where 0 = very well and 10 = very poor
- The erythrocyte sedimentation rate (ESR) standardized to a 0 and to 10 scale (ESR values less than 20 mm/h were referred to 0, and ESR values more than 120 mm/h were referred to 10)
- A numerical sum up of active joints.

The cutoff values for disease activity score [9] were as follows:

- For oligoarthritis: inactive disease (less than or equal 1), low disease activity (1.1:1.5), moderate disease activity (1.51:4), and high disease activity (More than 4.0).
- For polyarthritis: inactive disease (Less than or equal 1), low disease activity (1.1:2.5), moderate disease activity (2.51:8.5), and high disease activity (More than 8.5).

Laboratory investigations

- CBC with differential.
- Erythrocyte sedimentation rate(ESR)
- C- reactive protein (CRP).
- Calcium, Phosphorous, Alkaline phosphatase.
- Anti-nuclear antibody (ANA)
- ALT and AST

B-mode US and SWE examination

A-Imaging protocol

We used a Sony Aplio 400 brand device to perform B-mode US and SWE in all patients and volunteers. The application applied was Acoustic Radiation Force Impulse (ARFI) imaging-based SWE implementing a virtual touch tissue imaging quantification (VTIQ) option. Scanning the joint was done by the factory's

(MSK) preset using a 10-12 MHz linear transducer. Subjects were examined in the supine position with their knees in maximum flexion having the probe placed on the supra-patellar region in transverse plane.

B- Data analysis

The distance between the two hyperechoic lines marking the synovial space–cartilage interface was considered the cartilage thickness. We took 3 distal femoral cartilage thickness measurements at mid points of the medial and lateral condyles as well as the intercondylar area. This was followed by SWE software activation in split-screen mode taking 3 separate measurements using a 3mm. rounded region of interest (ROI) at the fore mentioned sites. Measurements were expressed in m/sec. The shear wave value (SWV) was defined as the mean value of the three measurements. The technique was performed by an experienced pediatric MSK radiologist (Seif H) with an 18 years' experience blinded to the clinical scores.

T2 mapping

A-Imaging protocol

Patients were examined by Siemens 1.5 Hdxt MRI with the routine MRI knee protocol: Proton-density-weighted sagittal and axial series (TR:2000ms-TE:20 ms), T2-weighted sagittal and coronal series (TR:2000 ms-TE:160 ms), and coronal T1-weighted series (TR:600 ms-TE: 20ms) adding T2* sequence (sagittal multi slice multi-echo spin-echo): repetition time 27 m.sec, 5 different echo times (10,19,37,46,55 ms), slice thickness 1.5 mm, gap 1 mm, field of view 10x10x2.4, flip angle 13°, the acquisition time for T2* sequence is 4 min and 26 seconds while the total acquisition time for the exam was 15 min and 41 seconds.

B-Data analysis

The width of the articular cartilage was measured in the axial proton density sequence at the same sites of US measurement.

T2/T2* map post-processing was performed on a standalone platform (Simens MMWP multimodality workplace); multiple region of interests (size 0.5 cm. each) were drawn on each examined part; the medial condyle, intercondylar area, and lateral condyle. The US and MRI were reported by an experienced reader Elzayat WA, with 10 years' experience in pediatric radiology who was blinded to the clinical history of the patients.

Statistical analysis

The studied variables were expressed as mean SD, minimum and maximum values. First, the normal distribution of parameters was confirmed by the Shapiro–Wilk test, and then parametric statistical analysis was performed. Independent t-test was used to compare group means in terms of continuous variables. Pearson correlation

coefficients were used to determine the relationship between variables. Statistical significance was set at $P < 0.05$, SPSS software (ver.23) was used for all statistical analyses.

Results

Clinical findings

Among the studied patients the age of the disease onset was ranging from 1 to 7 years with a mean of 3 years, the mean age at diagnosis was 4.75 years; ranging from 1 to 10.5 years, the disease duration range was 5:11.5 years with a mean of 6.5 years. Two patients had a positive family history of other autoimmune diseases (10%) and seven patients had consanguineous marriage (35%). Among the JIA studied group, there were 14 patients diagnosed as poly-articular JIA (70%) (Fig. 1) and 6 patients diagnosed as oligo-articular JIA (30%) (Fig. 2).

There was no statistically significant difference between cases and controls as regards complete blood picture (CBC), and the measured liver enzymes (P value > 0.05).

There was statistically significant difference between the cases and the control group as regard ESR and the C-reactive protein (CRP) (P value < 0.001) (Table 1).

The mean JADAS 10 score was variable among the poly-articular patients (range=1.2: 6.5, mean=1.55, median=2.8) and the oligo-articular patients (range=1: 2.5, mean=1.3, median=1.7) with no significant statistical difference (P value > 0.05).

Treatment regimen at time of the study

Among the studied JIA patients, the majority of the patients [15] were on biological treatment (75%) while others were on methotrexate and hydroxychloroquine (2 patients (10%) for each); 5 of the patients were on NSAIDs (25%) and the remaining 7 patients were on steroids (35%).

Regarding the steroids medications, 2 patients were on steroids for less than one-year duration, 3 patients for one to two years and 2 patients were on steroids for more than two years. As for the biological medications, tocilizumab and Akarina were the most used ones, taken by 4 patients each (26.6% each) while infliximab was the least used taken only by one patient (6.6%), and other medications were Etanercept and Adalimumab used by 3 patients (20%) each.

Imaging findings

B mode US and conventional MRI:

Comparing cartilage thickness measurements from the medial condyle, intercondylar area, and lateral condyle by both US and conventional MRI between the study group and the control group showed no statistical significance.

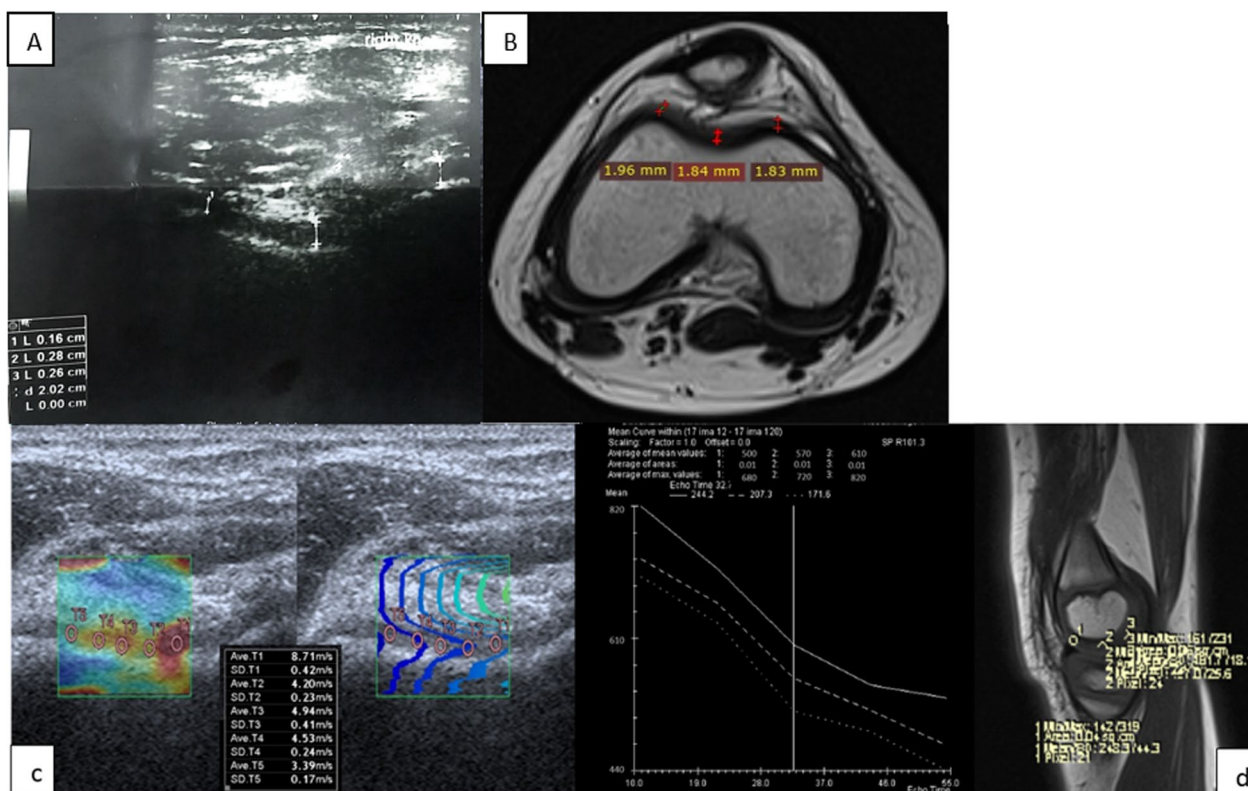


Fig. 1 A 16-year-old female patient diagnosed with poly-articular JIA; since the age of 5 years, presenting at time of examination by right knee pain, the patient was on Calcimate, Hydroquin, and folic acid, no biological treatment. **a & b** Cartilage measurement by US and conventional MRI, **c** Shear wave elastography measurement (average 8 m/sec), and **d** T2 mapping sequence (average T2 relaxation time 61 m/sec)

With progression of the disease activity (represented by the JADAS 10 score), the measured cartilage thickness by both MRI and US are noted to be decreased (Fig. 3) yet when comparing the p value for US versus MRI average cartilage thickness in the different disease activities, MRI was found statistically significant (p value=0.012) only in high disease activity (Table 2)

SWE

The SWE values measured from the medial condyle and intercondylar area and the lateral condyle were significantly higher in the study group than in the control group (P value is less than 0.005) (Table 3). SWE results were statistically significant in moderate and high disease activity (Table 4).

By ROC curve analysis (Fig. 4), we found that the best cutoff values for detection of cases using shear wave elastography velocity ratio (m/sec) about 4.445 with significant p value=0.02, sensitivity 59.3% and specificity=70.45%.

SWE velocity values higher than cutoff values are considered stiff and diseased.

3.3.3 T2 mapping findings

There was a statistically significant difference between the average T2 relaxation time values for the distal femoral cartilage in the study and the control groups (P value is less than 0.005) (Table 5).

Comparative P value for T2 mapping was much more significant than SWV value in detection of cartilage affection between the control and the study group (Fig. 5).

T2* revealed statistically significant p values in low as well as moderate and high disease activity (Table 4).

MRI T2 relaxation time is directly proportionate to the disease duration and inversely proportionate to the age of the disease diagnosis (Figs. 6 and 7).

Among the studied group, there was no statistical significance value between the measured ESR, CRP and the T2 relaxation time.

There was a statistically significant difference (P value 0.002) as regards the treatment regimen; patients on biological treatment were found to have the lowest mean T2* (with no statistical significant difference of neither the type nor the duration of treatment of biological treatment), while patients on non-steroidal anti-inflammatory drugs (NSAIDs) showing the highest T2* value (Fig. 8).

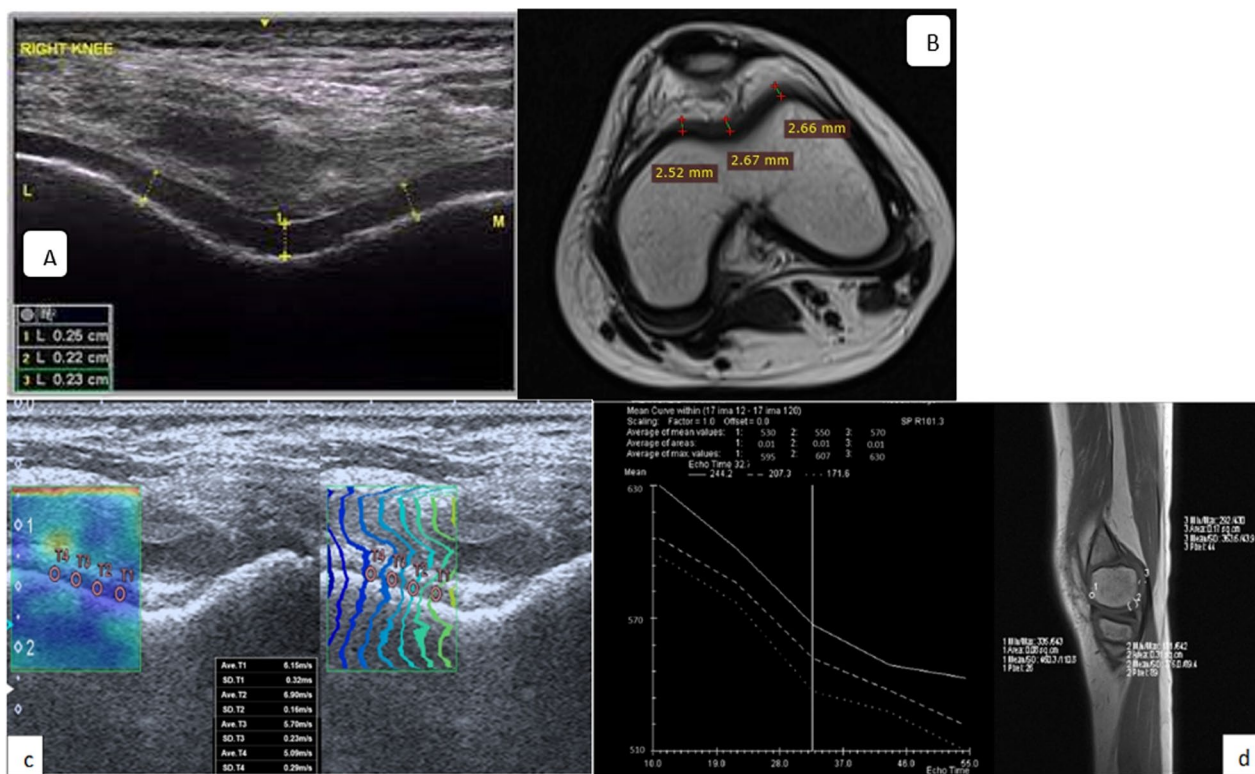


Fig. 2 A 16.5-year-old female patient diagnosed with oligo-articular JIA; since the age of 11, presenting at time of examination by left knee pain, the patient was on Apetoid and NSAIDs. **a & b** Cartilage measurement by US and conventional MRI, **c** Shear wave elastography measurement (average 6.15 m/sec), and **d** T2 mapping sequence (average T2 relaxation time 55 m/sec)

Table 1 Laboratory parameters in cases and control groups

	Study group					Control group					p value
	Mean	SD	Median	Min	Max	Mean	SD	Median	Min	Max	
TLC	9.05	2.3	8.5	5.5	13.5	8.9	1.5	8.5	6.2	10.9	>0.05
Hb	11.9	2.6	11.5	9.8	13.1	12.2	2.3	11.7	11.3	14.2	>0.05
Platelets	263	1.62	245	203	580	235	0.9	207	185	407	>0.05
ESR mm/h	52	37.5	41.2	7	111	10.4	7.3	8.6	2	22.8	<0.001
CRP mg/dl	9.54	6.6	6	2.5	21.58	2.5	0.87	2.1	0.4	4.6	<0.001
ALT	49	2.7	43	14	112	41	0.8	38	10	45	>0.05
AST	35	1.2	32.5	15	145	26	1.7	19.2	8	32	>0.05

Discussion

The most common chronic rheumatic disease in childhood is JIA. Disease onset before the age of 16 years and inflammation persisting for longer than 6 weeks are required criteria for diagnosis of JIA [10].

Qualitative imaging modalities for diagnosing JIA provide comprehensive information regarding synovial thickening, joint effusion as well as gross structural bone damage and periarticular soft tissue affection; this

is traditionally delivered by gray-scale US and conventional MRI imaging with additive value of Doppler US in vascularity assessment and post-contrast MRI in acute inflammation [11].

In order to introduce disease modifying therapeutic agents knowing their long term side effects warrants early detection of cartilage damage before being evident by conventional imaging and hence evolved the idea of a quantitative assessment of early changes in cartilage composition and elasticity.

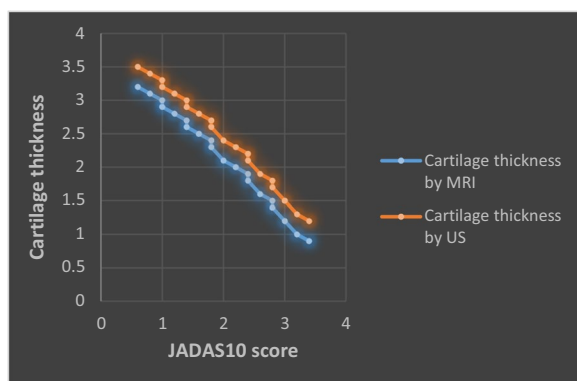


Fig. 3 Correlation between disease activity score and the measured cartilage thickness

Table 2 P values for US vs MRI average cartilage thickness in different disease activity

	Average cartilage thickness in low disease activity	Average cartilage thickness in moderate disease activity	Average cartilage thickness in high disease activity
US	0.67	0.6	0.52
MRI	0.62	0.58	0.012

Table 3 Comparative distal femoral cartilage SWV value between the study and the control groups

	Study group		Control group		P-Value
	Mean SWV value +_SD	Range	Mean SWV value +_SD	Range	
Medial condyle cartilage	6.78+_1.57	3.97–9.94	6.05+_1.34	3.61–9.06	0.0212
Intercondylar cartilage	8.14+_1.01	6.04–9.93	7.77+_1.03	5.48–9.91	0.02103
Lateral condyle cartilage	7.09+_1.48	4.07–9.93	6.67+_1.44	3.95–9.61	0.0185

Table 4 P values for SWE vs T2* in different disease activity

	low disease activity	moderate disease activity	High disease activity
SWV	0.59	0.012	0.023
T2*	0.0035	0.0023	0.0023

The study included forty subjects; twenty patients diagnosed by JIA presented with knee affection at time of study, and age matched 20 children with mean age 14.5years, most of the study group were poly-articular (70%) and only 30% were oligo-articular, in contrast to previous investigators [12] who postulated that the most prevalent subtype in Africa and Middle East is

oligo-articular JIA subtype, followed by poly-articular RF negative, and systemic subtype.

There was significant difference between the cases and the control group as regard ESR and CRP, and this biomarker panel is indicative of active synovitis [13] as for the treatment regimen at the time of the study; patients on biological treatment were found to have the lowest mean T2*, while patients on NSAIDs showed the highest T2* value. On the other hand among patients on biological treatment, T2 relaxation time showed no statistical significant difference between the used treatments. The emergence of biological treatment that targeted the pro-inflammatory cytokines presented a revolution in JIA treatment significantly improving patient’s functionality and stabilizing disease sequel.

To our knowledge, this study is the first to apply SWE on cartilage of JIA patients. The need to add this technique to our investigation was based on the postulation that non-disease-related normal cartilage maturation could possibly alter cartilage T2 relaxation time which is on the other hand should not alter its elasticity. We measured the mean SWE speed values in 20 healthy children at the different sites of the knee joint (the medial condyle cartilage, the intercondylar cartilage and the lateral condyle cartilage) which when compared to SWE speed values in JIA patients were significantly higher in children with JIA compared to healthy

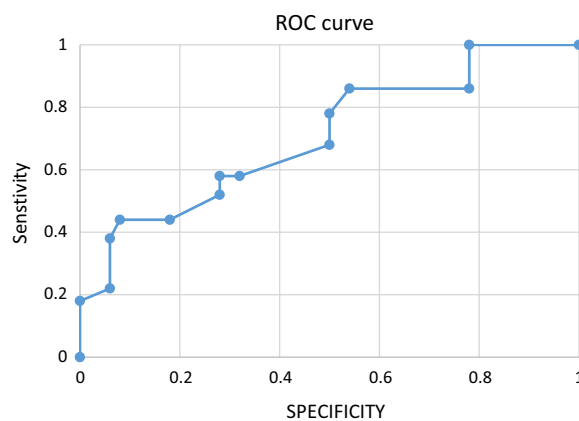


Fig. 4 Roc curve for the diagnostic performance of SWE

Table 5 Comparative distal femoral cartilage T2 relaxation time between the study and the control groups

	Study group		Control group		P-Value
	Mean T2*+_SD	Range	Mean T2*+_SD	Range	
Medial condyle cartilage	55+_7.1	40: 65	39.6±3.7 ms	29-47ms	0.0023
Intercondylar cartilage	53.9+_6.2	41: 63	33.5±3.3 ms	31–39 ms	0.0032
Lateral condyle cartilage	51.5+_8.3	39: 60	42.1±2.3 ms	30–44 ms	0.0027

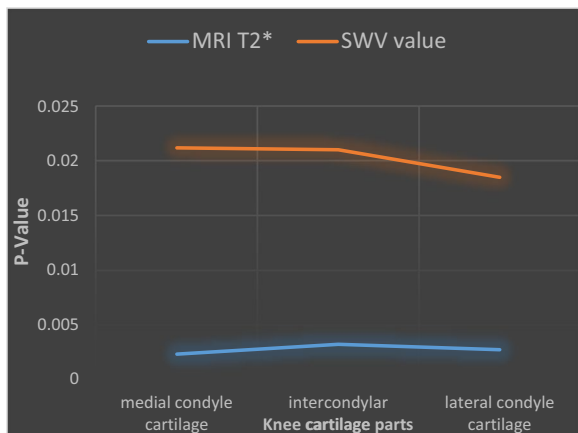


Fig. 5 P value for shear wave velocity Versus MRI T2 relaxation time in detection of cartilage affection between the control and the study group

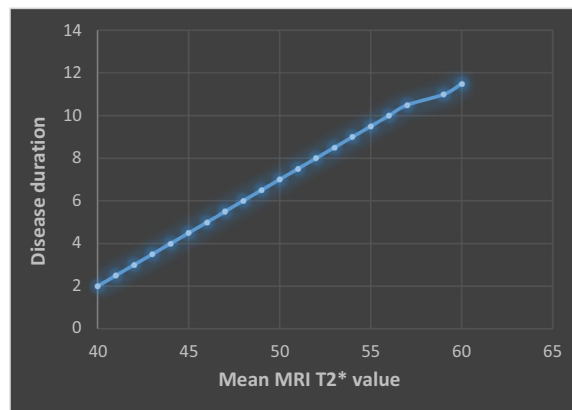


Fig. 7 Correlation between MRI T2 mapping and the disease duration

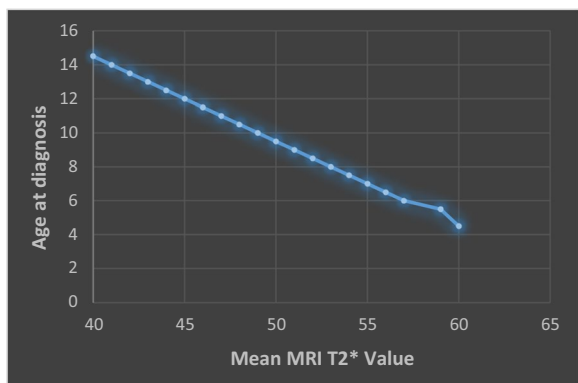


Fig. 6 Correlation between MRI T2 mapping and the age at diagnosis

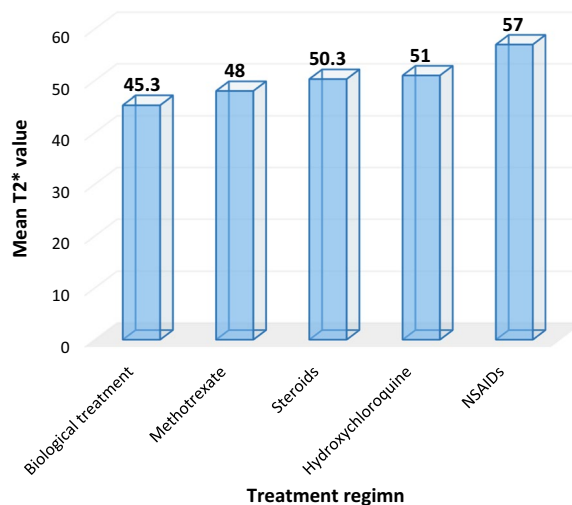


Fig. 8 Correlation between MRI T2 mapping and the used treatment regimen

controls. This reflects changes in viscoelastic cartilage properties and could be used as a quantitative tool to measure degree of stiffness as a result of active inflammation. In the present study, SWE showed statistical significant values in moderate and high disease activity but not in low disease activity. We preferred SWE to tissue elasticity, in agreement with a study concluding that shear wave-based techniques have strong advantages over quasi-static techniques, as they are

more reproducible, quantitative, rely on automatic shear wave generation and provide good elasticity contrast [14]. The same study was the reason we applied SWV in m/sec instead of tissue elasticity in kilopascals as they observed that the musculoskeletal system presents a challenge when calculating tissue elasticity using the Young modulus; owing to its heterogeneous

and anisotropic tissue, consequently they concluded that SWE measurements in the musculoskeletal system should be presented (m/sec), rather than (kPa). We found that the best cutoff values for detection of cases using shear wave elastography velocity ratio (m/sec) are about 4.445 with significant p value=0.02, sensitivity 59.3% and specificity=70.45%.

In the present study, the average T2 relaxation time values for the distal femoral cartilage in JIA were significantly higher than in healthy controls with this increase in T2 relaxation time reflecting increase in water content and water permeability and in turn inflammatory response of cartilage. Other investigators when studying relatively similar group of patients (21 healthy girls and 18 girls with JIA) reached similar results showing that MRI T2 relaxation time correlates closely with active inflammation [15]. MRI T2 relaxation time values were significant in all disease activities (Low, moderate and high scores) directly proportionate to the disease duration which was to be expected in any longitudinal study [16].

Upon comparing the T2 relaxation time values we obtained in healthy controls with that of a study performed on early osteoarthritis knee cartilage in adult population [17] their results were around 43.37 m/s being relatively higher than ours (mean values: at medial femoral condyle 39.6 ± 3.7 ms, at intercondylar notch at 33.5 ± 3.3 ms, and at the lateral femoral condyle 42.1 ± 2.3 ms).

This study was limited in several aspects, the limited number of patients is one of them, also the SWE examination motion artifacts rather prolonged the examination time with multiple exam repetitions to obtain an optimum image, lastly lacking correlation of findings with arthroscopic examination.

We believe that further studies are needed to evaluate the relationship of sono-elastographic and T2 mapping findings with cartilage damage in a larger sample size with longitudinal assessment and correlating these findings with arthroscopy in addition to clinical and laboratory data.

Conclusions

SWE and T2 mapping are reliable quantitative imaging tools in the assessment of hyaline cartilage integrity detecting early affection before changes are visible on routine imaging. MRI T2 mapping has a short acquisition time with no need for contrast agent administration rendering it a feasible addition to routine MRI knee protocol sequences.

Abbreviations

JIA	Juvenile idiopathic arthritis
VAS	Visual analog scale

JADAS	Juvenile arthritis disease activity score
ESR	Erythrocyte sedimentation rate
US	Ultrasound
MRI	Magnetic resonance imaging
ROI	Region of interest
SWE	Shear wave elastography
SWV	Shear wave velocity
VTIQ	Virtual touch tissue imaging quantification
CBC	Complete blood picture
CRP	C-reactive protein (CRP)
NSAIDS	Non-steroidal anti-inflammatory drugs

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Author contributions

HM is the guarantor of integrity of the entire study. WA, HE and MH contributed to the study concepts and design. WA, HS, and MH contributed to the literature research. HS, WA, and HM contributed to the clinical studies. All authors contributed to the experimental studies/data analysis. MH contributed to the statistical analysis. MH contributed to the manuscript preparation. MH and WA contributed to the manuscript editing. All authors have read and approved the final manuscript.

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Availability of data and materials

The corresponding author is responsible for sending the used data and materials upon request.

Declarations

Ethics approval and consent to participate

The study was approved by the ethical committee of the Radiology Department of Kasr-Al-Ainy Hospital, Cairo University which is an academic governmental supported highly specialized multidisciplinary Hospital. The included patients gave written informed consent.

Consent for publication

All patients included in this research were legible, above 16 years of age. They gave written informed consent to publish the data contained within this study.

Competing interests

The authors declare that they have no competing interests.

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