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ORIGINAL RESEARCH

Correlation Between T1 Rho Value of Magnetic Resonance and Clinical Characteristics of Patients with Knee Osteoarthritis and Analysis of Related Factors of T1 Rho Value

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Purpose: To investigate the correlation between magnetic resonance spin-lattice relaxation time (T1 rho) value and clinical characteristics of patients with knee osteoarthritis, and to analyze the related factors of T1 rho value.

Methods: This study was a cross-sectional study. Sixty patients with knee osteoarthritis diagnosed and treated in our hospital from October 2020 to March 2022 were selected as the arthritis group. Sixty patients with non-knee osteoarthritis detected in our hospital during the same period were selected as non-arthritis group. The clinical data of the subjects were collected and all of them were examined by magnetic resonance imaging (MRI). The mixed-effects model was used to control the correlation of multiple compartments in the knee joint, and the nonlinear relationship of T1 rho value (continuous variable) was treated by restricted cubic spline function. The relationship between T1 rho value and clinical characteristics was analyzed by mixed-effects linear regression, and the relationship between T1 rho value and WORMS score and ICRS grade was analyzed by mixed-effects ordinal logistic regression. The multiple comparisons were corrected by Holm-Bonferroni method.

Results: Compared with the non-arthritis group, the arthritis group had significantly higher T1 rho values on magnetic resonance imaging of the patella, femur, and tibia ($P < 0.05$). Mixed-effects linear regression showed that proteoglycans < 41% ($\beta = 5.82$, 95% CI: 3.76–7.88, Padj < 0.001), disordered collagen fiber arrangement ($\beta = 4.93$, 95% CI: 2.89–6.97, Padj < 0.001), overloading exercise ($\beta = 6.17$, 95% CI: 3.52–8.82, Padj < 0.001), and femoral septum (vs patella, $\beta = 2.31$, 95% CI: 0.98–3.64, Padj = 0.002) were significantly correlated with increased T1 rho values. Mixed-effects ordinal logistic regression showed that for every 1ms increase in T1 rho value, the OR for upgrading WORMS score was 1.18 (95% CI: 1.03–1.35, Padj = 0.021), and the OR for upgrading ICRS grading was 1.23 (95% CI: 1.05–1.44, Padj = 0.015). Moreover, the correlation strength of T1 rho values was higher in patients with WORMS ≥ II and ICRS ≥ II (all Padj < 0.001). Multivariate mixed-effects linear regression confirmed that proteoglycans < 41%, disordered collagen fiber arrangement, overload exercise, increased WORMS score, increased ICRS grading, age increase (every 10 years, $\beta = 0.82$, 95% CI: 0.21–1.43, Padj = 0.019), and BMI ≥ 24 kg/m ^{2} ($\beta = 0.95$, 95% CI: 0.18–1.72, Padj = 0.027) were all independent correlated factors with T1 rho values.

Conclusion: This cross-sectional study showed that the higher T1 rho value was significantly related to the lower proteoglycan content (< 41%), disordered collagen fiber arrangement, self-reported overload exercise history and higher WORMS and ICRS scores, which can provide a basis for understanding the pathophysiological background reflected by T1 rho value.

Keywords: magnetic resonance T1 rho value, knee osteoarthritis, clinical characteristics, related factors

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Introduction

Knee osteoarthritis is a chronic disease affecting the joint and its surrounding tissues, which can cause progressive damage to articular cartilage, subchondral bone and surrounding synovial structures. According to statistics, the incidence of knee osteoarthritis is more than 10% in adults over 60 years, and it is one of the main causes of disability in patients. It not only brings a health burden to patients, but also has a heavy impact on the healthcare system.[1,2] Early diagnosis and treatment may play an important role in reducing the rate of disability.

Medical imaging plays an important role in exploring the pathogenesis of knee osteoarthritis and causing disease-related structural damage. X-ray, magnetic resonance imaging (MRI) and ultrasound are commonly used clinical detection methods. However, ultrasound detection is easily affected by factors such as examination Angle and operator, while X-ray or CT has high radiation, and has poor diagnostic effect on menisci, ligaments or arthritis caused by soft tissues.[3,4] MRI is a non-invasive detection technology, which can be repeated many times in a short time, and has the advantages of high soft tissue resolution, multi-parameter and small diagnostic error.[5] Spin-lattice relaxation time (T1 rho) is highly sensitive to proteoglycan macromolecular movement of articular cartilage extracellular matrix, which can identify knee joint changes earlier.[6] The previous study has found that magnetic resonance T1 rho plays an important role in differentiating early from advanced knee osteoarthritis.[7]

T1 rho imaging is based on the principle of spin locking, which quantifies the interactions between slow-moving biological macromolecules (such as proteoglycans and collagen) and water molecules, reflecting the biochemical composition and structural integrity of the cartilage matrix. This technique is highly sensitive to proteoglycan content and collagen fiber arrangement, and still maintains a good signal-to-noise ratio even under the magic-angle effect. Therefore, it has unique advantages in the early detection of cartilage degeneration.[8,9] Previous studies have shown that the T1 rho value significantly increases in the early stage of osteoarthritis, and its threshold exhibits good diagnostic performance in distinguishing between early and late stage lesions.[10] Based on this, this study proposed the following hypothesis: the T1 rho value is significantly correlated with the cartilage structure scores (such as WORMS and ICRS), histological features (proteoglycans and collagen arrangement) and exercise load of patients with knee osteoarthritis. It is expected that the association between the T1 rho value and the above clinical and imaging indicators can be clarified through cross-sectional analysis, providing quantitative basis for the early diagnosis of knee osteoarthritis.

Materials and Methods

Research Subjects and Design

This study was a cross-sectional study. Sixty patients with knee osteoarthritis diagnosed and treated in our hospital from October 2020 to March 2022 were selected as the arthritis group. This research design is suitable for exploring the correlation between variables, but cannot be used to infer causal relationships. Patients with knee osteoarthritis were included in the flow (Figure 1). Inclusion criteria: (1) The patient met the relevant diagnosis and treatment criteria of knee osteoarthritis,[11] and was diagnosed by X-ray examination; (2) The patient had imaging features such as narrowing of the joint space and subchondral bone hardness, and the patient had recurrent knee pain within 4 weeks; (3) All patients had complete clinical and imaging data. Exclusion criteria: (1) Patients with cardiac insufficiency or hepatic and renal insufficiency; (2) Patients with previous history of knee disease or surgery; (3) Patients who had a history of using systemic corticosteroids, analgesics and anti-inflammatory drugs within 4 weeks before participating in the study; (4) Patients with rheumatoid arthritis, psoriatic arthritis and other diseases. Sixty patients with non-knee osteoarthritis who were tested in our hospital during the same period were selected as the non-arthritis group. Inclusion criteria: (1) No knee joint pain, swelling or other symptoms in the past 4 weeks (confirmed by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score of less than 10, excluding subclinical lesions); (2) No signs of osteoarthritis on X-ray and magnetic resonance imaging, such as knee cartilage injury and narrowed joint space. Exclusion criteria: (1) Cardiac dysfunction or liver and kidney dysfunction; (2) History of knee joint disease or surgery in the past; (3) History of using systemic corticosteroids, analgesics, and anti-inflammatory drugs within 4 weeks prior to participating in the study; (4) Complicated with diseases such as rheumatoid arthritis and psoriatic arthritis.

Sample size justification: To scientifically estimate the sample size, we conducted a priori sample size calculation using the G*Power software (version 3.1) based on the main purpose of this study (comparing the differences in T1 rho values between the arthritis group and the non-arthritis group).

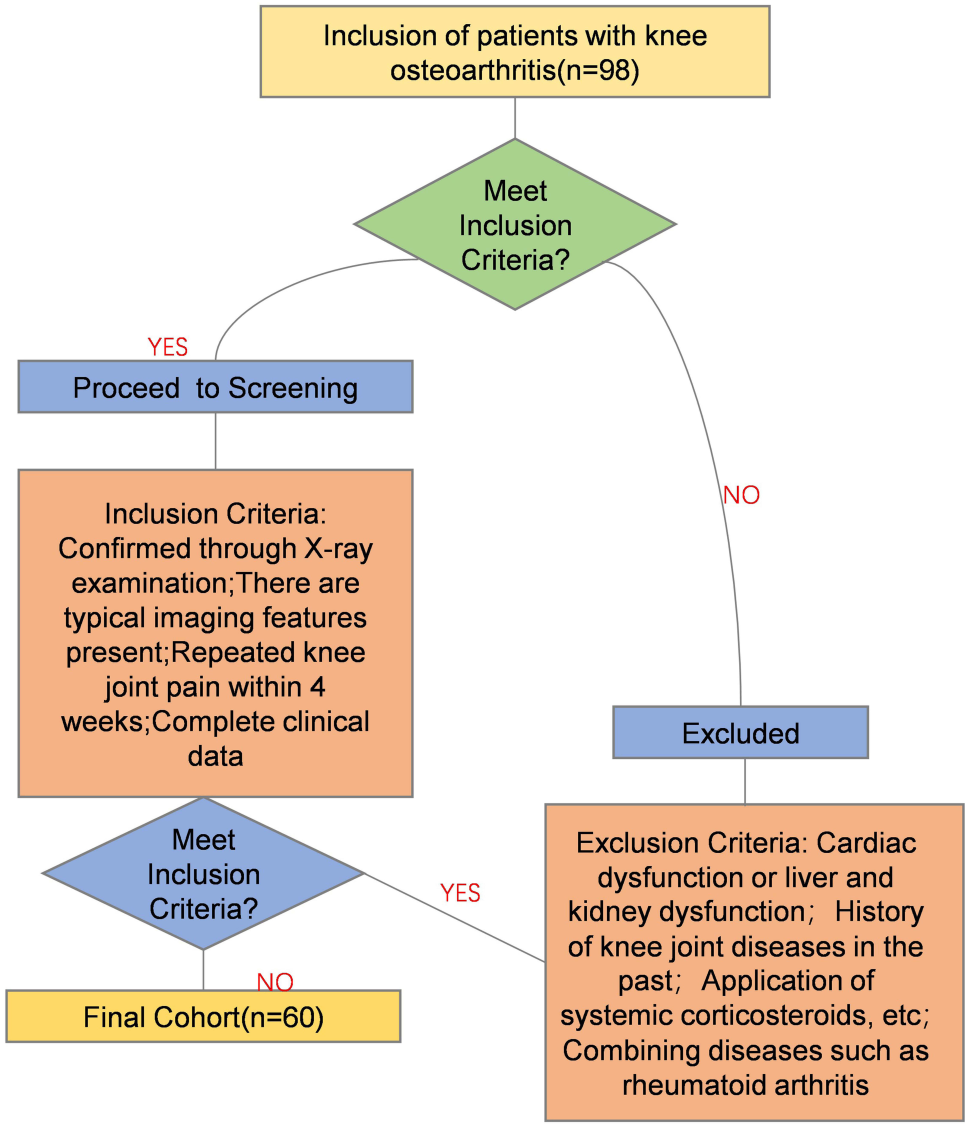

Figure 1 Flow chart for inclusion of patients with knee osteoarthritis.

Calculation basis and parameters: The calculation is based on the data (T1 rho values of the medial femoral condyle in osteoarthritis patients and the healthy control group) reported in a prior study that is highly similar to the design of this research.[10] Based on this, the effect size (Cohen's d) was calculated to be 0.74 (belonging to a moderately large effect). The parameters set were: $\alpha = 0.05$ (two-tailed), statistical power $(1 - \beta) = 0.90$.

Calculation result: Using the two independent samples *t*-test model, it was calculated that the minimum sample size required for each group is 38 cases.

Final setting: Considering the possibility of data loss and reserving sufficient validity for multi-factor analysis, this study set the sample size for each group to 60 cases, which is significantly higher than the estimated minimum requirement, ensuring that the study has sufficient statistical power.

Clinical Data Collection

The collection of the clinical data contained: (1) Data were collected from the two groups; (2) Data were collected only in the arthritis group.

Data were collected from the two groups including gender (female, male), age (≤60 years old, > 60 years old), body mass index (BMI) (< 24 kg/m^2, ≥24 kg/m^2), smoking history and drinking history.

Data were collected only in the arthritis group including Lesion location (left and right), proteoglycan (< 41%, ≥41%), collagen fibers (normal arrangement, disordered arrangement), and overloaded exercise. For proteoglycan, the cartilage tissue of the wear site collected during the surgical treatment was washed, placed in formalin solution, and decalcified. After paraffin section, the proteoglycan content was observed by Alcian blue staining. For collagen fibers, cartilage tissue was taken, collagen fibers were labeled with specific antibodies, and the arrangement and type of collagen fibers were observed by microscope. For overloaded exercise, the exercise habits of the patients over the past 6 months were evaluated using a standardized questionnaire designed by the researchers. The questionnaire included exercise type, frequency (times/week), duration (minutes/time), and intensity (subjective feelings, such as mild, moderate, or intense). Overloaded exercise was operationalized as meeting any of the following conditions: (1) engaging in high-intensity weight-bearing exercises (such as running, jumping, squatting, and weight-lifting stair climbing) ≥ 3 times per week, with each session lasting ≥ 30 minutes; (2) the patient reported recurrent or aggravated knee joint pain due to exercise, resulting in a reduction or cessation of exercise. All questionnaires were completed by researchers who had undergone unified training through face-to-face interviews to reduce recall bias.

Histological samples and blinded assessment: The histological analysis of proteoglycans and collagen fibers was only applicable to the subgroup of patients with arthritis who underwent knee joint surgery (such as arthroscopy, chondroplasty, or knee replacement surgery). The cartilage tissue samples obtained during surgery should be immediately processed and stained according to the aforementioned methods. The assessment of all histological sections was independently completed by two pathologists who were unaware of the patients' clinical data including group assignment, imaging results, and T1 rho values. If the assessment results were inconsistent, consensus was reached through joint review and discussion.

MRI

Sagittal T1 rho was measured using a 3.0t MRI diagnostic instrument (Philips Medical Devices, model: ingenia) and GE MEDICAL SYSTEMS, Discovery,750w 3.0T. The patient was placed in the supine position with the legs straight and naturally separated. Knee fixation bands were used to maintain the knee joint in a neutral position. And patients were required to remain still during the scanning process, and received training on breathing coordination and postural stillness before the scan. All images are immediately inspected by technicians after acquisition. If obvious motion artifacts were detected, the sequence is scanned repeatedly to ensure image quality. Metal accessories and clothing were removed to ensure that the scanning area was free of interference. Scanning parameters: Sequence: a multi-echo spin-lock sequence using spin-lock preparation pulse combined with rapid gradient echo readout. Slice thickness: 3 mm, slice spacing: 1.5 mm, FOV: 180×180 mm, matrix: 256×256, bandwidth: 400 Hz/pixel, and planar resolution: 0.70×0.70 mm^2. The spin-lock time (Tau) was 0, 10, 30, and 50 ms, the spin-lock frequency was 500 Hz, the repetition time (TR) was 80 ms, the echo time (TE) was 4 ms, the excitation number was 1, and fat suppression was achieved using the frequency attenuation inversion recovery (SPAIR) technique. Before scanning, automatic B0 field homogenization was performed.

Image processing and T1ρ value calculation: Image evaluation was performed by at least two radiologists who were unaware of the clinical groupings (blind to the clinical groups). A unified window/level setting T1 rho pseudo-color image was generated using GEADW4.6 software (Figure 2). The color bars of the pseudo-color image were in milliseconds (ms), and the same display range (eg, 0–80 ms) was used for all subjects' images to ensure visual comparability. Regions of interest (ROI) were delineated as follows: Based on the articular cartilage adjacent to the center of the posterior horn of the meniscus, the patella was divided into medial regions, middle regions, and lateral regions along the central axis. The femur and tibia were divided into medial and lateral regions along the long axis, respectively, with a total of 7 ROIs (3 patella, 2 femur, and 2 tibia). On the pseudo-color images used for display, the positions of the representative ROI should be clearly outlined (as shown in Figures 2C and D). Quantitative measurement: An oval area of 20–30 pixels was manually delineated in each ROI, avoiding subchondral bone and synovial tissue. The signal intensity values at each time point (Tau=0, 10, 30, and 50ms) were measured, and the T1ρ values were calculated by the formula:

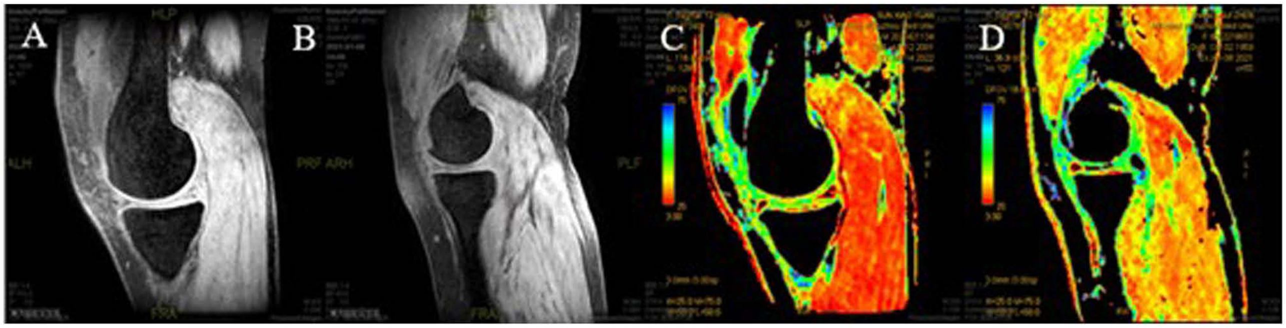

Figure 2 T1 rho diagram of knee cartilage. (**A**) T1 rho map of normal cartilage. (**B**) T1 rho plot in a patient with knee osteoarthritis. (**C**) T1 rho pseudo-color map of normal cartilage. It showed a uniform color bar (unit: ms) and the ROI of the lateral area of the patella (the white ellipse). (**D**) T1 rho pseudo-color map of patients with knee osteoarthritis. It showed a uniform color bar (unit: ms) and ROI of the medial femur region (white ellipse). All images were displayed using the same window settings.

$$T1\rho = \frac{1}{\text{slope}} \times \ln\frac{S0}{S}$$

Here, *S*0 was the signal intensity at Tau=0ms, *S* was the signal intensity at other time points, and slope was the slope of the linear fit. The signal attenuation curve was fitted using the linear least squares method, and only data points with a goodness of fit (R^2)>0.95 were retained to ensure the accuracy of the calculation. Data processing: Each ROI was measured three times, and the average value was used as the T1ρ value of the region. Finally, the average value of each region of patella, femur, and tibia was used for statistical analysis.

Measurement reliability analysis: To evaluate the repeatability of manually delineating ROIs, 20 subjects (a total of 140 ROIs) were randomly selected, and re-delineated and measured by the two aforementioned physicians one month later. The reliability was evaluated using the intra-class correlation coefficient (ICC), and the results showed that both intra-group and inter-group consistency were excellent (intra-group ICC = 0.92, inter-group ICC = 0.88).

Western Ontario and McMaster University Osteoarthritis Index (WOMAC) Score[12]

This score included a total of 24 items with 3 dimensions. Pain (5 items, total score 20): Pain intensity was assessed at rest, during movement, and at night, such as “pain degree during sleep at night”. Each item was scored from 0 to 4 (0 = none, 4 = extreme pain). Stiffness (2 items, total score 8 points): morning stiffness and stiffness during daily activities, such as “duration of joint stiffness after morning awakening”, were measured. Each item was scored from 0 to 4 (0 = none, 4 = > 60 minutes or severe stiffness). Physical function (17 items, total score 68): It covered the difficulty of daily activities such as dressing, walking, and going up and down stairs, such as “difficulty of bending down to pick up objects”. Each item was scored from 0 to 4 (0 = no difficulty, 4 = unable to complete). The total score ranged from 0 to 96 points. Higher scores indicated more severe joint dysfunction (usually < 20 as mild, 20–40 as moderate, and > 40 as severe). The internal consistency was good, Cronbach’s α coefficient was 0.85–0.95, and the test-retest reliability was 0.88–0.92.

Total Knee Joint Magnetic Resonance Imaging Score (WORMS)[13]

This score included cartilage injury, bone marrow edema, meniscus injury and ligament injury. Each score ranged from 0 to 3. 0 indicated normal, and the ranges of lesions of grade 1, 2 and 3 were < 25%, 25–50% and > 50%, respectively. The intra-class correlation coefficients of cartilage and meniscus scores were 0.75–0.90, and the ICC of bone marrow lesions was 0.65–0.85.

International Articular Cartilage Repair Society (ICRS) Classification[14]

This classification classified the cartilage injury into 0 to IV grades. Grade 0 indicated normal and healthy cartilage. Grade I indicated superficial and blunt chippings or cracking. Grade II indicated the degree of damage was less than 50% of the cartilage thickness. Grade III indicated the degree of damage ranges from 50% of the cartilage thickness to more than the subchondral bone. Grade IV indicated the full-thickness cartilage tear and subchondral bone exposure.

Statistical Methods

Descriptive statistics: The measurement data conformed to a normal distribution after normality testing, presented as ($x \pm s$), the count data were expressed as cases (%); ordinal data (WORMS score, ICRS grade) were expressed as median (interquartile range) [M (Q1, Q3)].

Inter-group comparison: The comparison of T1 rho values between the arthritis group and the non-arthritis group was conducted using a mixed-effect model (random effects for subjects and fixed effects for compartments). The correlation within individuals was controlled. No median grouping was required. The T1 rho values were analyzed as continuous variables throughout the entire process, and the restricted cubic spline function (with 3 nodes) was used to handle potential nonlinear relationships.

Correlation and relevant factor analysis: The association between the T1 rho value and clinical characteristics (proteoglycans, collagen fibers, overloaded exercise) was analyzed using a mixed-effect linear regression model (dependent variable: T1 rho value; independent variables: clinical characteristics + age + gender + BMI; random effect: subjects; fixed effect: compartments). The association between the T1 rho value and ordinal outcomes (WORMS score, ICRS grade) was analyzed using a mixed-effect ordinal logistic regression model (dependent variable: WORMS score/ ICRS grade; independent variables: T1 rho value + age + gender + BMI; random effect: subjects).

Multivariate control: All statistical tests were corrected for multiple comparisons using Holm-Bonferroni method, and the adjusted P-value (Padj) was reported. The 95% confidence intervals (95% CI) for quantitative data are calculated based on the corrected standard errors.

Software: Statistical analysis was conducted using SAS 25.0 software. A difference was considered statistically significant when P < 0.05 (after correction).

Results

Analysis of the Baseline Data of the Two Groups

There was no significant difference in gender, age, BMI, smoking history and drinking history between the arthritis group and the non-arthritis group (P > 0.05, Table 1).

Table 1 Analysis of the Baseline Data of the Two Groups [Case (%)]

Group	The Arthritis Group (n=60)	The Non-Arthritis Group (n=60)	χ^2/Z	P
Gender			0.134	0.714
Female	31 (51.67)	33 (55.00)		
Male	29 (48.33)	27 (45.00)		
Age (Year)			0.534	0.465
≤60	29 (48.33)	33 (55.00)		
>60	31 (51.67)	27 (45.00)		
BMI (kg/m^2)			0.409	0.522
<24	44 (73.33)	47 (78.33)		
≥24	16 (26.67)	13 (21.67)		
Smoking history			0.134	0.714
Yes	33 (55.00)	31 (51.67)		
No	27 (45.00)	29 (48.33)		
Drinking history			0.137	0.711
Yes	36 (60.00)	34 (56.67)		
No	24 (40.00)	26 (43.33)		
WORMS score [M (Q1, Q3)]	2.0 (1.0, 3.0)	0.0 (0.0, 1.0)	5.283	<0.001
ICRS grade [M (Q1, Q3)]	2.0 (1.0, 3.0)	0.0 (0.0, 0.0)	5.917	<0.001

Notes: The χ^2 test value represents the statistical measure of the chi-square test; the Z value is the statistical measure obtained from the Mann–Whitney *U*-test.

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Analysis of Magnetic Resonance T1 Rho Values in Patients with Knee Osteoarthritis

Compared with the non-arthritis group, the T1 rho values of patella, femur and tibia in the arthritis group were significantly increased (P<0.05, Table 2).

The Correlation Between T1 Rho Values and Clinical Characteristics

The results of the mixed-effects linear regression analysis (controlling for age, gender, and BMI) indicated that there were significant associations between clinical characteristics and T1 rho values (all Padj < 0.05). Among them, patients with proteoglycan < 41% had an average increase of 5.82 ms in T1 rho value compared to those with proteoglycans ≥ 41% (95% CI: 3.76–7.88, Padj < 0.001, Table 3). The T1 rho value in patients with disordered collagen fiber arrangement was on average 4.93 ms higher than that in patients with normal arrangement (95% CI: 2.89–6.97, Padj < 0.001, Table 3). Individuals with a history of overloaded exercise had an average increase of 6.17 ms in T1 rho values compared to those without a history of overloaded exercise (95% CI: 3.52–8.82, Padj < 0.001, Table 3). From the perspective of compartment differences, the T1 rho value of the femoral compartment increased by an average of 2.31 ms (95% CI: 0.98–3.64, Padj = 0.002, Table 3) compared to the patellar compartment, while the T1 rho value of the tibial compartment decreased by an average of 1.85 ms (95% CI: −3.12~-0.58, Padj = 0.008, Table 3) compared to the patellar compartment.

The Correlation Between T1 Rho Value and WORMS Score and ICRS Grade

The results of the mixed-effects ordinal logistic regression analysis showed that an increase in the T1 rho value was significantly correlated with the WORMS score and the upgrade of ICRS grade (Padj < 0.05, Table 4). This suggested that the T1 rho value was positively correlated with the degree of cartilage structural damage, and the more severe the damage, the stronger the correlation.

Independent Correlation Factors of T1 Rho Value in Patients with Knee Osteoarthritis

The results of the multivariate mixed-effects linear regression analysis showed that, after controlling for potential confounding factors, proteoglycan < 41%, disordered collagen fiber arrangement, overloaded exercise, WORMS score increasing by 1 level, ICRS grade increasing by 1 level, age increasing by 10 years, and BMI ≥ 24 kg/m^2 were all independent related factors of T1 rho value (all Padj < 0.05, Table 5). Among them, the influence intensity of ICRS grade on T1 rho value was the greatest, followed by overloaded exercise and proteoglycan (Table 5).

Table 2 Analysis of Magnetic Resonance T1 Rho Values in Patients with Knee Osteoarthritis (Linear Mixed-Effects Model Analysis)

Group	The Arthritis Group (n=60)	The Non-Arthritis Group (n=60)	t	P	Mixed-Effects Model Coefficient (β)	95% CI	Padj
Patella							
Medial regions	50.63±4.13	46.72±2.10	6.537	<0.001	3.91	2.85–4.97	<0.001
Middle regions	51.52±5.19	45.36±2.51	8.236	<0.001	6.16	4.89–7.43	<0.001
Lateral regions	50.29±4.37	46.40±2.30	6.102	<0.001	3.89	2.76–5.02	<0.001
Femur							
Medial regions	55.64±5.22	46.29±2.60	12.419	<0.001	9.35	7.98–10.72	<0.001
Lateral regions	53.60±7.35	47.26±2.05	6.436	<0.001	6.34	4.71–7.97	<0.001
Tibia							
Medial regions	44.72±4.05	37.25±3.92	10.266	<0.001	7.47	6.01–8.93	<0.001
Lateral regions	49.15±5.68	39.72±4.39	10.175	<0.001	9.43	7.85–11.01	<0.001

Notes: (x ± s) represents mean ± standard deviation. The t-value is the statistical measure of the *t*-test. β is the regression coefficient of the mixed effects linear regression model, representing the estimated difference between groups. CI is the confidence interval. Padj is the P-value corrected by Holm Bonferroni method.

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Table 3 Mixed-Effects Linear Regression Analysis of T1 Rho Values and Clinical Characteristics (Controlling for Age, Gender, and BMI)

Clinical Characteristics	β	95% CI	Padj
Proteoglycan <41% (vs ≥41%)	5.82	3.76–7.88	< 0.001
Collagen fiber disarrangement (vs normal)	4.93	2.89–6.97	< 0.001
Overloaded exercise (vs none)	6.17	3.52–8.82	< 0.001
Compartment (femur vs patella)	2.31	0.98–3.64	0.002
Compartment (tibia vs patella)	−1.85	−3.12~-0.58	0.008

Notes: β represents the regression coefficient of the mixed-effects linear regression model, indicating the change in T1 rho value when the independent variable increases by one unit (compared to the reference group). CI is the confidence interval. Padj is the P value corrected by the Holm-Bonferroni method.

Table 4 Mixed-Effects Ordinal Logistic Regression Analysis of T1 Rho Value with WORMS Score and ICRS Grade

Outcome Measure	Level (vs Reference Level)	OR (95% CI)	Padj
WORMS score	I level (vs 0 level)	1.18 (1.03–1.35)	0.021
	II level (vs 0 level)	1.42 (1.21–1.67)	< 0.001
	III level (vs 0 level)	1.69 (1.38–2.07)	< 0.001
ICRS grade	I level (vs 0 level)	1.23 (1.05–1.44)	0.015
	II level (vs 0 level)	1.57 (1.31–1.88)	< 0.001
	III level (vs 0 level)	1.82 (1.45–2.28)	< 0.001
	IV level (vs 0 level)	2.15 (1.53–3.02)	< 0.001

Notes: OR represents odds ratio, derived from the mixed-effects ordinal logistic regression model, indicating the odds ratio of the probability that the cartilage injury score increases by one or more levels for every 1 ms increase in the T1 rho value. CI represents confidence interval. Padj is the P value corrected by the Holm-Bonferroni method.

Table 5 Multivariate Mixed-Effects Linear Regression Analysis of Influencing Factors on T1 Rho Values in Patients with Knee Osteoarthritis (Final Model)

Influencing Factors	β	95% CI	Padj
Proteoglycan < 41%	5.69	3.58–7.80	< 0.001
Collagen fiber disarrangement	4.78	2.65–6.91	< 0.001
Overloaded exercise	5.93	3.27–8.59	< 0.001
WORMS score (increase of 1 level)	1.24	0.87–1.61	< 0.001
ICRS grade (increase of 1 level)	1.51	1.13–1.89	< 0.001
Age (increase of 10 years)	0.82	0.21–1.43	0.019
BMI ≥ 24 kg/m^2	0.95	0.18–1.72	0.027

Notes: β represents the regression coefficient of the multivariate mixed-effects linear regression model, indicating the change in T1 rho value when the independent variable increases by one unit (compared to the reference group). CI is the confidence interval. Padj is the P value corrected by the Holm-Bonferroni method.

Correlation Analysis Between T1 Rho Value and WOMAC Score

To explore the relationship between subjective symptoms of patients and biochemical changes in cartilage, Spearman correlation analysis was conducted on the arthritis group (n = 60, Table 6). The results showed that there was no significant correlation between T1 rho value and WOMAC total score (ρ = 0.18, P = 0.173), pain sub-score (ρ = 0.15, P = 0.254), stiffness sub-score (ρ = 0.11, P = 0.402), and physical function sub-score (ρ = 0.16, P = 0.210).

Table 6 Spearman Correlation Analysis of the T1 Rho Value and the WOMAC Score

Analysis Index	Spearman Correlation Coefficient (ρ)	P value
WOMAC total score	0.18	0.173
Pain sub-score	0.15	0.254
Stiffness sub-score	0.11	0.402
Physical function sub-score	0.16	0.210

Notes: ρ represents the Spearman correlation coefficient, and the closer its absolute value is to 1, the stronger the correlation. All analyses were based on the data of the arthritis group (n = 60). P > 0.05 indicates no statistical significance.

Discussion

Knee osteoarthritis is a common progressive musculoskeletal disease. As the main weight-bearing joint, the knee joint is characterized by structural changes in articular cartilage and subchondral bone, as well as structural changes in synovium, ligaments and muscles.[1] However, there are no obvious symptoms in the early stage of knee osteoarthritis, and there is often a lack of methods to evaluate the progress of the disease. In recent years, MRI technology has attracted more and more attention due to its non-invasive, multi-parameter, multi-plane and high-resolution characteristics. As a new MRI technique, T1 rho can detect the interaction between macromolecular substances and water molecules during slow motion and reflect the content and integrity of macromolecules in cartilage such as proteoglycan and collagen.[15] The study has found that T1 rho value of distal cruciate ligament in osteoarthritis patients is significantly increased, and T1 rho value has been widely used in the detection of cartilage, ligament, meniscus and other collagen rich tissues.[16] In this study, the T1 rho values of patella, femur, and tibia in the arthritis group were significantly higher than those in the non-arthritis group, suggesting that the increased T1 rho values were closely related to the pathological process of knee osteoarthritis. This is consistent with the high sensitivity of T1 rho technology to the changes of cartilage matrix macromolecules (such as proteoglycan and collagen), indicating that T1 rho value can be used as a potential quantitative index to reflect the early degeneration of cartilage, and provide imaging basis for clinical identification of subclinical lesions. This study also found that there was no significant correlation between T1 rho value and the WOMAC score, which reflects the subjective symptoms of patients. The possible reason for this may be that T1 rho imaging mainly reflects the early biochemical changes in the level of large molecules of cartilage matrix, while the WOMAC score assesses subjective feelings such as pain, stiffness, and functional limitation. The two represent different dimensions of the disease progression of osteoarthritis. In the early stage of the disease, abnormal biochemical metabolism of cartilage may occur before the clinical symptoms appear.[17] Secondly, subjective symptoms are influenced by various complex factors, such as the patient's pain threshold, psychological state, concurrent synovitis, meniscus injury, and muscle strength, which may weaken the direct correlation between symptoms and specific biochemical states of cartilage.[18] The results of this study suggested that objective imaging biomarkers (such as T1 rho) provide complementary information with subjective outcomes reported by patients, and their combined use may provide a more comprehensive disease assessment for clinical practice. The technical approach adopted in this study aimed to ensure the reliability of T1 rho measurement results. Although T1 rho technology is relatively insensitive to the magic-angle effect, this study still minimized its potential impact by maintaining the neutral position of the knee joint and standardizing the ROI delineation process. Secondly, the automatic B0 field homogenization performed before scanning helps to improve the homogeneity of the main magnetic field, while the use of coils and sequence parameters calibrated by the manufacturer aims to maintain the consistency of the B1 field. These measures are crucial for the accuracy of T1 rho quantification.[19] Finally, we confirmed through rigorous measurement reliability analysis that ROI delineation had excellent intra-group and inter-group consistency (ICC > 0.88), enhancing the reproducibility of quantitative results in this study.

In this study, a mixed-effects model was employed to control the correlation of repeated measurements within the multiple compartments of the knee joint. T1 rho was treated as a continuous variable and analyzed using restricted cubic spline. The results showed that the T1 rho value was linearly associated with the pathological features of knee osteoarthritis (P for non-linearity > 0.28). For every 1 ms increase in T1 rho value, the OR for WORMS score upgrade was 1.18 (95% CI: 1.03–1.35, Padj = 0.021), and the OR for ICRS grade upgrade was 1.23 (95% CI: 1.05–1.44, Padj = 0.015), indicating that T1 rho value can quantitatively reflect the severity of cartilage injury. Its specific mechanism of action is as follows: WORMS and ICRS are important tools for the evaluation of knee osteoarthritis. WORMS grade ≥ II represents reduced cartilage thickness, surface fibrosis, or partial defects. Such structural damage results in significant loss of matrix components (proteoglycan and collagen). T1 rho value reflects the overall degree of matrix destruction. ICRS grade ≥ II indicates cracks or local defects in cartilage, which directly exposes the collagen network, accelerates water diffusion, and prolongs T1 rho relaxation time. A number of studies have found that WORMS and ICRS are significantly related to the severity of knee osteoarthritis. With the aggravation of the disease, inflammatory factors are significantly increased and proteoglycan degradation is significantly accelerated.[20,21]

Multivariate mixed-effects regression analysis (adjusted for age, gender, BMI, and multiple comparisons) confirmed that proteoglycans < 41%, disordered collagen fiber arrangement, overloaded exercise, and the increase of WORMS score and ICRS grade were significantly correlated with increased T1 rho value (all Padj < 0.05). By analyzing the reason, proteoglycan is the main component of cartilage matrix, which maintains the osmotic pressure and compressive resistance of cartilage by fixing water molecules with negative charge.[22] When the proteoglycan content is lower than 41%, the cartilage water retention capacity decreases, resulting in an increase in the proportion of free water in the matrix.[23] T1 rho imaging is highly sensitive to the motion of water molecules, and the increase in the degree of freedom of free water molecules will prolong the T1 rho relaxation time.[8] Animal studies have found that the administration of proteoglycan to rats with osteoarthritis can significantly improve cartilage morphology, inhibit inflammatory response and apoptosis signaling pathway, and play a certain role in relieving osteoarthritis.[24] It has been proposed that compared with healthy subjects, the rho value of magnetic resonance T1 in patients with knee osteoarthritis is significantly increased, which may be affected by the hydroxyl group and amino group of proteoglycan side chain.[25,26] It has been reported that collagen fibers can change in early osteoarthritis through thinning of collagen fibers and formation of fibrocartilagin-like tissue, and collagen fibers can be used as a target for the detection of early osteoarthritis.[27] Type II collagen fibers constitute the reticular scaffold of cartilage, and their regular arrangement is the key to maintaining cartilage elasticity and tensile strength. Disordered collagen arrangement is associated with the disruption of matrix mechanical stability, abnormal local stress distribution, and accelerated cartilage degeneration. After structural destruction, the degree of water molecule diffusion limitation is reduced, which is manifested as an increase in T1 rho value.[28] The decrease of proteoglycan content and the disorder of collagen fiber arrangement may cause swelling and degeneration of articular cartilage, and then affect the change of T1 rho value. Evidence has shown that exercise training can improve pain, stiffness, muscle weakness and joint dysfunction in patients with knee osteoarthritis, but joint overload may lead to cartilage degradation and promote chondrocyte senescence, thereby accelerating the development of the disease.[28,29]

Limitations

This study has certain limitations. Firstly, this study is a single-center and cross-sectional study, and its results require multi-center and longitudinal studies for verification, and causal relationships cannot be inferred. Secondly, although this study attempted to match the control group, the possibility of selection bias still cannot be completely ruled out. At the same time, although the definition of "overloaded exercise" has been standardized, there may still be recall bias and measurement errors. Thirdly, the histological data only come from the subgroup of OA patients who underwent surgery, and there is a validation bias. Fourthly, the acquisition of T1 rho values depends on manual delineation of ROI, although the reliability is good, it still introduces a certain degree of subjectivity. Finally, this study evaluated the inter-rater reliability, but lacked data on test-retest reliability (ie, the repeatability of scans of the same subject at different time points). This study is an incremental validation study, and its findings mainly focus on confirming and refining the known associations. The innovation is reflected in the rigor of methodology and the comprehensiveness of indicators, rather than proposing a new mechanism. Future research needs to adopt a prospective design and integrate emerging technologies to achieve a leap towards predictive and mechanistic studies.

Given the limitations of this study, future research can be further developed in the following aspects: Firstly, a multi-center and longitudinal follow-up design should be adopted, and the sample size should be expanded to verify the universality of the findings of this study and clarify the temporal relationship and causal direction between the T1 rho value and the progression of osteoarthritis. Secondly, more objective equipment (such as accelerometers and smart wearable devices) can be used to quantitatively assess the exercise load in order to reduce recall bias and measurement errors caused by subjective definitions. Thirdly, new technologies for non-invasive acquisition of cartilage biochemical information in a broader population of OA patients should be explored to reduce reliance on surgical subgroups samples and the resulting validation bias. Finally, in the future, it is necessary to conduct multi-center prospective cohort study combined with artificial intelligence and multi-omics technologies, with the aim of achieving a breakthrough from association verification to disease prediction and mechanism exploration.

Conclusion

In summary, this cross-sectional study indicated that higher T1 rho value were significantly associated with lower protein proteoglycan (<41%), disordered collagen fiber arrangement, self-reported history of overloaded exercise, as well as higher WORMS and ICRS scores. These findings provided a basis for understanding the pathological physiological background reflected by T1 rho value. Future longitudinal studies are needed to confirm the temporal sequence of these associations and to explore the potential value of T1 rho imaging in predicting the progression of osteoarthritis and monitoring treatment.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author Kai Xu on reasonable request.

Ethics Approval and Consent to Participate

This study was approved by The Ethics Committee of The Affiliated Hospital of Xuzhou Medical University (Approval number: XYFY2022-KL309-01) and Xuzhou First People's Hospital (Approval number: xyyll[2022]073). This study was complies with the Declaration of Helsinki. Informed consent was obtained from participants for the participation in the study and all methods were carried out in accordance with relevant guidelines and regulations.

Consent to Participate

The patients participating in the study all agree to publish the research results. Written informed consent to participate was obtained from all of the participants in the study.

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Disclosure

The authors declare that they have no competing interests in this work.

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