Original Article

The effect of cartilage dehydration and rehydration on quantitative ultrashort echo time biomarkers

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Background: The effect of dehydration of *ex vivo* cartilage samples and rehydration with native synovial fluid or normal saline on quantitative ultrashort echo time (UTE) biomarkers are unknown. We aimed to investigate the effect of cartilage dehydration-rehydration on UTE biomarkers and to compare the rehydration capabilities of native synovial fluid and normal saline.

Methods: A total of 37 cartilage samples were harvested from patients (n=5) who underwent total knee replacement. Fresh cartilage samples were exposed to air to dehydrate for 2 hours after baseline magnetic resonance (MR) scanning, then randomly divided into two groups: one soaking in native synovial fluid (n=17) and the other in normal saline (n=20) to rehydrate for 4 hours. UTE-based biomarkers [T_1, adiabatic $T_{1\rho}$ (Adiab$T_{1\rho}$), macromolecular fraction (MMF), magnetization transfer ratio (MTR), and T_2*] and sample weights were evaluated for fresh, dehydrated, and rehydrated cartilage samples. Differences and agreements between groups were assessed using the values of fresh cartilage samples as reference standard.

Results: Dehydrating in air for 2 hours resulted in significant weight loss (P=0.000). T_1, Adiab$T_{1\rho}$, and T_2* decreased significantly while MMF and MTR increased significantly (all P<0.02). Non-significant differences were observed in cartilage weights after rehydrating in both synovial fluid and normal saline, with P values being 0.204 and 0.769, respectively. There were no significant differences in T_1, Adiab$T_{1\rho}$, MMF, and MTR after rehydrating in synovial fluid (P>0.0167, with Bonferroni correction) while T_2* (P=0.001) still had significant differences compared with fresh samples. However, no significant differences were detected for any of the evaluated UTE biomarkers after rehydrating in normal saline (all P>0.05). No differences were detected in the agreement of UTE biomarker measurements between fresh samples and samples rehydrated with synovial fluid and normal saline.

Conclusions: Cartilage dehydration resulted in significant changes in UTE biomarkers. Rehydrating with synovial fluid or normal saline had non-significant effect on all the evaluated UTE biomarkers except T_2* values, which still had significant differences compared with fresh samples after rehydrating with synovial fluid. No significant difference was observed in the rehydration capabilities of native synovial fluid and normal saline.

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Keywords: Cartilage; fresh; dehydration; rehydration; ultrashort echo time magnetic resonance imaging (UTE-MRI)

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Introduction

Ex vivo hyaline articular cartilage samples are commonly used in magnetic resonance imaging (MRI) research to study osteoarthritis and related joint diseases. These samples facilitate destructive and invasive testing that may otherwise be prohibitive. It is widely accepted that the optimal condition of cartilage samples is immediately after harvest from a living host with extreme care to avoid dehydration. In reality, this is often not possible and even after a few minutes of dehydration in room air, measurable changes in cartilage thickness are present (1). For accurate correlation of results obtained from such *in vivo* scenarios, a thorough understanding of how tissue handling and preparation affect quantitative measures of interest is mandatory (2-5). To our knowledge, changes in cartilage subject to dehydration and rehydration have not been systematically studied. Researchers may be unaware of the amount of dehydration that has occurred in their samples and thusly unaware of the effect this may have on their quantitative magnetic resonance (MR) results as well.

In recent years, a range of quantitative ultrashort echo time (UTE) MRI techniques have been used to assess cartilage properties (6,7), including T_1 (8), adiabatic $T_{1\rho}$ (Adiab$T_{1\rho}$) (9-11), macromolecular fraction (MMF) (12), magnetization transfer ratio (MTR) (13), and T_2* (14). The current study aimed to evaluate the effect of cartilage dehydration and rehydration on these quantitative UTE biomarkers and to investigate what type of solution is able to adequately rehydrate the cartilage without significantly confounding biomarker measurements, using results from fresh cartilage samples as the reference standard. We have the hypothesis that cartilage dehydration will affect the results of UTE biomarkers and that the changes may be reversed by rehydration with synovial fluid or normal saline.

Methods

Sample preparation

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of VA San Diego Healthcare System (No. H170124). Written informed consent was obtained from all patients. Thirty-seven osteochondral cores were harvested from patients (n=5, mean age was 71±3.2 years old) who underwent total knee arthroplasty (TKA). The osseous parts were removed by a scalpel. The entire process from surgical resection to cartilage procurement was performed within 30 minutes using an air humidifier to mitigate sample dehydration. Fresh cartilage cores were weighed before baseline MR scan. Then the cartilage samples were put in syringes with perfluoropolyether immediately after they were weighed and notched to minimize dehydration. The time between cartilage collection and baseline MR scanning was within 30 minutes. Native synovial fluid was collected during surgery.

MR sequences

All cartilage wafers were piled up in a 10-mL syringe. Perfluoropolyether (Fomblin; Ausimont, Thorofare, NJ, USA) was added in the syringe to minimize air-tissue susceptibility and dehydration during MRI. Each sample was carved a small notch to keep the orientation across scans to minimize the influence of dipole effects on UTE measurements (15-18). A 3T clinical MRI scanner (MR750, GE Healthcare Technologies, Milwaukee, WI, USA) with a self-developed birdcage coil (30 mm) was used for image scanning. The imaging protocols were as follows: (I) 3D UTE-cones with actual flip angle imaging and variable flip angles (3D UTE-Cones AFI-VFA) with four flip angles (FA) of 5°, 10°, 20°, and 30°, and a TR of 20 ms (8); (II) 3D UTE-Cones with Adiab$T_{1\rho}$ preparation (3D UTE-Cones-Adiab$T_{1\rho}$) with seven spin-locking times (TSL) of 0, 12, 24, 36, 48, 72, and 96 ms (9); (III) 3D UTE-Cones magnetization transfer (3D UTE-Cones-MT) with three saturation pulse powers of 400°, 600°, and 800° and five frequency offsets of 2, 5, 10, 20, and 50 kHz (19); (IV) 3D UTE-T_2* with six TEs of 0.032, 4.1, 8.1, 12.1, 16.1, and

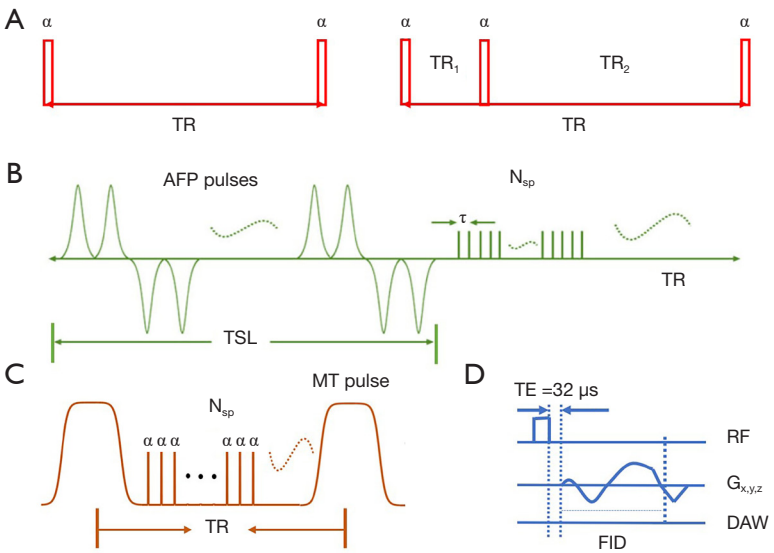

Figure 1 UTE pulse sequence diagram. (A) T_1 is measured by the VFA method using the 3D UTE-Cones sequence with a single TR. B_1 mapping is obtained by the UTE-AFI method with two different TRs. Accurate T_1 value can be obtained by the combination of 3D UTE-VFA and UTE-VFI methods. (B) A train of AFP pulses are used in the 3D UTE Cones Adiab$T_{1\rho}$ sequence to obtain $T_{1\rho}$ values. (C) A Fermi pulse is used in the 3D UTE-MT sequence followed by multi-spoke (Nsp) excitation. The usage of Nsp reduces the scan time effectively. (D) 3D UTE sequence is used for T_2* acquisition with a short rectangular hard pulse excitation followed by an initial short TE of 32 μs. TR, repetition time; AFP, adiabatic full passage; MT, magnetization transfer; TE, echo time; RF, radio frequency; FID, free induction decay; DAW, data acquisition window; TSL, spin-locking time; UTE, ultrashort echo time; VFA, variable flip angle; AFI, actual flip angle imaging; Adiab$T_{1\rho}$, adiabatic $T_{1\rho}$.

32 ms (*Figure 1*). Other imaging parameters were as follows: number of excitation (NEX) =1, receiver bandwidth (BW) =83.3 KHz, field of view (FOV) =5×5 cm^2, acquisition matrix =160×160, slice thickness =0.5 mm, 60 slices, under sampling factor =1. The scan times for single T_1, $T_{1\rho}$, MT and T_2* sequences were 2.02, 2.33, 2.05, and 1.25 min, respectively, and the total scan time was 78 min. The representative fitting curves of UTE-based T_1, $T_{1\rho}$, MMF and T_2* are shown in *Figure 2*.

Dehydration and rehydration process

After baseline MRI scanning, samples were exposed to air and allowed to dehydrate for 2 hours. Sample weights were recorded before and after dehydration. Then samples were stacked back into the syringe filled with perfluoropolyether in the same order and orientation as the baseline for repeated MR scanning using the same imaging protocol. After the second-time MR scanning, samples from individual patients were then randomly divided into two rehydration groups, with one soaking in native synovial fluid (n=17) and the other soaking in normal saline (n=20). After 4 hours of rehydration, samples were removed from the solution and their surfaces were wiped with Kimwipes. Kimwipes were used to wipe the surface each time the cartilage samples were taken from the solution before weighing. Weights were recorded before and after rehydration. The third-time MR scanning was performed following the rehydration process using the same method as the baseline and the second-time MR scanning.

Imaging data analysis

The DICOM images obtained by the MR sequences described above were used for imaging data analysis using MATLAB (The MathWorks Inc., Natick, MA, USA). Regions of interests (ROIs) were drawn on the first image of UTE series manually, then copied to the subsequent images. Non-linear least-squares curve fitting was based on the mean intensity within each ROI using the Levenberg-Marquardt method. Single-component fitting method was used for T_1 measurement by the 3D

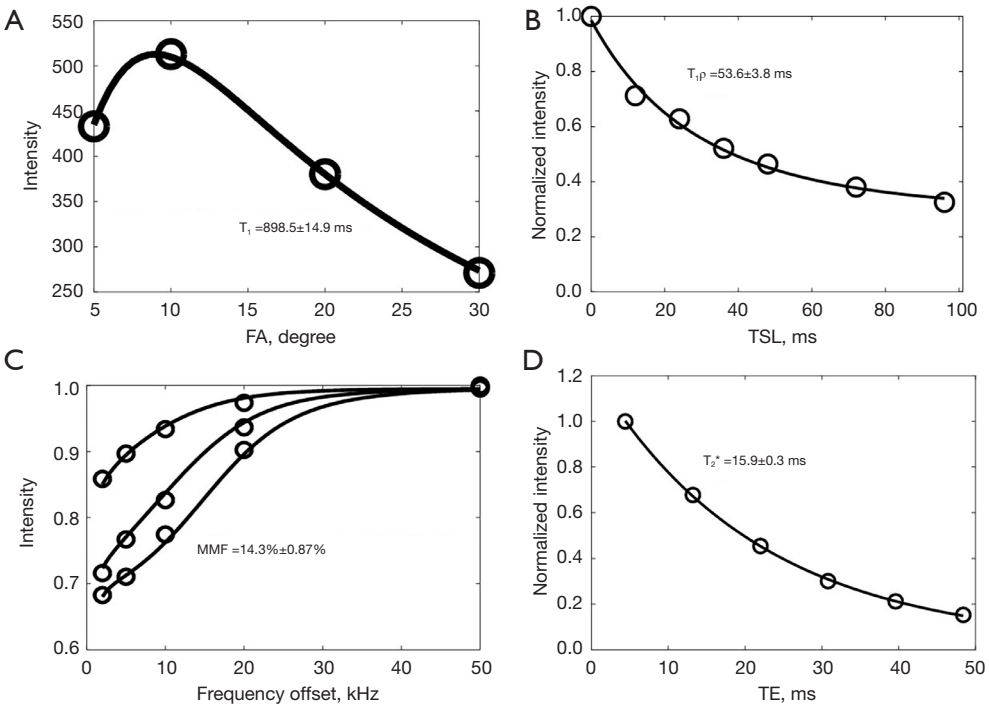

Figure 2 Representative fitting curves for UTE-based biomarkers for an articular cartilage sample, with the dots being the experimental data points. Data are presented as mean ± standard deviation. (A) The representative fitting curve for T_1, with uncertainties of 2%. (B) The representative fitting curve for $T_{1\rho}$, with uncertainties of 7%. (C) The representative fitting curve for MMF, with uncertainties of 6%. (D) The representative fitting curve for T_2*, with uncertainties of 2%. FA, flip angle; TSL, spin-locking time; MMF, macromolecular fraction; TE, echo time; UTE, ultrashort echo time.

UTE-AFI and UTE-VTR sequences. A fitting algorithm based on the equation:

$$S(TSL) \propto \frac{e^{-TSL/T_{1\rho}} \times \left(1-e^{-(TR-TSL)/T_1}\right)}{1-e^{-TSL/T_{1\rho}} \times e^{-(TR-TSL)/T_1}\cos(\alpha)} \times \sin(\alpha) + C \quad [1]$$

where α accounts for flip angle was used for $T_{1\rho}$ analysis (20). A two-pool model (19) was used for MTR (21) and MMF calculation based on UTE-MT data set. A single-component fitting model, $S(TE) \propto \exp(-TE/T_2^*) + C$, was utilized for T_2* decay analyses where C accounts for background noise (22).

Three consecutive layers in the center of each cartilage sample were manually drawn for global ROI analysis (The mean ROI size was 18.6±1.3 mm^2) (*Figure 3*). UTE-based biomarkers, including T_1, Adiab$T_{1\rho}$, MMF, MTR, and T_2*, were measured for all cartilage samples at fresh, dehydration, and rehydration time points. Representative T_1, $T_{1\rho}$, and MMF maps of fresh, dehydrated, and rehydrated cartilage samples are shown in *Figure 3*.

Statistical analysis

Statistical analyses were performed using SPSS software (SPSS 24.0, IBM, New York, NY, USA). The normality of the data distribution was evaluated by the Kolmogorov-Smirnov test. A two-sided paired *t*-test with Bonferroni correction (to calibrate type I errors, where P values less than 0.0167 were considered statistically significant) was performed to evaluate biomarker differences between fresh, dehydrated, and rehydrated samples. Repeated measures ANOVA analysis was used to determine the effects of dehydration and rehydration by synovial fluid and normal saline on UTE-based biomarkers. A P value less than 0.05 was statistically significant. The agreement of the UTE biomarkers between the rehydrated and fresh samples was accessed by Bland-Altman analysis.

Results

Figure 4 depicts the significant weight loss observed in

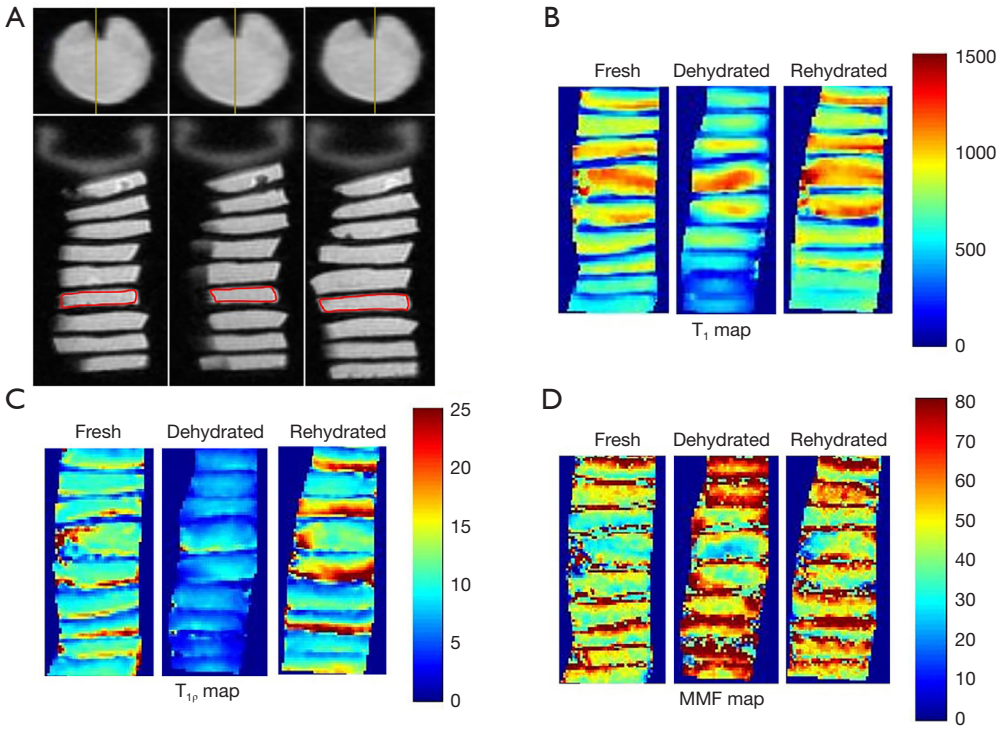

Figure 3 The representative images of ROI and pixel maps for UTE biomarkers. (A) The three consecutive layers in the center of each cartilage sample (the nicked notch was shown as signal void) used for ROI analysis. (B) The representative T_1 map of fresh, dehydrated, and rehydrated cartilage samples. (C) The representative $T_{1\rho}$ map of fresh, dehydrated, and rehydrated cartilage samples. (D) The representative MMF map of fresh, dehydrated, and rehydrated cartilage samples. MMF, macromolecular fraction; ROI, region of interest; UTE, ultrashort echo time.

samples after dehydration in air for 2 hours. With 4 hours of submersion, no differences were detected between the fresh and rehydrated cartilage samples in both synovial fluid and normal saline groups (all P>0.0167). Across samples, significant changes were observed in all evaluated UTE biomarkers after dehydration, with T_1, Adiab$T_{1\rho}$, and T_2* values decreasing, and MMF and MTR values increasing. There are no significant differences observed in T_1, Adiab$T_{1\rho}$, MMF, and MTR values after rehydrating in synovial fluid, whereas T_2* values still exhibited significant post-rehydration differences compared to fresh samples. On the other hand, all the UTE biomarkers, including T_1, Adiab$T_{1\rho}$, MMF, MTR, and T_2* values after rehydrating with normal saline had non-significant differences with the measurements taken when samples were still fresh.

The results of repeated measures ANOVA indicate that all the P values were <0.001 for weights, T_1, Adiab$T_{1\rho}$, MMF, MTR, and T_2* when only the factor of time points was taken into consideration, indicating that the differences at each time point were statistically significant for both synovial fluid and normal saline groups. All P values were >0.05 for weights (P=0.811), T_1 (P=0.255), Adiab$T_{1\rho}$ (P=0.117), MMF (P=0.543), MTR (P=0.720), and T_2* (P=0.091) when both time points and group factors were taken into account, indicating that there is no interaction between time points and group, which means the weights and UTE biomarkers of cartilage samples at different time points (fresh, dehydration, and rehydration) did not vary by groups (synovial fluid and normal saline groups).

The Bland-Altman plots of all biomarkers, including T_1, Adiab$T_{1\rho}$, MMF, MTR, and T_2* for cartilage samples in the synovial fluid group and the normal saline group are shown in *Figures 5,6*, respectively, with measurements taken from the fresh samples considered as baseline. The differences between baseline and the rehydration state are depicted on the vertical axis, with their averages depicted on the horizontal axis. In the synovial fluid group, only 1/17 was outside the 95% limit of agreement (LoA) for T_1,

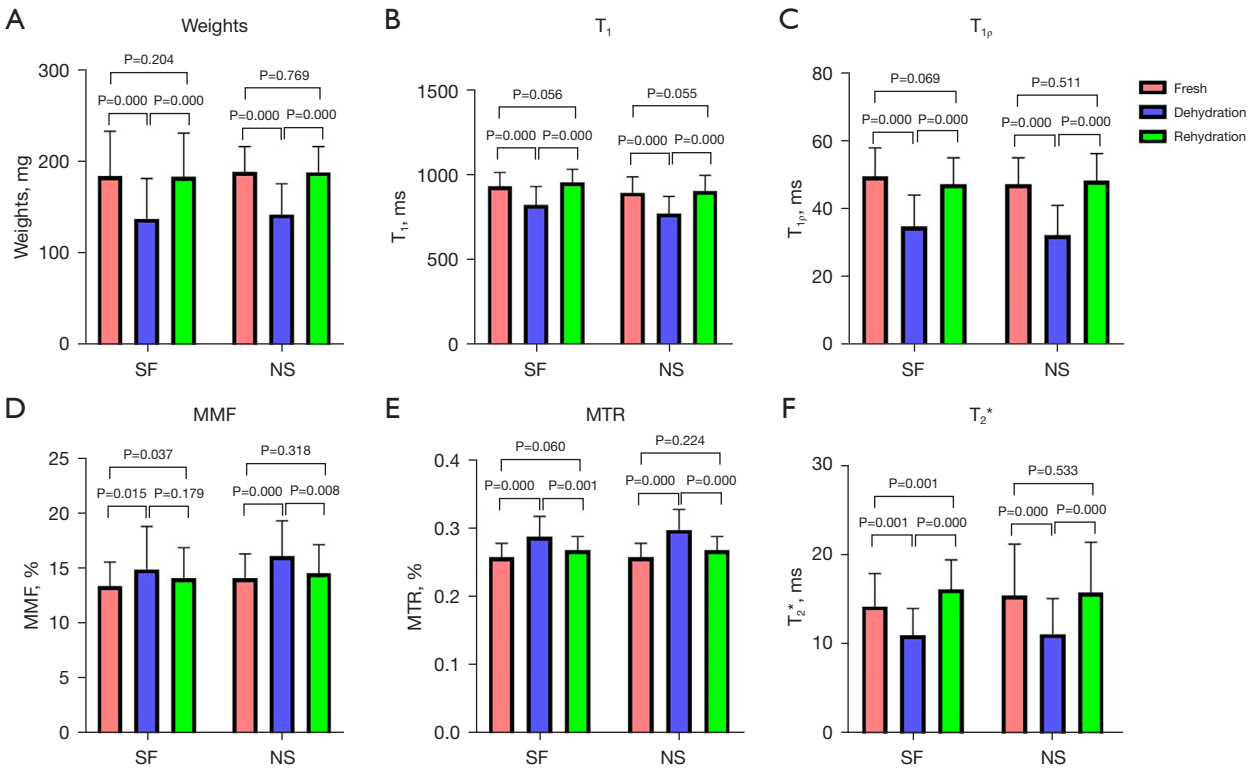

Figure 4 The bar chart of cartilage weights and UTE biomarkers of fresh, dehydrated, and rehydrated cartilage samples in SF and NS groups and the corresponding P values. (A) The weights of cartilage decreased significantly after dehydration in air for 2 hours. No significant differences were detected between the fresh and rehydrated cartilage samples in both SF and NS groups after 4 hours of submersion. (B) T_1 values decreased significantly after dehydration across samples. There were no significant differences observed in T_1 values after rehydrating in SF or NS. (C) $T_{1\rho}$ values decreased significantly after dehydration in both SF and NS groups. Non-significant differences were observed after rehydrating in SF or NS compared to the fresh samples. (D) MMF increased significantly after dehydration. MMF values after rehydrating with SF and NS had non-significant differences with the values of fresh samples. (E) Significant increases were observed in MTR after dehydration. MTR values had non-significant differences after rehydrating with SF and NS compared with the values of fresh samples. (F) T_2* values decreased significantly in both SF and NS groups after dehydration. Rehydrated with SF, T_2* values still exhibited significant post-rehydration differences. However, T_2* values after rehydrating with NS had non-significant differences with the measurements taken when samples were still fresh. Bonferroni correction was performed to calibrate type I errors, so P values less than 0.0167 were considered statistically significant. SF, synovial fluid; NS, normal saline; MMF, macromolecular fraction; MTR, magnetization transfer ratio; UTE, ultrashort echo time.

AdiabT$_{1\rho}$, and MTR, while all data points were within the 95% LoA for MMF and T_2*. In comparison, the Bland-Altman plots of the normal saline group (*Figure 6*) showed that all data points were within the 95% LoA for T_1 and MMF, while only 1/20 data points was outside the 95% LoA for AdiabT$_{1\rho}$, MTR, and T_2*. These findings suggest that there is high reproducibility of UTE biomarkers after the rehydration process either with synovial fluid or normal saline and that cartilage samples rehydrated in normal saline demonstrate no differences in reproducibility with samples rehydrated using synovial fluid.

Discussion

The purpose of this study was to evaluate the effects of dehydration and rehydration with synovial fluid and normal saline on quantitative UTE biomarkers in an *ex vivo* cartilage study. In this study, we found that MR imaging of dehydrated cartilage rehydrated with normal saline did not significantly alter UTE-based T_1, AdiabT$_{1\rho}$, MMF, MTR,

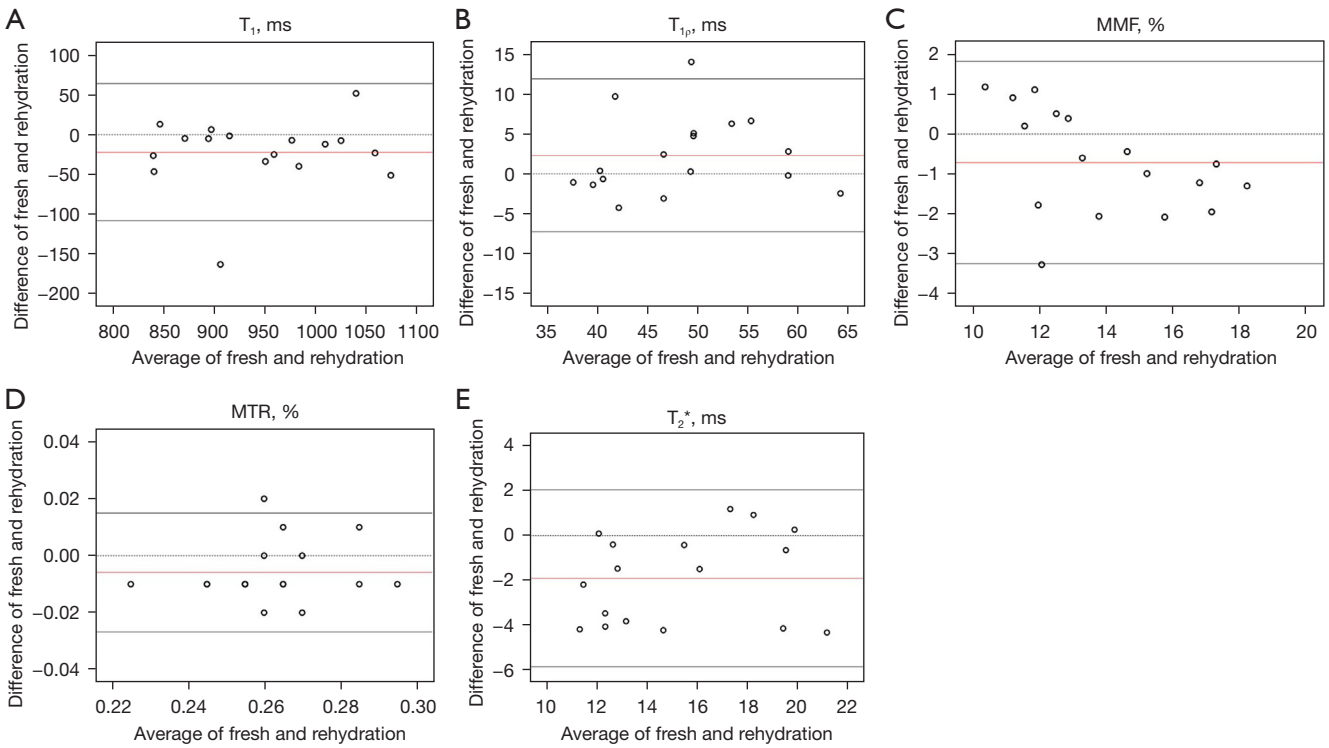

Figure 5 The Bland-Altman plots of UTE biomarkers for synovial fluid-rehydrated cartilage samples, comparing the rehydration states with fresh states. The differences between baseline and the rehydration state are depicted on the vertical axis, with their averages depicted on the horizontal axis. (A) 1/17 data points were outside the 95% LoA for T_1. (B) 1/17 data points were outside the 95% LoA for $T_{1\rho}$. (C) All data points were within the 95% LoA for MMF. (D) 1/17 data points were outside the 95% LoA for MTR. (E) All data points were within the 95% LoA for T_2*. MMF, macromolecular fraction; MTR, magnetization transfer ratio; UTE, ultrashort echo time; LoA, limit of agreement.

and T_2* measurements. The findings of our current study are important as they suggest that rehydration of the dehydrated cartilage samples with normal saline can be used effectively in an MR study of imaging characteristics of cartilage *ex vivo*.

Our results demonstrate that while there was significant sample dehydration after exposure to typical ambient air for 2 hours, both synovial fluid and normal saline brought weights of cartilage back to normal without causing the samples to swell, which is consistent with the result of a previous literature that the mass of 40% dehydrated cartilage appeared to be steady after 5 hours of submersion in normal saline and was not statistically different from that level of rehydration after 16 hours (23). Cartilage dehydration resulted in significant changes in all the evaluated UTE biomarkers, with T_1, Adiab$T_{1\rho}$, and T_2* values decreased while MMF and MTR values increased. One possible explanation for this is that cartilage moisture loss during dehydration results in relative increases in proteoglycan (PG) and collagen concentration (2). Previous studies have reported that T_1 and Adiab$T_{1\rho}$ increase with PG loss (24-26), so it is reasonable that significant decreases were observed in T_1 and Adiab$T_{1\rho}$ after dehydration in our study. MMF and MTR value increases with cartilage dehydration, consistent with previous studies where MMF and MTR were directly proportional to collagen concentration (10,12,27). The unexpected increase in T_2* values after rehydrating in synovial fluid was observed. More research is still needed to investigate whether rehydration with synovial fluid affects cartilage microstructure (e.g., via polarized light microscopy), glycosaminoglycans (GAGs) content (e.g., via dimethylmethylene blue assay), and other macromolecules (and thereby, tissue osmolarity).

Our results showed no statistical differences in UTE biomarkers between fresh samples and samples rehydrated with normal saline in comparison to samples rehydrated with synovial fluid. The most likely reason for this is that

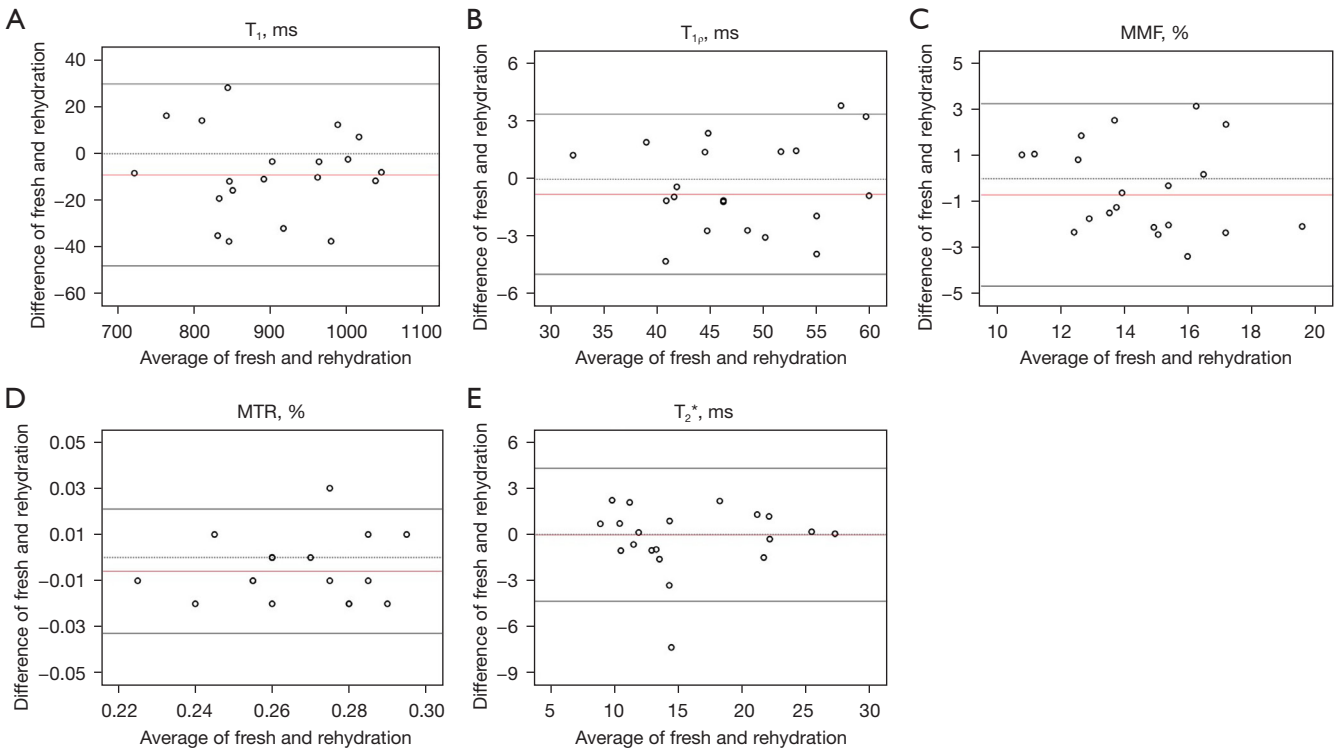

Figure 6 The Bland-Altman plots of UTE biomarkers for normal saline-rehydrated cartilage samples, comparing the rehydration states with fresh states. The differences between baseline and the rehydration state are depicted on the vertical axis, with their averages depicted on the horizontal axis. (a) All data points were within the 95% LoA for T_1. (B) 1/20 data points were outside the 95% LoA for $T_{1\rho}$. (C) All data points were within the 95% LoA for MMF. (D) 1/20 data points were outside the 95% LoA for MTR. (E) 1/20 points were outside the 95% LoA for T_2*. MMF, macromolecular fraction; MTR, magnetization transfer ratio; UTE, ultrashort echo time; LoA, limit of agreement.

cartilage dehydration is mainly a loss of water content without changes to the internal microstructure of the tissue [as opposed to storage at a low temperature such as –20 ℃ or –80 ℃ without cryopreservation, which might result in a significant loss of GAGs in cartilage (3)]. Not only does normal saline contain more water than synovial fluid, but the osmolarity of native synovial fluid obtained from TKA patients may also change as a result of disease (28). Additionally, normal saline is relatively easy to obtain, while the collection of native synovial fluid during surgery is more complicated and sometimes the amount of synovial fluid might be small. Therefore, in the case of cartilage dehydration, it is feasible to rehydrate with normal saline instead of synovial fluid in practice.

There are several limitations to our study. First, the sample size of this study is relatively small, especially in each sub-group with 17 cartilage samples in the synovial fluid group and 20 in the normal saline group. Second, the cartilage samples only came from five donors, which inherently limits the variability of the data. Third, histological or immunohistochemical tests were not performed but might have been useful in demonstrating the biochemical changes in cartilage samples during the dehydration-rehydration process. Fourth, only the effects of dehydration and rehydration were evaluated in this current study. Given that freezing samples at –80 ℃ is one of the most common sample processing methods, it is important to investigate the effects of freezing on the quantitative MRI measures of cartilage samples. Fifth, cartilage samples in our study were obtained from patients who underwent TKA, so samples were of varying levels of degeneration, with some relatively healthy and some degenerated tissues. It remains to be investigated whether degeneration of cartilage may affect its overall ability to be rehydrated. Finally, the values of fresh cartilage samples were used as the reference standard for rehydrated and dehydrated samples, but they

were also subject to measurement error and bias.

Conclusions

Based on our preliminary results, cartilage dehydration caused significant changes in the quantitative results of UTE biomarkers with a significant decrease in T_1, Adiab$T_{1\rho}$, and T_2* values and an increase in MMF and MTR values. Rehydrating with synovial fluid or normal saline had non-significant effect on all the evaluated UTE biomarkers except T_2* values, which still had significant differences compared with fresh samples after rehydrating with synovial fluid. No significant difference was observed in the rehydration capabilities in native synovial fluid and normal saline.

Acknowledgments

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-359/coif). JD serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and approved by the Institutional Review Board of VA San Diego Healthcare System (No. H170124). Written informed consent was obtained from all patients.

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