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Journal

Magnetic Resonance Imaging, 34(5)

ISSN

0730-725X

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Publication Date

2016-06-01

DOI

10.1016/j.mri.2015.12.034

Peer reviewed

HHS Public Access

Author manuscript

Magn Reson Imaging. Author manuscript; available in PMC 2017 June 01.

Published in final edited form as:

Magn Reson Imaging. 2016 June ; 34(5): 632–637. doi:10.1016/j.mri.2015.12.034.

Quantification of Bone Marrow Water and Lipid Composition in Anterior Cruciate Ligament-Injured and Osteoarthritic Knees Using Three-Dimensional Magnetic Resonance Spectroscopic Imaging

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Abstract

Purpose—To quantitatively evaluate longitudinal changes in water and lipid in knee bone marrow with and without bone marrow edema-like lesions (BMELs) in subjects with acutely ruptured anterior cruciate ligaments (ACLs) or osteoarthritis (OA) using three-dimensional magnetic resonance spectroscopic imaging (3D MRSI).

Material and Methods—Ten ACL and 10 OA subjects who presented with BMEL and seven BMEL-free controls were scanned at 3T. All ACL and OA subjects had one-year follow-up scans. 3D MRSI was acquired in BMEL and adjacent bone marrow, and water content (WC) and unsaturated lipid index (UI) were calculated in each region of interest.

Results—At baseline, ACL BMEL WC was significantly higher than ACL non-BMEL, OA BMEL, and control WC; ACL non-BMEL WC, ACL BMEL UI, and OA BMEL WC were significantly higher than control. ACL BMEL WC decreased significantly one year post-reconstruction; UI decreased non-significantly ($p = 0.09$). No significant changes in OA BMEL or ACL and OA non-BMEL WC and UI were observed.

Conclusion—3D MRSI is a powerful method of quantitatively assessing the biochemical composition of bone marrow in OA and ACL-injured knees, which may serve as imaging markers to improve comprehension of primary and secondary OA pathology.

Keywords

Three-Dimensional Magnetic Resonance Spectroscopic Imaging; Knee; Osteoarthritis; Anterior Cruciate Ligament Tear; Bone Marrow; Bone Marrow Edema-Like Lesions

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1. Background

Osteoarthritis (OA) is a multifactorial disease affecting the entire knee joint, including bone and bone marrow [1]. Using ex vivo specimens, Plumb et al have shown that the amount and composition of fat is significantly altered in OA bone marrow compared to healthy controls [2]. This has led some investigators to hypothesize that OA may be a systemic disorder involving lipid metabolism [3]. Therefore, it is of great interest to non-invasively quantify marrow lipid, which may be a potential imaging marker for evaluating OA.

Furthermore, previous studies have shown that in both acutely injured knees [4-6] and knees with OA [7-9], bone marrow edema-like lesions (BMELs) are commonly present. These patterns are defined as areas of high signal intensity in T_2-weighted, fat-saturated magnetic resonance (MR) images [10-13]. Many previous studies have shown that BMELs are correlated with cartilage degeneration and disease progression in OA [8, 14], which also suggests an intrinsic connection between cartilage degeneration and bone/bone marrow pathology in OA. Despite promising results, most of the previous studies on BMEL were limited to evaluating the volume of the lesion. Published data on biochemical changes within BMELs and surrounding regions of OA bone marrow and acutely injured knees are very limited [12]. It is not clear either if the biochemical changes within BMELs are different between OA and acutely injured knees.

MR spectroscopy (MRS) has been used to noninvasively and quantitatively assess biochemical changes, particularly regarding water and lipids, in bone marrow [7, 12, 15-16, 22]. Compared to MR imaging techniques that separate water and fat, MRS and multi-voxel MR spectroscopic imaging (MRSI) have the advantage of quantifying different types of lipids, such as saturated and unsaturated lipids. Single-voxel MRS has been previously utilized to analyze compartment-specific unsaturation index levels in the knee joint. One study found a general decrease in the lipid unsaturation index in subjects with mild OA compared to control [15]. Another noted that anterior cruciate ligament (ACL)-injured subjects had a significantly increased index of unsaturation compared to subjects with OA; they also reported no significant differences in the lipid unsaturation index between ACL-injured and control knees or between OA and control knees [21]. MRSI can provide further spatial information of these biochemical changes. Using this method, Li et al observed a significantly higher water content and unsaturated lipid index in the BMEL regions of ACL-injured and OA knees compared to those of the surrounding BMEL-free regions of bone marrow [12].

However, to our knowledge, no study has documented the longitudinal changes in marrow water and lipid in ACL-injured and OA knees within and outside of BMEL. As such, this study aimed to use multi-voxel three-dimensional (3D) MRSI to: (i) cross-sectionally and longitudinally quantify and compare BMEL and non-BMEL water and lipid composition in ACL-injured, OA, and control knees and (ii) longitudinally assess changes in BMEL volume in ACL-injured and OA knees.

2. Materials and Methods

2.1 Subjects

Ten subjects with acute complete ACL tears (37.7±7.3 years; 7 female) and 10 subjects with knee OA (defined as having a Kellgren–Lawrence score of at least 1; 49.9±12.7 years; 4 female) who showed BMELs in the knee and seven healthy subjects who showed no BMELs in the knee (36.9±9.7 years; 3 female) were recruited for this study. Of the ACL cohort, six subjects had BMELs in the lateral tibia, and four subjects had BMELs in the lateral femoral condyle. Eight and two OA subjects had BMELs in the lateral and medial femoral condyles, respectively.

ACL-injured subjects were scanned at baseline (within two months after injury and prior to ACL reconstructive surgery) and one year post-reconstruction; among this cohort, five additionally returned for a two-year follow-up scan. OA subjects were scanned twice, one year apart, with the first scan being arbitrarily defined hereafter as “baseline” and the second as “one year.” Controls were only scanned once because the biochemical composition of bone marrow in healthy controls is not expected to change significantly in one year. The study was approved by the Committee for Human Research at our institution. Informed consent was obtained from all of the subjects.

2.2 MR imaging and spectroscopic imaging protocol

MR data were acquired with a 3T MR scanner (Signa HDx, General Electric, Milwaukee, WI) using a transmit/receive quadrature knee coil (Clinical MR Solutions, Brookfield, WI, USA) for the ACL cohort and an 8-channel phased array knee coil (Invivo, Orlando, FL, USA) for the OA and control cohorts. The protocol included the sagittal T_2-weighted fat-saturated fast spin-echo (FSE) images (TR/TE = 4300/51 ms, FOV = 14 cm, matrix = 512×256 slice thickness = 2.5 mm, gap = 0.5 mm, echo train length = 9, bandwidth = 31.25 kHz, NEX = 2), followed by the 3D MRSI sequence.

A point-resolved spectral-selection (PRESS) volume selection technique was used to obtain 3D MRSI data. The PRESS box, overlaid on the volume of interest (VOI), was prescribed on sagittal T_2-weighted fat-saturated images to not only cover as much BMEL as possible, but to also include some BMEL-free bone marrow for comparison. To minimize background noise and erroneous measurements of the desired water and lipid signals, very selective suppression pulses [17] were used to suppress signals from surrounding tissues. The 3D data were phase-encoded with 8×8×8 matrices, providing a nominal voxel size of 5×5×5 mm^3. A TR of two seconds and a TE of 35 milliseconds (ms; as short as the sequence allowed) were used to minimize T_1 and T_2 weight in the spectral data. Each free induction decay signal was sampled with 1024 points, a dwell time of 0.5 ms, and a sweep width of 2000 Hz. Because the acquisition of one 3D MRSI sequence takes 17 minutes, only one BMEL lesion per knee was studied; if a subject had more than one BMEL, the most significant BMEL was covered. Three ACL subjects whose BMEL in the lateral femoral condyle was considered in this study also had BMEL in their lateral tibia. One ACL subject analyzed for their lateral tibial BMEL also had BMEL in their lateral femoral condyle. No OA subjects had more than one BMEL region. During follow up scans, a PRESS box with the same size as the baseline

PRESS box was positioned carefully using anatomical landmarks to include the same VOI covered during the baseline scan.

2.3 Post-Processing of MR Data

2.3.1 BMEL Volume Quantification—The volume of all of the BMELs in the femur and/or tibia were quantified for each ACL and OA subject. BMELs were quantified using the fat saturated FSE T2-weighted images with a previously developed algorithm in IDL (Boulder, Colorado, USA) that utilizes a threshold method to automatically segment 3D BMEL volume contours [12]. The threshold was calculated as 90.05 + 0.87×NBM.mean + 0.83×NBM.SD, where NBM.mean and NBM.SD are the mean and standard deviation of the signal intensity of a region of normal-appearing bone marrow free of BMEL in the same knee compartment as the BMEL, respectively.

2.3.2 3D MRSI Post-Processing—The spectral data were reconstructed and then corrected for baseline, phase, and frequency shift using another previously developed program [18]. Based on previous studies [16, 19], olefinic protons (–CH=CH–), water, the CH_2 methylene protons α- to a double bond (– $CH=CHCH_2$–), and bulk methylene protons ($–(CH_2)_n–$) were determined to be identifiable around 5.35, 4.65, 2.06, and 1.3 ppm, respectively.

To quantify the amplitudes of the desired water and lipid signals, voigt functions that were previously developed [20] were used to fit the peaks in the frequency domain. Water content (WC) and lipid unsaturation index (UI), as defined below, were calculated for each voxel, where I_{water}, $I_{olefinic}$, and $I_{methylene}$ are the signal amplitudes of water, olefinic (unsaturated lipids), and bulk methylene (dominating saturated lipids), respectively.

$$WC = I_{water} / (I_{water} + I_{olefinic} + I_{methylene}) \times 100\%$$
$$UI = I_{olefinic} / (I_{olefinic} + I_{methylene}) \times 100\%$$

These ratios, as opposed to the values of the individual peaks, were used in our analyses to allow for inter-subject comparisons.

For cross-sectional analysis within and between the ACL, OA, and control cohorts, the mean values of WC and UI were calculated and averaged from voxels either completely engulfed by or entirely without BMEL at the baseline timepoint of each subject. For longitudinal within-cohort analysis, only the same voxels completely overlaying identical BMEL-containing or BMEL-free regions of bone marrow at all timepoints were considered, as illustrated in **Figure 1**. For both cross-sectional and longitudinal analysis, voxels that partially overlaid BMEL were excluded to allow for a strict comparison between BMEL and non-BMEL regions.

2.4 Statistical Analysis

For cross-sectional analysis, unpaired, two-tailed heteroscedastic student's t-tests were used to compare the BMEL WC and UI between the ACL-injured, OA, and control subjects. Unpaired, two-tailed heteroscedastic student's t-tests were also used to compare the WC and

UI between the BMEL and non-BMEL regions within the ACL-injured and OA cohorts. For longitudinal analysis, paired, two-tailed t-tests were used to compare the change in WC and UI in the BMEL and non-BMEL regions and the change in BMEL volume of the ACL-injured and OA subjects. No multi-comparison correction was performed due to the small sample size.

3. Results

3.1 Cross-Sectional Comparison of WC and UI between ACL-injured, OA, and Control Knees

Within the baseline ACL and OA BMEL regions, both WC and UI were higher than control WC and UI (**Figure 2**). Specifically, ACL BMEL WC and UI were significantly higher than control (WC = 23.0±12.5% vs. 2.2±0.8%, $p < 0.001$; UI = 5.3±4.6% vs. 1.0±0.6%, $p = 0.02$). OA BMEL WC (7.5±5.8%) likewise was significantly greater than control ($p = 0.02$), but OA BMEL UI (3.8±4.4%) was only greater by an edge significance ($p = 0.08$). ACL BMEL WC was significantly greater than OA BMEL WC ($p=0.004$); the difference between ACL and OA BMEL UI was not significant ($p=0.5$).

Regarding the baseline non-BMEL region, both ACL and OA WC and UI were higher than control. ACL non-BMEL WC (4.3±2.4%) was significantly higher than control WC ($p = 0.04$). ACL non-BMEL UI (2.0±1.4%) and OA non-BMEL WC (4.2±3.1%) and UI (2.7±3.0%) were only higher than control by an edge significance ($p = 0.08, 0.08, 0.1$, respectively). No significant difference was found between ACL and OA non-BMEL WC ($p = 0.9$) or UI ($p = 0.5$).

For the cross-sectional comparison within ACL and OA knees, the BMEL WC was higher than that of the non-BMEL region for both ACL and OA. Specifically, the difference between ACL BMEL and non-BMEL WC was significant ($p < 0.001$). ACL BMEL UI was higher than ACL non-BMEL UI by an edge significance ($p = 0.06$). Neither the differences between OA BMEL and non-BMEL WC nor UI were statistically significant ($p = 0.1$ and 0.5, respectively).

3.2 Longitudinal Changes in Marrow WC and UI in ACL-Injured and OA Knees

Both ACL BMEL WC and UI were observed to decrease from baseline to one year (WC: 22.1±11.3% vs. 5.6±2.1%, $p < 0.001$; UI: 4.8±3.8% vs. 2.6±1.9%, $p = 0.09$; **Figure 3a**). For the ACL subjects who additionally had a two-year follow-up scan (**Figure 3b**), congruent with the changes observed in the whole ACL cohort, WC significantly decreased (18.8±10.7% vs. 4.7±1.9%, $p = 0.03$) and UI non-significantly decreased (4.4±4.3% vs. 2.7±1.0%, $p = 0.2$) from baseline to one year. Also observed was a non-significant increase in both WC and UI from one to two years post-reconstruction (WC = 4.7±1.9% vs. 6.1±3.3%, $p = 0.2$; UI: 2.7±1.0% vs. 5.4±4.0%, $p = 0.2$). Additionally, two-year ACL WC and UI were both greater than control WC and UI with edge significances of $p = 0.06$ and $p = 0.07$, respectively. OA BMEL WC and UI did not change significantly over time (WC: 7.8±6.1% vs. 5.6±6.0%, $p = 0.1$; UI: 4.0±4.6% vs.3.1±4.4%, $p=0.4$; **Figure 3c**).

ACL non-BMEL WC and UI remained stable from baseline to one year (WC: 3.7±2.1% vs. 3.3±2.5%, p=0.8; UI: 1.6±1.4% vs. 1.4±1.1%, p=0.4). Among the two-year follow-up subjects, the WC and UI did not change significantly from baseline to one year (WC: 4.0±2.3% vs. 2.5±0.9, p=0.5; UI: 1.6±1.5% vs. 1.1±0.8%, p=1.0), or from one year to two years post-reconstruction (two-year WC = 4.1±2.8%, p=0.6; two-year UI = 3.7±2.4%, p=0.2). Neither OA non-BMEL WC (4.8±3.7% vs. 2.6±1.0%, p=0.1) nor UI (3.8±4.3% vs. 1.3±1.3%, p=0.2) changed significantly from baseline to one year.

3.3 Longitudinal Changes in BMEL Volume in ACL-Injured and OA Knees

ACL BMEL volume decreased significantly from baseline to one year post-reconstruction (4.0±2.7 cm^3 vs. 0.3±0.5 cm^3, p=0.002); BMEL was completely resolved in one ACL subject. For the five ACL-injured subjects with a two-year follow-up scan, BMEL volume decreased significantly from baseline to 1 year (3.9±2.7 cm^3 vs. 0.6±0.6 cm^3, p=0.05), and continued to decrease from 1 year to 2 year (0.2±0.2 cm^3), albeit not significantly, (p=0.3). Within this sub-cohort, BMEL had completely resolved in one subject by one year and in two additional subjects by two years post-reconstruction. No statistically significant longitudinal changes were found in OA BMEL volume (5.2±6.6 cm^3 vs. 6.1±5.9 cm^3, p=0.6).

4. Discussion

This study compared the water and lipid composition of bone marrow within and outside BMEL regions in ACL-injured and OA knees both cross-sectionally and longitudinally. To our knowledge, this study is the first to document longitudinal marrow composition changes in these knees. Evidence was found suggesting: (i) biochemically different pathologies underlying ACL and OA BMEL; (ii) biochemical changes occurring throughout the entire knee not just within ACL and OA BMEL; and (iii) the presence of continuing bone marrow pathology in ACL-injured knees despite the general resolution of BMEL by one year after reconstructive surgery.

The first aim of this study was to quantify and compare bone marrow water and lipid composition between ACL-injured, OA, and control knees within and outside BMEL regions. WC and UI were calculated using 3D MRSI because its ability to define WC as a ratio of water to fat and quantitatively assess levels of both saturated and unsaturated lipids. Another advantage of using multi-voxel 3D-MRSI, as opposed to single-voxel MRS, is that having multiple voxels provides greater anatomical coverage and a more representative insight into the biochemical composition of the knee joint, including both BMEL and non-BMEL regions.

Elevated WC and UI were observed within BMEL regions in ACL-injured and OA knees compared to control. These results are congruent with observations from a previous cross-sectional study [12] and indicate pathological changes in bone marrow within BMEL regions. One study conducted by Wang et al [15] found a general decrease in UI in subjects with mild OA compared to control, and another [21] found no significant differences in UI between ACL-injured and control knees or between OA and control knees. However, Wang et al's studies employed single-voxel MRS and focused on the UI of different compartments

within the knee joint as opposed to BMEL and non-BMEL regions. As such, these methodological differences in study design complicate the direct comparison of these results.

Despite this, Li et al [12] and Wang et al's more recent study [21] interestingly both observed ACL-injured knees to have a higher UI than their OA counterparts, suggesting the possibility of different biochemical changes occurring within ACL and OA BMEL. This study saw a non-significant increase and decrease in UI in the BMEL and non-BMEL regions of ACL-injured knees compared to those with OA, respectively. Regardless, our observation of higher WC and UI levels in ACL BMEL than in OA BMEL (significant with regards to WC) similarly suggests the idea that the BMEL in ACL-injured knees and OA-afflicted knees are biochemically distinct.

This study also observed that the WC and UI of non-BMEL regions in ACL-injured and OA knees were greater than control WC and UI. This implies that biochemical changes may be occurring throughout the entire knee and not just within the BMEL region. It could be argued that the WC and UI in the non-BMEL regions could be affected by the increased signal intensity of the neighboring BMEL regions. However, the consistency of the longitudinal non-BMEL WC and UI levels despite the significant decrease in BMEL volume from baseline to one-year in the ACL cohort suggests otherwise and reaffirms the reliability of our findings.

The second aim of this study was to analyze the longitudinal change in BMEL volume in ACL-injured and OA subjects. BMEL from ACL injuries is thought to be the result of the translational impact between the posterolateral tibia and anterolateral femur [6, 22]. Regarding OA, it has been speculated that BMEL may be the result of abnormal loading [23] and limb malalignment, which increases stress unilaterally on the joint and leads to cartilage loss [8]. However, the causal relationship between BMEL and cartilage degeneration has not yet been elucidated; in addition, while the role of bone degeneration in BMEL formation has been strongly suggested by the observed correlation between an increased rate of bone turnover and the presence of BMEL, a definite causal relationship has also yet to be determined [8].

BMEL volume was quantified using a previously developed program [12]; because it automatically calculates BMEL volume using a threshold method, it helps minimize inaccuracy due to intra- and inter-observer variability. Consistent with previous studies, this study found that most of the BMEL in ACL-injured knees had decreased, if not completely resolved, by 1 year [13, 24]. For the five ACL patients who had two-year follow-ups, BMEL volume continued to decrease, although not significantly. However, BMEL WC and UI were still higher than control by an edge significance, and even increased (although not significantly) from the one to two years post-reconstruction. This suggests the presence of continuing bone marrow pathology in ACL-injured knees even after the resolution of BMEL, and also possibly suggests permanent damage being sustained due to ACL rupture, which has been proposed by multiple previous studies [25-29]. This possible continued cartilage degeneration may also contribute to the previously observed high risk of ACL patients not only developing post-traumatic OA [30-32], but potentially developing it 15 to

20 years earlier than those who develop primary OA [33-36]. As such, there is great need for future research aimed at elucidating the exact origins of increased water and unsaturated lipids in ACL-injured and OA knees and the causal relationship between these changes in water and fat content, ACL injury, and primary and secondary OA pathology.

This study also quantified the longitudinal change in OA BMEL volume. BMEL volume decreased in three subjects (defined as a decrease in BMEL volume by more than 5% at one-year follow-up), remained steady in one subject, and increased in six subjects after one year. This observation is consistent with previous large-cohort studies, which showed that OA BMEL volume is more likely to increase than decrease in size, and that there is much variation regarding changes in BMEL volume among OA patients [14]. This, coupled with the general understanding of OA as a biochemically very heterogeneous disease, emphasizes the importance of additional future research into regional longitudinal changes in water and fat in a large cohort of OA subjects.

There are several limitations of this study. First, the ACL, OA, and control cohort sizes are relatively small. Also, the control cohort was not invited to return for follow-up scans; it would be ideal to similarly acquire longitudinal control data to have the capability of determining clinically relevant biochemical changes in ACL-injured and OA knees with respect to the natural changes that inherently occur in healthy bone marrow. Additionally, due to lengthy spectral acquisition times, the MR PRESS box was positioned to only cover the largest BMEL if there were multiple BMELs in the knee. And, in some cases, the BMEL region extended beyond the dimensions of the PRESS box and thus were unable to be evaluated in this study; however, this was largely due to the fact that the BMEL regions were located within close proximity to the edge of the subchondral bone. It will be important to consider these limitations in future studies conducting similar analyses with larger cohort sizes.

5. Conclusion

In conclusion, for the first time, longitudinal changes of marrow composition in ACL-injured and OA knees were investigated, and evidence suggesting the possibility of distinct biochemical changes occurring in ACL and OA BMEL was found. Evidence suggesting that permanent damage may have been sustained from ACL injuries was also elucidated. More research into these longitudinal changes must be conducted, as quantification of marrow composition shows strong promise as a potential imaging marker for evaluating joint degeneration in OA and acutely injured knees.

Acknowledgements

This work was supported by NIH K25 AR053633 and R01 AR46905. These funding sources did not play any role in study design or data collection or analysis.

Abbreviations

OA osteoarthritis

BMEL	bone marrow edema-like lesion
MR	magnetic resonance
MRS	MR spectroscopy
MRSI	MR spectroscopic imaging
ACL	anterior cruciate ligament
3D	three-dimensional
FSE	fast spin-echo
PRESS	point-resolved spectral-selection
VOI	volume of interest
ms	millisecond
WC	water content
UI	lipid unsaturation index

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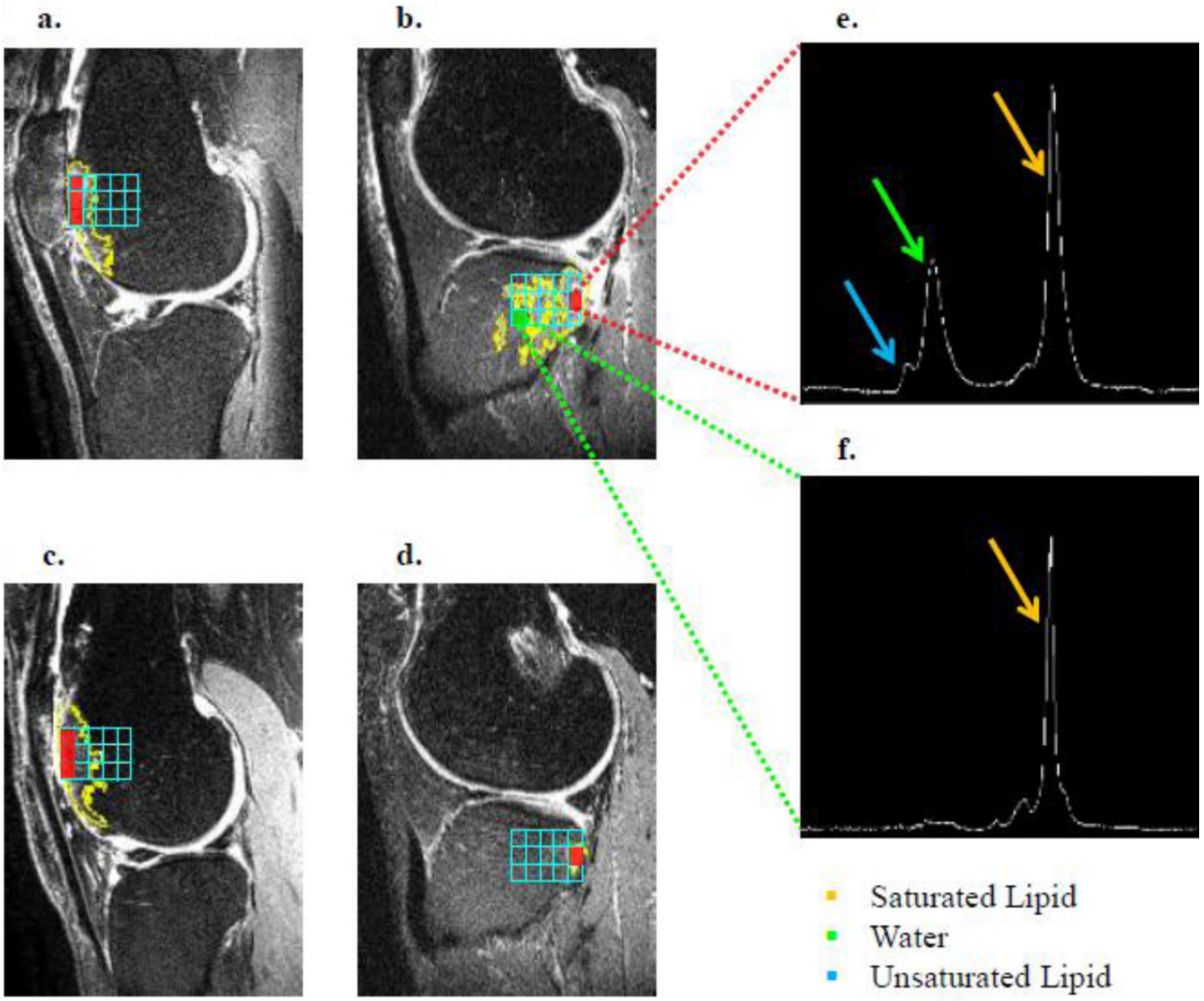

Figure 1.

Demonstration of the longitudinal biochemical analysis of the BMEL region (outlined in yellow). Regardless of whether (**a, b**) the baseline BMEL volume (**c**) increased or (**d**) decreased at follow-up, only the voxels that completely overlaid identical regions of BMEL-containing bone marrow at both timepoints (shaded red) were considered.

Sample spectra of a voxel (**e**) with and (**f**) without BMEL (shaded red and green in **1b**, respectively). BMEL-free bone marrow spectra are largely dominated by the saturated lipid peak at 1.3 ppm. BMEL bone marrow spectra show marked elevation of water and unsaturated lipid levels at 4.65 and 5.35 ppm, respectively.

BMEL: bone marrow edema-like lesion

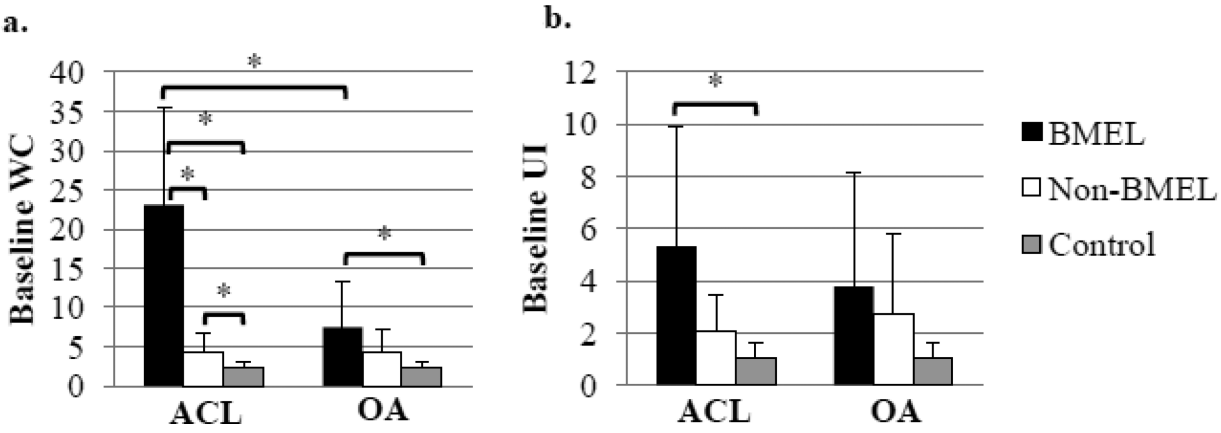

Figure 2.

Comparison of baseline **(a)** WC and **(b)** UI between ACL and OA BMEL and non-BMEL regions and control (*$p < 0.05$).

WC = water content; UI = unsaturation index; BMEL = bone marrow edema-like lesion.

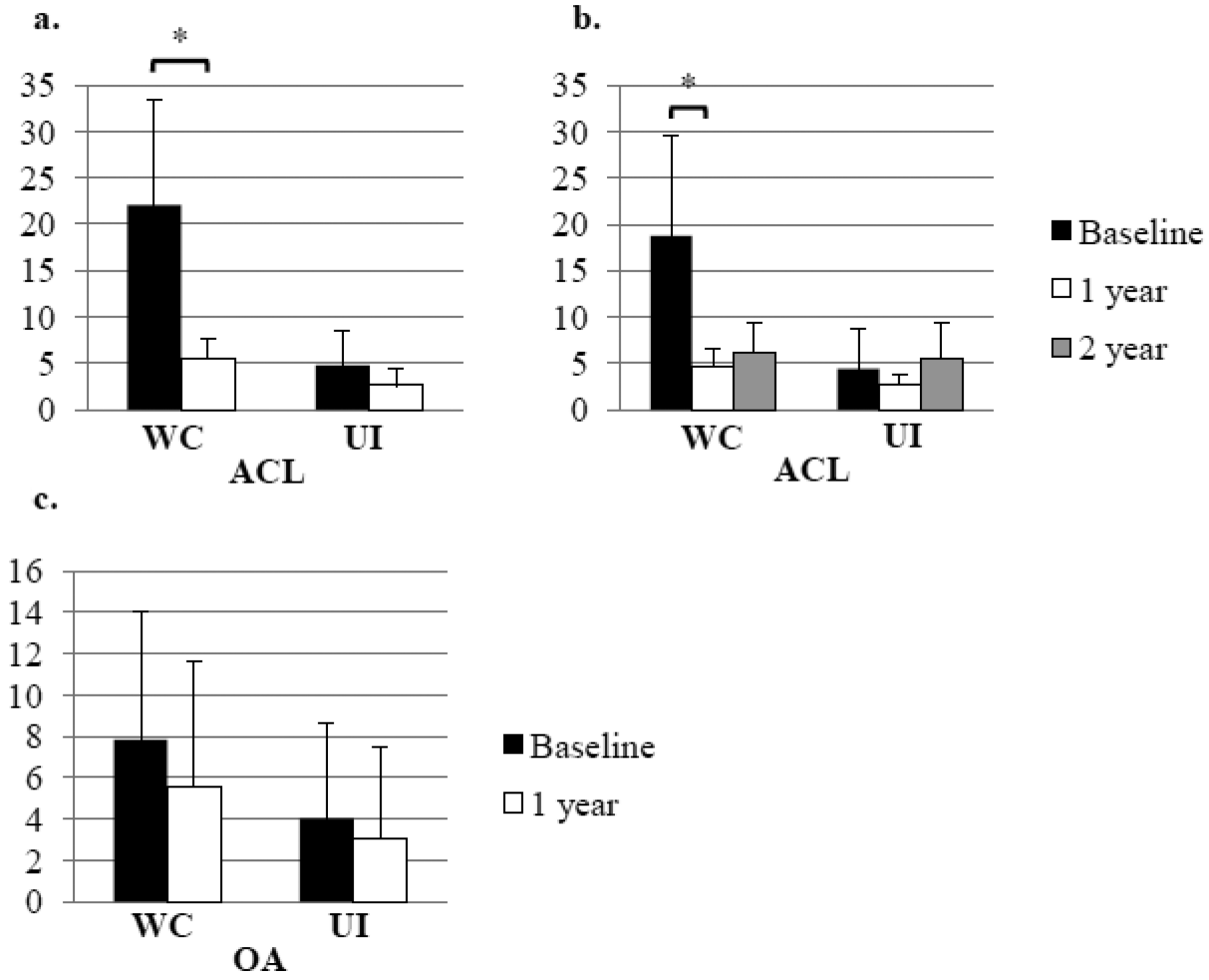

Figure 3.

Longitudinal BMEL WC and UI changes in **(a)** the complete ACL cohort, **(b)** the five ACL-injured subjects who returned for a two-year follow-up scan, and **(c)** the complete OA cohort. (*$p < 0.05$).

WC: water content; UI: unsaturation index; BMEL: bone marrow edema-like lesion.