INTRODUCTION:
Osteoarthritis is a multifactorial disease affecting not only cartilage but also other tissues in the joint including bone and bone marrow, and abnormal marrow lipid amount and composition may also contribute to OA. In both acutely injured knees and knees with OA, bone marrow edema-like lesions (BMELs; areas of high signal intensity in T2-weighted, fat-saturated magnetic resonance (MR) images) are commonly present. BMELs have been correlated with cartilage degeneration and disease progression in OA. However, few studies investigated in vivo marrow composition in OA and acute injured knees, and no study has been documented on the longitudinal marrow composition changes in such joints. The goals of this study were: 1) to quantify and compare bone marrow water and lipid composition between control, OA, and acutely anterior cruciate ligament (ACL)-injured knees within and outside the area of BMEL using 3D MR spectroscopic imaging (MRSI); 2) to quantify longitudinal changes in BMEL volume in OA and ACL-injured knees; and 3) to quantify longitudinal narrow marrow composition changes within and outside the area of BMEL in these knees.

METHODS:
Seven healthy subjects (36.9±9.7 years, 3 female, 4 male) who showed no BMELs in the knee, and 10 subjects with acute ACL injuries (37.7±7.3 years, 7 female, 3 male) and 10 subjects with OA (49.9±12.7 years, 4 female, 6 male) who showed BMELs in the knee were recruited for this study. The ACL subjects were scanned at baseline (within two months after injury and prior to ACL reconstruction), 1 year (n=10), and 2 years (n=5) after ACL reconstruction. The OA subjects have data for two scans performed at baseline and 1 year. The study was approved by the Committee for Human Research at our institution. Informed consent was obtained from all of the subjects.

MR data were acquired at a 3T GE MR scanner (General Electric Healthcare, Milwaukee, WI). The protocol included the spectral T1-weighted fat-saturated spin-echo (FSE) images (TR/TE = 4300/51 ms, FOV = 14 cm, matrix = 512x256, slice thickness = 2.5 mm, gap = 0.5 mm) followed by the 3D MRSI sequence using point-resolved spectral-selection (PRESS) sequence (TR/TE = 2000/35ms, matrix = 8x8x8, voxel size = 5x5x5mm³). The spectral box was prescribed in the FSE images to not only cover as much BMEL as possible, but to also include some “normal,” BMEL-free areas of bone marrow.

BMEL was segmented semi-automatically in FSE images and the volume was quantified using previously developed methods. Three peaks were quantified from the spectral data using in-house software: olefinic protons (unsaturated lipids), water, and bulk methylene protons (saturated lipids) at 5.35, 4.65, and 1.3 ppm, respectively. Two parameters, Water Content (WC) = I_water/I_olefin + I_water + I_methylene)*100% and Unsaturation Index (UI) = I_olefin/I_water + I_methylene)*100%, were quantified within and outside BMELs in each knee at each time point.

For baseline, non-paired t-tests were used to compare WC and UI in non-BMEL regions between control, ACL-injured and OA knees, and within BMEL between ACL-injured and OA knees. Paired t-tests were used to compare WC and UI between BMEL and non-BMEL regions in ACL-injured and OA knees, respectively. For the longitudinal comparison, the volume of BMEL in ACL-injured and OA knees were compared at different time points using paired t-tests, respectively. WC and UI at follow up in the original baseline BMEL regions were compared to baseline in ACL-injured and OA knees, respectively.

RESULTS:
At baseline, WC and UI of both ACL-injured and OA knees were higher than control (Figure 1), with the differences being significant between the: (1) ACL BMEL and control WC (23.0±12.5% vs. 2.2±0.8%, P<0.001) and UI (5.3±4.6% vs. 1.0±0.6%, P=0.02); (2) WC of OA BMEL (7.5±5.8%) and control (P=0.02); (3) WC of ACL BMEL and non-BMEL (4.3±2.4%, P<0.001); (4) WC of ACL and OA BMEL (P=0.004); and (5) WC of ACL non-BMEL and control (P=0.04).

The BMEL volume in ACL-injured knees significantly decreased from baseline to 1 year (4.0±2.7 cm³ vs. 0.3±0.5 cm³, P=0.002); but there was no significant change from 1 year to 2 year (0.2±0.2 cm³). No significant changes were observed in OA BMEL volume from baseline to 1 year (5.2±6.6 cm³ vs. 6.1±5.9 cm³).

In comparing the longitudinal marrow changes in the area of baseline BMEL of ACL-injured knees, it was observed that the both WC and UI decreased from baseline to 1 year with the difference being significant for WC (P<0.001, Figure 2). Among the five ACL-injured knees that had a 2 year follow-up scan, both WC and UI increased from 1 year to 2 year although not significantly (P=0.05, Figure 2). The 2 year WC (6.1±3.3%) and UI (5.4±4.0%) of ACL-injured knees were both greater than control with edge significances of P=0.06 and P=0.07, respectively. The OA WC and UI stayed relatively constant from baseline to 1 year.

Figure 1. Comparison of (a) WC and (b) UI between ACL and OA BMEL and non-BMEL regions and with control (*P<0.05). Figure 2. Longitudinal WC and UI changes in the ACL patients with 2 year follow-up. (*P<0.05).

DISCUSSION:
Elevated WC and UI were observed within BMEL in ACL-injured and OA knees. These results are congruent with observations from a previous cross-sectional study and suggest pathological changes in bone marrow within BMEL. Furthermore, WC within BMEL in ACL-injured knees are significantly higher than WC in OA BMEL, suggesting different biochemical changes taking place in ACL and OA BMEL.

It was also observed that WC and UI non-BMEL regions of ACL-injured and OA knees were greater than control. This implies that there may be biochemical changes throughout marrow within the entire knee and not just within the BMEL region, which in turn may be related to the cartilage degeneration of the joint.

Consistent with a previous study, this study found that most of the ACL BMEL had been resolved by 1 year. However, the WC and UI within the baseline BMEL regions were still higher than control. The WC and UI in the same region even increased (although not significantly) from year 1 to year 2 despite further decrease of BMEL volume. This suggests the presence of continuing bone marrow pathology in ACL-injured knees even after the BMEL has disappeared, and also possibly suggests permanent damage. This may contribute to the high risk of developing post-traumatic OA in ACL-injured knees.

The limitations of this study include small cohort size and no follow up data for control knees, and the MR spectral data being limited to only cover one BMEL if there were multiple BMELs in the knee.

SIGNIFICANCE:
For the first time, longitudinal changes of marrow composition in ACL-injured and OA knees were investigated, and evidence suggesting the possibility of different biochemical changes occurring in ACL and OA BMELs, and of permanent damage being sustained from ACL injuries, was found. Quantification of marrow composition may be a potential imaging marker for evaluating the joint degeneration in OA and acutely injured knees.

ACKNOWLEDGEMENTS:
The study was supported by NIH K25 AR053633, K25 AR053633-S and RO1 AR46905.