Osteoarthritis and Cartilage

Brief Report

3D bone-shape changes and their correlations with cartilage T1ρ and T2 relaxation times and patient-reported outcomes over 3-years after ACL reconstruction

Q. Zhong † ‡, V. Pedoia †, M. Tanaka †, J. Neumann †, T.M. Link †, B. Ma §, J. Lin ‡, X. Li † ‖ *

† Department of Radiology and Biomedical Imaging, University of California, San Francisco, San Francisco, CA, USA
‡ Arthritis Clinic and Research Center, Peking University People's Hospital, Beijing, China
§ Department of Orthopedic Surgery, University of California, San Francisco, San Francisco, CA, USA
‖ Program of Advanced Musculoskeletal Imaging (PAMI), Department of Biomedical Engineering, Cleveland Clinic, Cleveland, OH, USA

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SUMMARY

Purpose: (1) To identify bone-shape changes from baseline to 3-years after anterior cruciate ligament reconstruction (ACLR). (2) to assess association between changes in bone-shape from baseline to 6-months and changes in cartilage matrix and patient functions and symptoms from baseline to 3-years after ACLR.
Methods: Bilateral knees of 30 patients with unilateral ACL injuries were scanned at baseline, 6-months, 1-, 2-, and 3-years after ACLR. Bilateral knees of 13 controls were scanned at baseline, 1- and 3-years. Mean T1ρ and T2 values of each cartilage compartment were computed. Bone shape was quantified using statistical shape modeling (SSM) and 3D-MRI. Patient functions and symptoms were evaluated using Knee Injury and Osteoarthritis Outcome Score (KOOS).
Results: Statistically significant changes were observed in Femur 2 (medial femoral condyle [MF] shape), Femur 6 (intercondylar notch width), Tibia 1 (tibia plateau area), and Tibia 7 (medial tibia slope) over 3-years after ACLR. Statistically significant differences were observed between injured and control knees in several modes. Statistically significant correlations were found between changes in bone shape (ΔFemur 6, ΔFemur 8 [trochlea inclination and MF height], ΔTibia 1) from baseline to 6-months and that of cartilage T1ρ and T2 and KOOS from baseline to 3-years after ACLR.
Conclusion: Bone shape remodeling occurs after ACLR, and early bone shape changes (within 6 months) correlated with cartilage matrix and patient outcomes at 3-years after ACLR. Bone shape can be a promising imaging biomarker that stratifies patients at high risk for post-traumatic osteoarthritis (PTOA).

Introduction

Patients with anterior cruciate ligament (ACL) have a high risk of developing post-traumatic osteoarthritis (PTOA) even after ACL reconstruction (ACLR). Therefore, it is crucial to identify the predictors of PTOA development and clinical outcomes following ACL injury and reconstruction.

* Address correspondence and reprint requests to: X. Li, Department of Biomedical Engineering/ND20, 9500 Euclid Avenue, Cleveland Clinic, Cleveland, OH, USA. Tel: 216/442-8848.
E-mail addresses: drzqj@hotmail.com (Q. Zhong), Valentina.Pedoia@ucsf.edu (V. Pedoia), Matthew.Tanaka@ucsf.edu (M. Tanaka), Jan.Neumann@ucsf.edu (J. Neumann), Thomas.Link@ucsf.edu (T.M. Link), MaBen@ucsf.edu (B. Ma), linjianhao@pkuph.edu.cn (J. Lin), lix6@ccf.org (X. Li).

Using radiographs, Eggerding et al.[1] showed that the bone shape after ACL rupture predicted clinical outcomes 2 years later. Hunter et al.[2] reported longitudinal tibial curvature changes after ACL injury. Using statistical shape modeling (SSM), Pedoia et al.[3] developed 3D bone shape quantification methods and reported significant bone shape differences between ACL-injured and control knees and correlations between bone shape features and cartilage health at 1-year after anterior cruciate ligament reconstruction (ACLR).

Despite these promising results, no studies have yet investigated longitudinal changes of bone shape after ACL injury using comprehensive 3D modeling. The goals of this present study were to[1] identify distinct bone shape changes from baseline (after injury and before ACLR) to 3-years after ACLR; and[2] explore the

association between changes in bone shape from baseline to 6-months vs changes in cartilage T1ρ and T2 relaxation times and Knee Injury and Osteoarthritis Outcome Score (KOOS) from baseline to 3-years after ACLR.

Methods

Subjects

Bilateral knees of 30 patients with unilateral ACL injury were scanned prior to ACLR (at BL), and at 6-months (6M), 1-year (1Y), 2-years (2Y), and 3-years (3Y) time points after reconstruction; Bilateral knees of 13 healthy controls were imaged at BL, 1Y and 3Y. The KOOS results of each participant were recorded at every visit. All patients underwent single-bundle ACLR with either hamstring or posterior tibialis grafts, and standard rehabilitation protocols were implemented postoperatively. The patients' activities were evaluated at BL (patients were asked to fill for the pre-injury activity), 6-months, 1-years, 2-years and 3-years using Marx scores. Informed consent was obtained from all of the participants.

MRI imaging protocols

All MRI examinations were performed using a 3.0 T MRI scanner (GE Healthcare, Milwaukee, WI, USA) with an 8-channel phased array knee coil (Invivo, Orlando, FL, USA) (Appendix Table 1).

Quantification of bone shape

An in-house developed 3D MRI-based SSM was applied for the tibia and femur of all subjects to extract and compare relevant bone shapes[3]. First, tibia and femur were segmented semi-automatically. Then, a fully automatic landmark-matching algorithm on the basis of the analysis of local curvatures and spectral coordinates was implemented to map all vertices of the reference on the surface of all cases in the dataset. Last, principal component analysis was used to extract the key variation modes of all surfaces from the mean surface. The first 10 modes that demonstrated >90% of the total variations in the dataset were evaluated.

Quantification of cartilage T1ρ and T2 relaxation times

CUBE images from the injured knees were rigidly registered and down-sampled in the sagittal direction to match the first T1ρ images. Cartilage was segmented semi-automatically using in-house developed software on the CUBE images into six compartments (lateral femoral condyle [LF], lateral tibia [LT], medial femoral condyle [MF], medial tibia, femoral trochlea, and patella)[4]. All follow-up T1ρ and T2 images, were registered non-rigidly to the first T1ρ-weighted image of the injured knees at BL. The intensity-based multi-resolution pyramidal approach was implemented to accomplish the registration[5]. T1ρ and T2 maps were generated by fitting T1ρ- and T2-weighted images with mono-exponential decay pixel-by-pixel. Mean T1ρ and T2 values were calculated for each cartilage compartments.

Semi-quantitative MRI analysis

Abnormalities of the cartilage, meniscus, and bone marrow were evaluated blindly by musculoskeletal radiologists on the CUBE images using a modified whole-organ MRI score (WORMS)[6].

Statistical analysis

Longitudinal bone shape changes of injured and control knees were analyzed using generalized estimating equation (GEE) adjusted for age, gender, and body mass index (BMI).

Bone shapes of injured and control knees were compared cross-sectionally at BL, 1Y and 3Y by using unpaired t-tests.

Partial Pearson correlation coefficients were calculated in the injured knees between bone mode changes from BL to 6M defined as:

$$\Delta Femur = Femur_{6M} - Femur_{BL}; \quad \Delta Tibia = Tibia_{6M} - Tibia_{BL} \tag{1}$$

and T1ρ and T2 changes from BL to 3Y defined as:

$$\Delta T1_\rho = T1\rho_{3Y} - T1\rho_{BL}; \quad \Delta T2 = T2_{3Y} - T2_{BL} \tag{2}$$

adjusted for demographics (age, gender, BMI), meniscus injury and treatment, time from injury to surgery, and cartilage WORMS of corresponding compartment at BL. Partial Pearson correlation coefficients were also calculated in the injured knees between bone mode changes from BL to 6M (ΔFemur and ΔTibia) and KOOS changes from BL to 3Y (ΔKOOS), adjusted for demographics (age, gender, BMI), meniscus injury and treatment, time from injury to surgery, and corresponding KOOS item at BL.

All the statistical analyses above were performed with IBM SPSS Statistics Version 20.0. The level of significance was $P < 0.05$.

Results

Demographic and clinical characteristics

The demographics of all subjects are shown in Appendix Table 2. No significant differences in age, gender and BMI were observed between patients with ACL injury and healthy controls.

The cartilage and meniscus WORMS gradings of injured knees at BL are shown in Appendix Table 3. Twelve patients had no meniscal tear and no treatment; 10 had tears but no treatment; eight had tears and partial meniscectomy. No significant differences were found between Marx scores at BL and after 3 years, as shown in Appendix Table 4.

Bone shape analysis

Statistically significant longitudinal changes were observed in two femur (Femur 2 and Femur 6) and two tibia (Tibia 1, Tibia 7) modes of the injured knees (Fig. 1). Statistically significant differences were observed between injured and control knees in Femur 6 at BL, in Femur 6, Tibia 7 at 1Y, and in Femur 2, Femur 6, and Tibia 1 at 3Y (Fig. 1).

We illustrated the major bone-shape features associated with each mode that showed significance in the study (Appendix Fig. 1), with an effort to illustrate the physical meaning of bone modes. It shall be noted that these shape features are the major ones associated with these modes. Each mode represents a whole set of 3D bone shape features beyond a single shape feature.

Correlation between the changes of bone shape and that of cartilage T1ρ and T2 and KOOS

Statistically significant relationships between changes in bone shape (ΔFemur 6, ΔFemur 8, ΔTibia 1) from BL to 6M and changes in cartilage T1ρ and T2 and KOOS from BL to 3Y were found (Table I). Increasing width of the intercondylar notch (ΔFemur 6) was predictive of more cartilage degeneration in LT and MF, and increasing
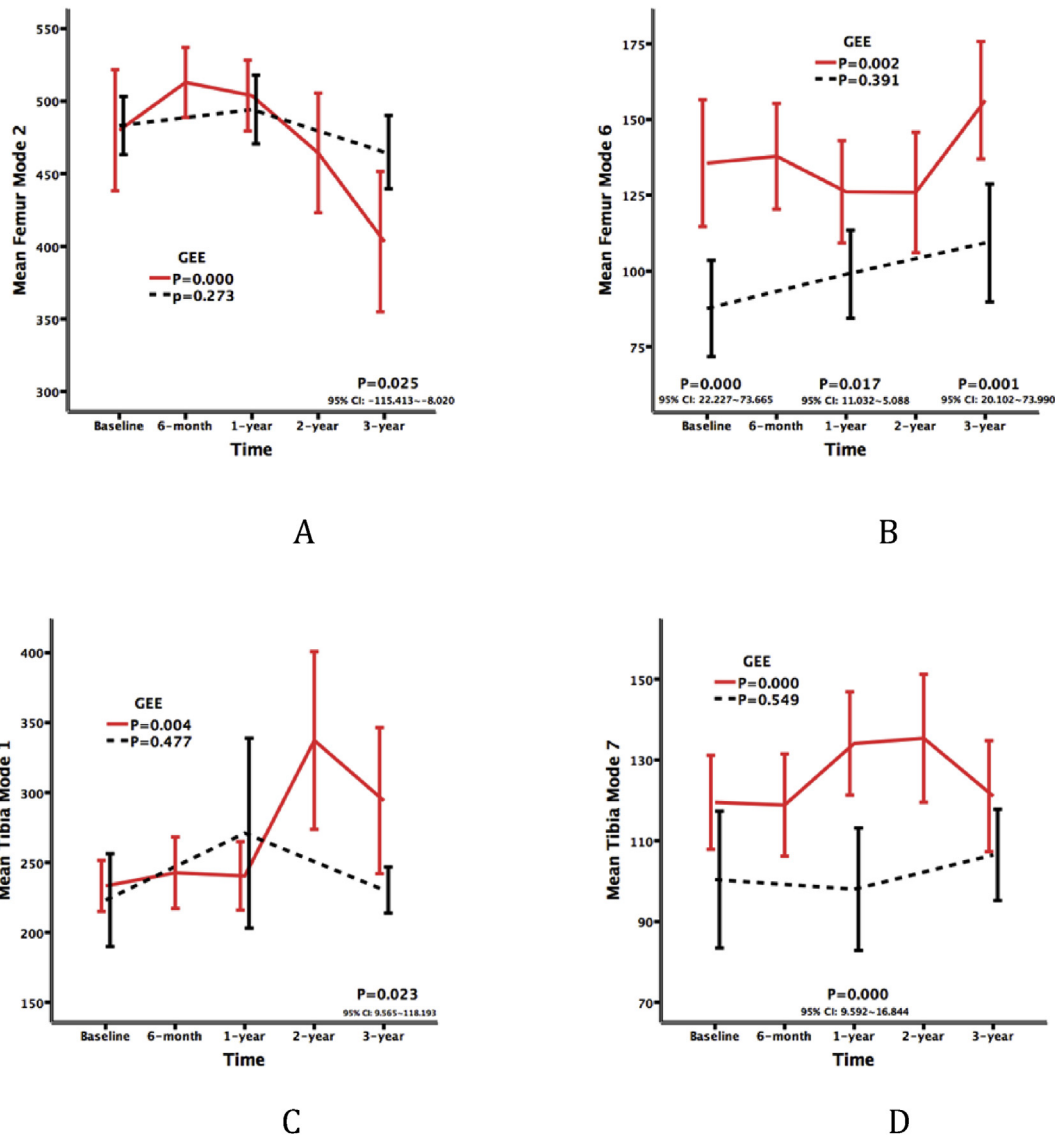
Fig. 1. Longitudinal changes in bone-shape modes. (A) Femur Mode 2 (associated with medial femoral condyle [MF] shape); (B) Femur Mode 6 (associated with notch width); (C) Tibia Mode 1 (associated with tibia plateau area); (D) Tibia Mode 7 (associated with medial tibia slope). Red line, Injured knees group; black dashed line, Control knees group. *P* values of generalized estimating equation (GEE) models are shown on the right of each graph. *P* values < 0.05% and 95% CI of cross-sectional comparison between injured and control knees at baseline, 1 year, and 3 years are shown within the text boxes above the X axis of each graph.

Table I
Relationship between the changes of bone shape and that of cartilage T1ρ & T2 and Knee Injury and Osteoarthritis Outcome Score (KOOS)

Bone Shape Δ F6		Cartilage LT Δ T1ρ		Cartilage MF Δ T2	
BL F6	6M F6	BL T1ρ	3Y T1ρ	BL T2	3Y T2
135.60 ± 56.11	137.87 ± 46.64	34.33 ± 2.94 R=−0.419···P=0.023	34.60 ± 3.55	30.17 ± 2.23 R=−0.472···P=0.010	33.33 ± 2.17
		95% CI: −0.681~−0.063		95% CI: −0.715~−0.172	
Bone Shape Δ F8		Cartilage Patella Δ T2		KOOS Δ Pain	
BL F8	6M F8	BL T2	3Y T2	BL	3Y
264.97 ± 49.03	256.70 ± 39.13	28.23 ± 2.39 R=0.510···P=0.005	29.53 ± 3.19	76.89 ± 17.37 R = −0.556···P = 0.003	91.8 ± 9.07
		95% CI: 0.177~0.739		95% CI: −0.773~−0.223	
Bone Shape Δ T1		Cartilage LT Δ T2			
BL T1	6M T1	BL T2	3Y T2		
233.27 ± 48.92	242.67±68.28	25.50 ± 2.24 R=0.433···P=0.019	25.73±2.27		
		95% CI: 0.080~0.690			

area of the tibial plateau (ΔTibia 1) was predictive of more cartilage degeneration in LT. The MF's becoming more proximal and increases of the inclination of trochlea (ΔFemur 8) were predictive of more cartilage degeneration in the patella and more pain.

Discussion

In this study, statistically significant bone shape changes, including femur sphericity, notch width, and tibial area and slope, were observed over 3-years after ACLR. The early bone shape changes (within the first 6-months after surgery), specifically femur notch width and alignment, and tibial area, were correlated with changes in cartilage T1ρ and T2 relaxation times and patients' symptoms and function as measured with KOOS at 3-years after ACLR.

The tibia plateau area (Tibia 1) of injured knees started to increase from 1Y, and it was larger than the counterpart of control knees at 3Y. This increasing area of the tibia plateau might be an early sign of the joint degeneration after ACLR, as in the literature the area of the tibia plateau was reported to increase in response to risk factors for knee OA in healthy subjects and to increase over time in subjects with knee OA[2]. In addition, increasing in tibia plateau area from BL to 6M was predictive of more cartilage degeneration in LT from BL to 3Y in this study. Similarly, Antony et al.[7] suggested higher BL tibia bone area is associated with greater knee cartilage loss over 2 years by measuring a total of 324 subjects at BL and at 2Y. Haverkamp et al.[8] found out the width of tibia bones was increased in patients with OA, and knees with cartilage defects also had wider tibia bones compared with knees without cartilage defects.

Increased posterior tibia slope has been suggested as not only a risk factor for initial ACL injury and the failure of ACLR graft[9,10], but also a risk factor for OA[11]. Increased posterior tibia slope, as indicated by Tibia 7, was observed in this study especially from 6M to 1Y. The posterior tibia slope was statistically significant higher in ACLR knees at 1Y compared with that of control knees. However, a decrease of tibia slope was observed from 2Y to 3Y, and a longer follow up is warrant to investigate this bone shape feature further.

For the femur, the sphericity of the MF condyle (Femur 2) of injured knees changed over time from oval to spherical at 6M. The sphericity change is probably due to the abnormal kinematics of ACLR. Lansdown et al.[12] found correlations of more spherical MF condyle with an increasingly anteriorly positioned tibia relative to the contralateral knee after injury and at 1-year after ACLR.

The intercondylar notch width (Femur 6) of injured knees was narrower than that of control knees at BL, which is consistent with results from previous studies that have demonstrated narrower width of the intercondylar notch is a morphological risk factor for ACL rupture[13]. Furthermore, our study suggested increasing width of the intercondylar notch from BL to 6M is predictive of more cartilage degeneration in LT and MF from BL to 3Y. This was a surprising finding, because, normally, osteoarthritic knees tend to have a narrower intercondylar notch, and we would expect subjects with decreasing notch width would have more cartilage degeneration. It is not clear what the potential mechanism might be for the association between increasing notch width at the early postoperative stage (6M) and more cartilage degeneration at the later stage (3Y), which warrants further investigation.

Our results suggest the MF's becoming more proximal and inclination of trochlea increasing (Femur 8) from BL to 6M are predictive of not only more cartilage degeneration in the patella,

but also more knee pain at later stages. Previously, Landsdown et al.[12] reported the association between MF becoming more proximally and greater side-to-side difference in the tibia position at the extended position measured by loaded MRI 1-year after ACLR. This observation, with results from our study, suggests there is an interrelationship between bone geometry, joint biomechanics, and degeneration after ACL injuries.

Interestingly, the Femur eight mode was the only one that showed a statistically significant correlation with patient-reported symptoms, specifically pain, at 3Y after ACLR. This correlation may be partially due to the trochlear geometry changes as presented by this mode. Previously, Kalichman et al.[14] found that increasing trochlear angle was associated with WOMAC pain levels in subjects with symptomatic knee OA. In another study with 70 patients 5–10 years after ACLR, Culvenor et al.[15] observed that patellofemoral OA was associated with worse knee-related symptoms.

Despite the promising outcomes above, several limitations must be acknowledged[1]: Patellae were not included in the SSM[2]; The interval between ACL injury and ACLR spanned 4–37 weeks, which may have introduced variations to the data[3]; WORMS grading has limitations for evaluating acutely injured knees and other scoring system such as ACLOAS shall be considered for future studies. It should be noted, however, that the cartilage lesion grading is very similar with WORMS and ACLOAS. Also meniscal grading is similar but ACLOAS adds post-operative findings such meniscal repair and meniscectomy, which is not applicable to our study as pre-operative lesions were analyzed;

[4] The study sample size was relatively small and since this is an exploratory and hypothesis forming study results were not adjusted for multiple comparisons[5]. The clinical significance of the observed bone shape findings remains unclear and needs to be explored in future studies.

In conclusion, our results suggest statistically significant bone shape changes occur after ACL injury and reconstruction. Early bone shape changes predicted cartilage degeneration and patient self-reported outcomes including pain at later stages. Such imaging markers could help to stratify patients who have high risks of developing PTOA after ACLR.

Author contributions

- Conception and design: Xiaojuan Li, C. Benjamin Ma
- Analysis and interpretation of the data: Qunjie Zhong; Valentina Pedoia; Xiaojuan Li, Jianhao Lin, C. Benjamin Ma
- Drafting of the article: Qunjie Zhong; Xiaojuan Li
- Critical revision of the article for important intellectual content: all authors
- Final approval of the article: All authors
- Provision of study materials: Xiaojuan Li, Benjamin Ma
- Statistical expertise: Qunjie Zhong; Xiaojuan Li
- Obtaining of funding: Xiaojuan Li; Benjamin Ma
- Administrative, technical, or logistic support: Matthew Tanaka
- MRI WORMS grading: Jan Neumann, Thomas M. Link

Conflict of interest
All authors have no conflicts of interests to disclose.

Role of the funding source

Appendix Table 1
MRI image protocol for cartilage and bone shape

Sequence	TR/TE (ms)	ETL	Matrix	FOV (cm)	Slice thickness (mm)	Other parameters
Sagittal T2 fast spin-echo (FSE)	4,000/49.3	9	512*512	16	1.5	—
Sagittal 3D fast spin-echo (CUBE)	1500/25	32	384*384	16	1	—
Sagittal Combined T1 ρ/T2-weighted (MAPSS)	9/3		256*128	14	4	Spin-lock frequency 500 Hz T1ρ time spin-lock [0, 10, 40, 80] ms T2 preparation TE [0, 13.7, 27.3, 54.7] ms

TR: repetition time; TE: echo time; ETL: Echo train length; FOV: field of view.

Appendix Table 2
The baseline demographic characteristics

	ACL injury subjects ($N = 30$)	Healthy controls ($N = 13$)
Age (Years old)	32.00 ± 7.97	33.84 ± 5.03
Gender		
Female	15 (50.00%)	8 (61.54%)
Male	15 (50.00%)	5 (38.46%)
BMI (Kg/m2)	24.10 ± 2.71	23.62 ± 2.52
Time from Injury to Surgery (Days)	74.38 ± 53.52 (28−257)	
Time from Injury to Baseline MRI Scanning (Days)	17.70 ± 28.80 (1−158)	

Appendix Table 3
The baseline WORMS of cartilage and meniscus of injured knees

Cartilage WORMS

	Grade	Frequency	Percent (%)		Grade	Frequency	Percent (%)		Grade	Frequency	Percent (%)
MFC	0	27	18	LFC	0	25	16.67	P	0	23	15.33
	1	1	0.67		1	2	1.33		1	2	1.33
	2	1	0.67		2	2	1.33		2	2	1.33
	3	1	0.67		3	1	0.67		3	3	2
MT	0	25	16.67	LT	0	16	10.67	TrF	0	26	17.33
	1	5	3.33		1	9	6		1	2	1.33
	2	0	0		2	5	3.33		2	0	0
	3	0	0		3	0	0		3	2	1.33

Meniscus WORMS

|	Grade	Frequency	Percent (%)		Grade	Frequency	Percent (%)
MM	0	14	46.67	LM	0	12	40
	1	4	13.33		1	5	16.67
	>=2	12	40		>=2	13	43.34

Cartilage WORMS grading scales: 0 = normal cartilage; 1 = normal thickness but increased or otherwise abnormal signal on fluid sensitive sequences; 2 = partial thickness focal defect <1 cm in greatest width; 3 = multiple areas of partial-thickness defects intermixed with areas of normal thickness, or a partial-thickness defect wider than 1 cm but <75% of the region.
Meniscus modified WORMS grading scales: 0 = normal; 1 = intrasubstance abnormalities; 2 = non-displaced tear.

Appendix Table 4
Marx Scores of the patients' activities at each time point (BL was for pre-injury activity)

Running

BL	6-Months	1-Years	2-Years	3-Years
2.33 ± 0.69	1.78 ± 0.81	1.83 ± 0.79	2.22 ± 0.65	2.22 ± 1.00

Cutting

BL	6-Months	1-Years	2-Years	3-Years
2.08 ± 1.00	1.58 ± 1.16	1.50 ± 0.90	1.58 ± 0.79	1.92 ± 0.90

Decelerating

BL	6-Months	1-Years	2-Years	3-Years
2.29 ± 0.83	1.71 ± 0.99	1.86 ± 0.77	1.93 ± 0.62	2.43 ± 0.65

Pivoting

BL	6-Months	1-Years	2-Years	3-Years
2.22 ± 0.67	1.89 ± 1.05	1.56 ± 0.88	1.78 ± 0.83	2.11 ± 0.60
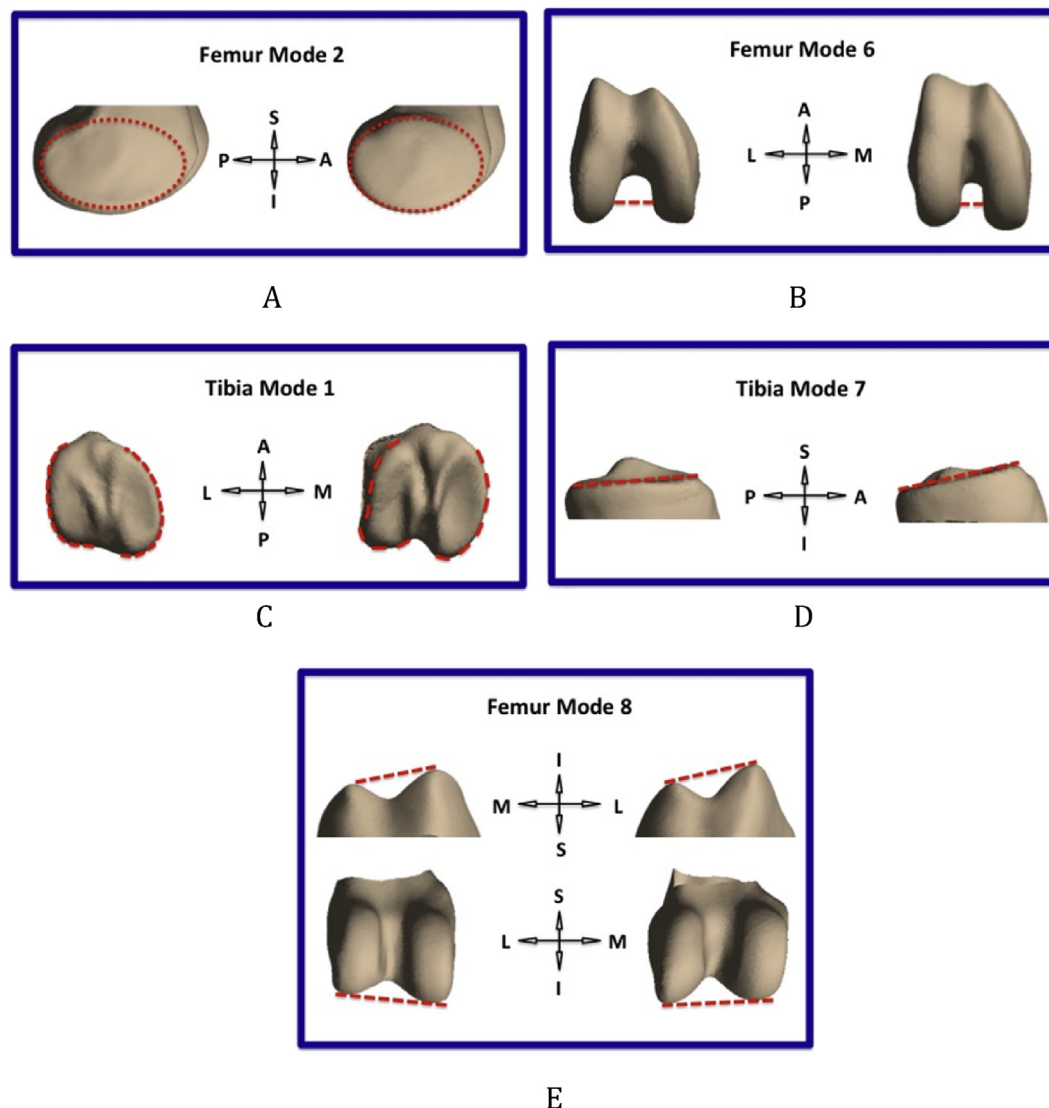
Appendix Fig. 1. The physical interpretation of bone shape modes. Left: representative shapes from control knees; right: representative shapes from ACL injured knees. (A) Femur Mode 2: (medial femoral condyle shape); (B) Femur Mode 6: (notch width); (C) Tibia Mode 1: (tibia plateau area); (D) Tibia Mode 7: (medial tibia slope); (E) Femur Mode 8: (trochlea inclination and medial femoral condyle height). A: anterior; P: posterior; S: superior; I: inferior; M: medial; L: lateral. Note: these shape features are the major ones associated with these modes. Each mode represents a whole set of 3D bone shape features beyond a single shape feature.

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