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Greater Lateral Femorotibial Cartilage Loss in Osteoarthritis Initiative Participants with Incident Knee Replacement: a Prospective Cohort Study

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Abstract

Purpose—To explore whether baseline to 12-month follow-up (M) change in femorotibial cartilage thickness (differs between subjects who received a KR between 24M and 60M from those without KR.

Methods—In this prospective cohort study, 531 right knees from Osteoarthritis Initiative participants with definite radiographic KOA (KLG2–4) were studied. Segmentation was applied to coronal fast low angle shot (FLASH) magnetic resonance images (MRI), to quantitatively determine cartilage thickness in 16 femorotibial subregions. Unadjusted p-values (t-tests) and p-values adjusted for age, baseline BMI, KLG and sex (generalized estimating equation models) were used to evaluate differences in longitudinal one-year rates of cartilage thickness between KRs and non-KRs, with TKA status as fixed effect.

Results—Of the 531 participants (age 63±9y, BMI 30±4.8) 40 received a femorotibial KR within 4 years. At baseline, KRs had thinner medial and lateral femorotibial cartilage (−15%; $p<0.001$) than non-KRs. Longitudinal cartilage thickness change was significantly greater in KRs than in non-KRs in a) the total femorotibial joint (area under curve [AUC]=0.64), b) the lateral compartment (AUC=0.66), c) both tibiae (AUC≥0.61), and d) the first 9 (of 16) ordered values

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CONTRIBUTIONS

All authors made substantial contributions to all three sections: (1) the conception and design of the study, data acquisition, analysis and interpretation; (2) drafting the article or revising it critically; (3) final approval of the version to be submitted.

COMPETING INTERESTS

Wolfgang Wirth, Susanne Maschek, and Sebastian Cotofana have part time appointments with Chondrometrics GmbH, a company providing quantitative MR image analysis services to researchers and pharmaceutical industry. Wolfgang Wirth and Susanne Maschek are co-owners of Chondrometrics GmbH; Felix Eckstein is CEO and co-owner of Chondrometrics GmbH. Felix Eckstein has provided consulting services to Mariel Therapeutics and MerckSerono; he has received funding support for this study from NIH, Pfizer, Eli Lilly, Novartis, MerckSerono, Glaxo Smith Kline, Wyeth, and Centercor, and funding support not related to this study from Stryker, Abbvie, Kolon, Synarc, BICL, and Ampio. At the time of the study, Mari John was employed by Novartis Pharma AG; Christoph Ladel is employed by Merck KGaA, Darmstadt, Germany. Wolfgang Hitzl and Michael Nevitt have no competing interests to declare.

(OVs) of subregion change (AUC=0.64–0.69). Discrimination was stronger for KRs that occurred at 24/36M (n=18) than for those at 48M/60M (n=22).

Conclusions—Knees with incident KR displayed smaller baseline cartilage thickness and greater lateral as well as location-independent (OV) femorotibial cartilage loss than non-KRs. Discrimination of cartilage loss was greater for KRs occurring within 2 years after the measurement than for those occurring later.

Keywords

Imaging Biomarker Qualification; Knee replacement; Knee Osteoarthritis; Cartilage Thickness; Magnetic Resonance Imaging

INTRODUCTION

Knee osteoarthritis (OA) is associated with increased health care utilization, a large part of the costs being related to knee replacement (KR) surgery (1). Currently, more than 4% of the U.S. adults aged ≥50 years live with a KR, and the lifetime risk of primary KR at age 25 is 7.0/9.5% in men/women. Over the last decade, the number of KRs in the U.S. has doubled (2), and it has been estimated that these numbers increase further over coming years (3, 4).

Magnetic resonance imaging (MRI) has been developed for quantitatively measuring structural progression of knee OA, by virtue of directly and accurately delineating articular cartilage and other synovial tissues (5, 6). Yet, regulatory guidance for the approval of disease modifying OA drugs (DMOADs) requests that reductions in structural pathology should be associated with improvements in clinical outcomes (5, 6). Part of the “imaging biomarker qualification process” hence is to study, to what extent structural outcomes are related to clinical outcomes. Imaging biomarkers capable of predicting relevant clinical endpoints with socioeconomic impact, such as KR, are of particular value for testing DMOAD efficacy in clinical trials (5, 6).

Previous nested case-control studies from the Osteoarthritis Initiative (OAI) (7) reported that medial (MFTC), but not lateral femorotibial compartment (LFTC) cartilage loss was significantly elevated in knees undergoing KR in the subsequent year, compared with matched controls (8, 9). However, no prospective cohort study from the OAI has yet examined to what extent rates of cartilage loss over a defined observation interval are related to the advent of KR in following years, and to what extent location-independent analysis approaches of subregional cartilage change, i.e. ordered values (OVs) (12, 14–15) predict KR. The purpose of the current analysis therefore was to elucidate whether location-independent analysis of femorotibial cartilage thickness change between baseline and 12 month follow-up [12M]) is related to the risk of subsequent KR. Further, this study was performed using the double oblique coronal spoiled gradient echo (specifically fast low angle shot; FLASH) MRI sequence (7), a protocol commonly used in multicenter clinical trials. The DESS sequence previously used in OAI case-control studies (10, 11) is currently available from one manufacturer only, whereas spoiled gradient echo can be acquired on platforms of most current MRI vendors (6) and can hence be more readily applied in multicenter studies.

METHODS

Radiographic classification and sample selection

The OAI (7), the subsample studied here, and its demographics have been described previously (12, 13). Radiographic classification of the knees relied on the central radiographic readings (release 0.5) at Boston University assigning a Kellgren Lawrence grade (KLG) and independently, an Osteoarthritis Research Society International (OARSI) atlas osteophyte and joint space narrowing (JSN) grade to each knee (7). Cartilage thickness measurements (please see below) were available for the right knees of 837 OAI participants (12, 13): 112 were from the healthy reference cohort; of those from the incident/progression cohort, 93 were KLG0, 100 KLG1, 309 KLG2, 162 KLG3, and 61 KLG4, based on central radiographic readings. The 532 knees with definite radiographic knee OA (KLG2–4) were included in the analysis, since none of the knees without baseline radiographic knee OA developed incident KR.

To be eligible as a case in this study, a KR had to be recorded at 24, 36, 48, or 60M. KRs were confirmed by radiography and/or by review of hospital records. One of the 532 knees received a femoro-patellar KR and was excluded from the study.

MRI acquisition and analysis

The OAI MRI acquisition and image analysis technology used here have been described previously (12, 13). 3 Tesla double oblique coronal FLASH MRIs of the right knees were acquired (7), and longitudinal analysis of femorotibial cartilage thickness change in this subsample was funded by a consortium of industry partners, the OAI coordinating centre, and an image analysis company (Chondrometrics GmbH) (12).

Segmentation of baseline and 12M follow-up MRIs was performed by 12 experienced readers with blinding to time-point, all segmentations being quality controlled by one expert (S.M.) (12). Mean cartilage thickness (ThCtAB.Me) change between baseline and 12M was computed in the total femorotibial joint (FTJ), MFTC, LFTC, medial (MT) and lateral tibia (LT), medial (cMF) and lateral weight-bearing femoral condyles (cLF) and across 16 femorotibial subregions (12, 14). Non-location-dependent rates of subregional cartilage loss were determined using an extended ordered value (OV) approach (12, 14): To that end, the cartilage thickness change (in μm) in the subregion with the greatest loss was assigned to OV1, the one with the second greatest loss to OV2, and so forth, and the one with the least loss or the greatest increase to OV16 (14).

Statistical analysis

All analyses were performed using SPSS 19 (IBM Corp. release 2010) and STATISTICA (Statsoft; Version 10). Continuously distributed data were checked for possible outliers and for deviations from normal distributions using probability plots. Unadjusted p-values of the cartilage thickness loss (μm) between baseline and 12M were determined between the 40 femorotibial KRs and the 491 non-KRs, using 2-sided, unpaired Student t-tests and Welch's t-tests. Generalized estimation equation models (GEE) were applied, with TKA status at 60M as fixed effect, and with age, BMI, KLG and sex as covariates. The Huber/White

sandwich estimator was used to estimate the covariance matrix. The GEEs were based on covariate means of 63.2y for age and of 30 for the BMI. 95% confidence intervals (CIs) were determined for mean changes of positive and negative TKA status at 60M. A p-value <5% indicated a statistically significant difference. Corresponding area under the curve values (AUCs) and their 95% CIs were computed using receiver operator curve (ROC) analyses. No adjustments for multiple comparisons were made in this exploratory study. However, the primary analytic focus was set on FTJ longitudinal cartilage loss, as a global measure of change, and the secondary focus on OV1, as a location-independent measure of maximum subregion cartilage loss. Sensitivity analyses were performed by separate analysis of knees replaced and 24/36M (early), those at 48/60M (late) and those with KLG 3 or 4.

RESULTS

Demographics and baseline cartilage thickness

Of the 531 knees (age 63±9y; BMI 30±4.8; 63% from women), 308 (58%) were KLG2, 162 (30%) KLG3, and 61 (12%) KLG4; 103 (19%) had no or medial=lateral JSN, 328 (62%) medial>lateral JSN, and 100 (19%) lateral>medial JSN.

40 knees (7.5% of the entire sample) were replaced by a femorotibial KR within 48M: 8 (17%) at 24M and 10 (21%) at 36M (“early”), and 10 (21%) at 48M and 12 (25%) at 60M (“late”). Of these (age 65.2±9y; BMI 29.7±4.9; 75% from women) 10 (25%) were baseline KLG2 and a higher percentage, i.e. 15 (37.5%) were KLG3, and 15 (37.5%) were KLG4. The higher the baseline KLG, the higher was the percentage of KR within 48M. i.e. 2.3% (7/308) for KLG2, 5.6% (9/161) for KLG3, and 19.7% (12/61) for KLG4 knees. Two KRs (5%) had no or medial=lateral JSN, 25 (62.5%) medial>lateral JSN, and 13 (32.5%) lateral>medial JSN. At the time point prior to KR, 4 did not have a central KLG reading; of those remaining, 3 (8%) were KLG2, 13 (36%) KLG3, and 20 (56%) KLG 4; the distribution of medial>lateral vs. lateral>medial JSN was similar to that at baseline.

KRs had thinner baseline femorotibial cartilage than non-KRs (6.05±1.2mm vs. 7.12±1.10 mm; difference −15.0%; AUC=0.74, 95% CI [0.65,0.83]); the differences was of similar magnitude in the MFTC (-15.3%; AUC=0.66, 95% CI [0.56,0.76]) and LFTC (-14.7%; AUC=0.68, 95% CI [0.58,0.78]), respectively.

Longitudinal change in KRs vs. non-KRs

Cartilage thickness change was significantly greater in KRs than non-KRs in the FTJ (primary analytic focus; AUC=0.64, 95%CI: 0.54–0.74), and in OV1 (secondary analytic focus; AUC=0.69, 95%CI: 0.60–0.77). The mean changes, 95% CIs for the difference of means, the unadjusted and adjusted p-values, and AUCs for all measures are displayed in Table 1. There was significantly greater loss in KRs vs. non-KRs in LFTC but not in MFTC (Table 1). These results were confirmed when limiting the analysis to KLG3/4 cases vs. KLG3/4 controls (Supplement Table 1), and the GEEs confirmed that, in this sample of KLG3/4 knees, KR status was significantly associated with cartilage loss whereas KLG was not (data not shown).

Cartilage loss was significantly greater in KRs than in non-KRs in the MT and LT, but not in the cMF and cLF (Table 1). The cLF showed significant differences between KRs and non-KRs when adjusting for age, BMI, and KLG, but not in the non-adjusted analysis. (Table 1). Further, cartilage thickness loss was significantly greater in KRs than non-KRs in the first 9 (of 16) OVs according to unadjusted p-values, and significant in the first 12 OVs according to adjusted p-values. They were not significantly different in OV13–16, in which cartilage thickening was observed in KRs and non-KRs (Table 1). Amongst femorotibial subregions, cartilage loss was significantly greater in the central lateral tibia ($p<0.01$), and in the anterior medial tibia, anterior lateral tibia, and external weight-bearing lateral femur (all $p<0.05$; data not shown). In KRs, cLT and ccLF were amongst the most frequent locators corresponding to OV1, both in cases with medial and lateral disease. The location of OV1 in KRs and non-KRs is listed in Table 2.

Discrimination between KRs and non-KRs was stronger for KRs that occurred early (24/36M follow-up) than for those than occurred late (48M/60M) (Fig. 1); in early KRs, the AUC in LFTC was 0.69 (95% CI 0.54–0.82) and in late KRs it was 0.63 (95% CI 0.51–0.76).

DISCUSSION

Imaging biomarkers capable of predicting relevant clinical endpoints with socioeconomic impact, such as KR, are of particular value for testing the efficacy of disease modifying intervention in clinical trials (6). From that perspective, the results of this study confirm that quantitative loss in cartilage thickness may be a valuable drug target, and a powerful marker for evaluating the efficacy of DMOAD intervention. Yet, the AUCs were only moderate, and this clearly highlights limitation in using “cartilage thickness loss by MRI” as a diagnostic radiological test for predicting KR at an individual level.

A limitation of the current study is that only a subsample of the OAI was studied, and that KRs had more advanced radiographic disease than non-KRs. Given greater rates of cartilage loss with more advanced radiographic disease (12–15), this was, however, accounted for by computing p-values adjusting for KLG (age, sex and BMI) using GEEs and by confirming the findings when limiting the analysis to KLG3/4 cases vs. KLG3/4 controls. Also, due to the low sample size and small number of KRs observed, the study did not have sufficient power to study knees with primarily medial and lateral radiographic disease separately, Our current study extends previous findings in several important ways: In contrast to two previous nested case-control studies (8, 9), this is the first prospective cohort study on quantitative cartilage loss in KRs and non-KRs in the OAI. Further, the current study relied on imaging with a double oblique coronal FLASH rather than on the DESS MRI sequence (8, 9), with the FLASH being more widely available across different vendors and therefore more commonly used in multicenter clinical trials (6, 10, 11). In contrast to the previous case-control (8, 9) and other prospective cohort studies (5), our findings highlight the importance of cartilage loss in the LFTC, particularly in the LT, in predicting KR. Previous studies reported a more important role of the MFTC, particularly the MT. The reason for the discrepancy may be the relatively high proportion of knees with lateral disease in the current sample, particularly in those that had incident KR (about one third). This proportion is

somewhat greater than that in the right knees of the total OAI sample, in which 18% of knees with JSN had a lateral JSN grade > the medial JSN grade, 81% had medial JSN>lateral JSN; and 1% had lateral JSN = medial JSN. Lateral JSN was shown to be a strong predictor of LFTC but not MFTC cartilage loss, and vice versa (15). Use of non-location-dependent analysis approaches, such as OVs (14), may be of particular benefit in this context, as these were at least as discriminatory between KRs and non-KRs as LFTC cartilage loss. Since OVs are independent of the location at which cartilage loss occurs in the joint, they are less sensitive than location-specific structural outcomes as to whether knees have predominantly medial or lateral disease (15), in a given sample. Our results confirm recent findings that cartilage loss is more predictive of KR if the observation interval immediately precedes surgery, rather than being in the more distant past (9). Yet, LFTC cartilage loss was predictive of KR, even if surgery occurred 2–4 years after the observation interval.

In conclusion, in this prospective cohort study in OAI participants, knees with incident KR had greater longitudinal cartilage loss than non-KRs, in the LFTC and using non-location-dependent analyses. Discrimination between KRs and non-KRs was greater for KRs occurring within 2 years after the measurement. The results confirm quantitative cartilage loss to be a potent structural outcome in clinical trials on DMOAD efficacy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance and innovation

- First study to identify differences in lateral femorotibial cartilage loss, between knees with subsequent replacement (KR) compared with controls.
- First study to show that location-independent analysis of (subregional) cartilage thickness change (OVs) predicts with future knee replacement (KR).
- First study to use the spoiled gradient echo sequence (FLASH) commonly used in clinical trials using a prospective cohort design in OAI participants who receive knee replacement (KR), whereas previous case-control designs have relied on the vendor-specific DESS sequence.

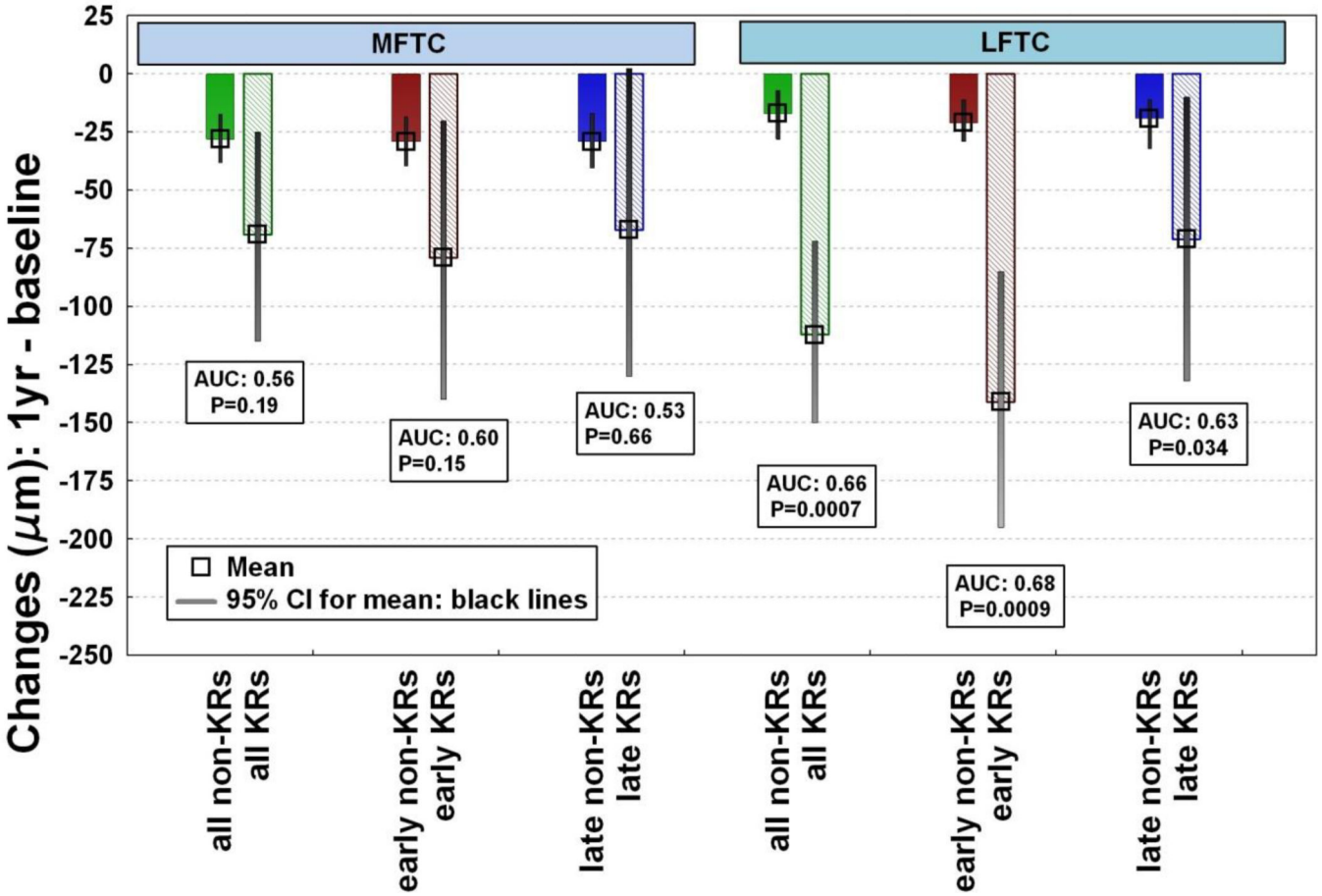

Figure 1.

12 month change in medial (MFTC) and lateral femorotibial compartment (LFTC) cartilage thickness (mm) in knees with surgical knee replacement (KR) and in those without replacement (non-KRs), in KRs vs. non-KRs at 24M and 36M follow-up (early), and in KRs vs non-KRs at 48M and 60M follow-up (late). Results based on model adjusted model.

Table 1

12 month change in femorotibial cartilage thickness (μm) in knees with surgical knee replacement (KR; n= 40) and without replacement (non-KRs; n=491).

	KRs	Non-KRs		t-and Welch's t-tests	GEE-model	
Measure	**Mean±SD**	**Mean±SD**	**95% CI difference of means**	**unadjusted p-value**	**adjusted p-value**	**AUC [95% CI]**
FTJ	−152±291	−45±180	[−168,−45]	0.027*	0.037*	0.64 [0.54,0.74]
MFTC	−67±204	−28±117	[−80,1]	0.23	0.41	0.56 [0.45,0.67]
LFTC	−86±150	−17±108	[−104,−32]	0.007*	0.004*	0.66 [0.57,0.76]
MT	−38±80	−8±51	[−47,−12]	0.024*	0.037*	0.61 [0.51,0.71]
cMF	−28±137	−20±87	[−38,21]	0.7	0.95	0.53 [0.42,0.64]
LT	−46±58	−16±61	[−50,−10]	0.003*	0.01*	0.65 [0.56,0.74]
cLF	−40±121	−2±72	[−63,−14]	0.053	0.22	0.6 [0.49,0.71]
OV1	−241±165	−164±131	[−121,−35]	0.005*	0.007*	0.69 [0.6,0.77]
OV2	−184±145	−112±85	[−101,−43]	0.004*	0.022*	0.68 [0.58,0.77]
OV3	−141±130	−83±64	[−81,−35]	0.008*	0.006*	0.65 [0.55,0.75]
OV4	−112±98	−64±52	[−67,−30]	0.004*	0.004*	0.67 [0.57,0.77]
OV5	−90±87	−49±48	[−58,−24]	0.005*	0.004*	0.66 [0.56,0.76]
OV6	−67±62	−37±47	[−45,−14]	0.005*	0.006*	0.65 [0.55,0.75]
OV7	−51±59	−25±43	[−40,−12]	0.009*	0.014*	0.64 [0.54,0.75]
OV8	−37±56	−14±40	[−36,−9]	0.016*	0.027*	0.64 [0.53,0.75]
OV9	−24±54	−4±39	[−34,−7]	0.024*	0.035*	0.63 [0.53,0.74]
OV10	−11±55	7±39	[−31,−4]	0.054	0.062	0.63 [0.53,0.74]
OV11	2±52	18±38	[−29,−3]	0.07	0.07	0.63 [0.53,0.73]
OV12	17±50	29±38	[−25,1]	0.14	0.18	0.61 [0.51,0.72]
OV13	37±51	43±39	[−19,6]	0.44	0.54	0.57 [0.46,0.67]
OV14	54±60	60±43	[−20,8]	0.53	0.67	0.58 [0.48,0.67]
OV15	80±75	82±50	[−19,15]	0.88	0.90	0.53 [0.43,0.64]
OV16	124±103	116±64	[−14,30]	0.63	0.78	0.49 [0.39,0.59]

SD = standard deviation; CI = confidence interval; AUC = area under the curve; Means are based on the unadjusted models; FTJ= total femorotibial joint; MFTC = medial femorotibial compartment; LFTC = lateral femorotibial compartment; MT = medial tibia; LT = lateral tibia; cMF = weight-bearing medial femorotibial compartment; cLF = weight−bearing lateral femorotibial compartment; OV = ordered values (of 16 femorotibial subregions)

Table 2

Location of the subregion with greatest change in cartilage thickness from baseline to 12 month follow-up (OV1) in knees with surgical knee replacement (KR; n=40) and without replacement (non-KRs; n=491); locations are also listed for KRs with primarily medial disease (medial JSN > lateral JSN; n=25) and for those with primarily lateral disease (lateral JSN > medial JSN; n=13).

	All KRs	Controls	Medial OA	Lateral OA KRs
	(n=40) %	(n=491) %	(med>latJSN; n=25) (n=15) %	(lat>medJSN; n=13) %
cMT	5	11	4	0
eMT	10	4	16	0
iMT	5	6	8	0
aMT	3	2	0	7
pMT	0	2	0	0
ccMF	10	13	12	7
ecMF	0	3	0	0
icMF	5	5	8	0
cLT	15	15	20	22
eLT	8	4	0	22
iLT	2	7	4	0
aLT	5	3	0	14
pLT	10	9	4	7
ccLF	17	6	16	21
ecLF	5	4	8	0
icLF	0	6	0	0
Total %	100%	100%	100%	100%

c,e,i,a,pMT = central, external, internal, anterior, and posterior medial tibia
c,e,i,cMF = central, external, internal weight-bearing medial femur
c,e,i,a,pLT = central, external, internal, anterior, and posterior lateral tibia
c,e,i,cLF = central, external, internal weight-bearing lateral femur