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original research

Posttraumatic Bone Marrow Lesion Volume and Knee Pain Within 4 Weeks After Anterior Cruciate Ligament Injury

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Context: After an anterior cruciate ligament (ACL) injury, a majority of patients have a traumatic bone marrow lesion (BML, or *bone bruise*). The clinical relevance of posttraumatic lesions remains unclear.

Objective: To explore the cross-sectional associations between traumatic BML volume and self-reported knee pain and symptoms among individuals within 4 weeks of ACL injury.

Design: Cross-sectional exploratory analysis of a randomized clinical trial.

Setting: Orthopaedic departments at 2 hospitals in Sweden.

Patients or Other Participants: As part of a randomized trial (knee anterior cruciate ligament nonoperative versus operative treatment [KANON] study), 121 young active adults (74% men, age = 26 ± 5 years, height = 1.8 ± 0.1 m, weight = 76 ± 13 kg) with an ACL tear were studied.

Main Outcome Measure(s): The BML volume in the proximal tibia and distal femur was segmented using magnetic resonance images obtained within 4 weeks of injury. A radiologist evaluated the presence of depression fractures on the images. Pain and symptoms of the injured knee (Knee Injury and Osteoarthritis Outcome Score [KOOS] pain and symptoms subscales) were obtained the same day as imaging. We used linear regression models to assess the associations.

Results: Most knees had at least 1 BML (96%), and the majority (57%) had a depression fracture. Whole-knee BML volume was not related to knee pain for the entire cohort ($\beta = -0.09$, $P = .25$). Among those without a depression fracture, larger whole-knee BML volume was associated with increased knee pain ($\beta = -0.46$, $P = .02$), whereas no association was found for those with a depression fracture ($\beta = 0.0$, $P = .96$). Larger medial ($\beta = -0.48$, $P = .02$) but not lateral ($\beta = -0.03$, $P = .77$) tibiofemoral BML volume was associated with greater pain. We found no association between BML volume and knee symptoms.

Conclusions: We confirmed the absence of relationships between whole-knee BML volume and pain and symptoms within 4 weeks of ACL injury. Our findings extend previous reports in identifying weak associations between larger BML volume in the medial compartment and greater pain and between BML volume and greater pain among those without a depression fracture.

Key Words: knee injuries, magnetic resonance imaging, sprains, trauma, patient-reported outcomes

Key Points

- Within 4 weeks of anterior cruciate ligament injury, total-knee bone marrow lesion volume and self-reported pain and symptoms were not associated.
- More pain was weakly related to greater medial compartment and greater total-knee bone marrow lesion volume and to greater bone marrow lesion volume among participants without a depression fracture.

After an anterior cruciate ligament (ACL) injury, a majority of patients have a traumatic bone marrow lesion (BML, or *bone bruise*).[1–6] A *traumatic BML* is an ill-defined region of high-signal intensity within the subchondral bone on fluid-sensitive magnetic resonance (MR) images that is associated with compression injury, trabecular fracture, edema, necrosis, or bleeding in the marrow.[7–9] The location and size of a traumatic BML may be influenced by the mechanism of injury (ie, loading during injury) or the presence of concurrent injuries (eg, compression fracture, meniscal lesion, collateral ligament sprain).[4,10–15] Therefore, the size and location of a traumatic BML within the first few weeks of an ACL injury may provide useful information about the initial injury. Furthermore, the size of a traumatic BML may relate to knee pain or symptoms either because it is a proxy for the severity of the initial injury or because the lesion causes knee pain.

The clinical relevance of posttraumatic lesions remains unclear. Previous researchers[10,16] have suggested that posttraumatic BMLs are associated with pain. However, contradictory findings have also been reported,[6,17] and these may be due to the mechanism of injury, concurrent injuries, study population, or time between injury and evaluation.[10] In a large cohort study,[6] no associations were identified between the presence of a traumatic BML and knee pain after controlling for concurrent injuries, study population characteristics, and time between injury and evaluation; unfortunately, the size and location of the BMLs were not evaluated. Assessing the relationship between traumatic

Table 1. Baseline Characteristics

Variable	n (%) or Mean ± SD		
	Overall Cohort (N = 121)	Depression Fracture?	
		No (n = 52)	Yes (n = 69)
Male	89 (74)	38 (73)	51 (74)
Injured knee: right	66 (55)	31 (59)	35 (51)
Presence of depression fracture	69 (57)	Not applicable	Not applicable
Age, y	26.0 ± 4.9	25.6 ± 4.7	26.4 ± 5.1
Height, m[a]	1.77 ± 0.08	1.75 ± 0.08	1.79 ± 0.08[b]
Weight, kg[a]	75.8 ± 12.8	72.4 ± 10.2	78.4 ± 14.1[b]
Knee Injury and Osteoarthritis Outcome Score (range = 0–100)			
Pain subscale	57.3 ± 17.2	57.6 ± 17.9	57.1 ± 16.8
Symptoms subscale	47.9 ± 16.5	46.8 ± 18.8	48.8 ± 14.5
Bone marrow lesion			
Lateral tibia	116 (96)	47 (90)	69 (100)[c]
Lateral femur	101 (83)	41 (79)	60 (87)
Medial tibia	101 (83)	35 (67)	66 (95.7)[c]
Medial femur	64 (53)	24 (46)	40 (58)

[a] Height and weight were not recorded for 1 participant with a depression fracture.

[b] Independent-samples *t* tests indicated a difference between knees with and knees without a depression fracture ($P < .05$; precise P values for significant results are in the text).

[c] Fisher exact test indicated a difference between knees with and knees without a depression fracture ($P < .05$; precise P values for significant results are in the text).

BML size and location and knee pain within the first 4 weeks after injury is important because these attributes may be markers for the mechanism and severity of injury.

Individuals with ACL injury are at high risk of poor long-term outcomes (eg, osteoarthritis,[18–20] knee pain,[21] diminished quality of life[21-23]), and early symptoms predict more severe knee pain and symptoms 6 years after an ACL injury.[24] Furthermore, preoperative knee and body pain are important predictors of postsurgical outcomes 1 or 2 years after an ACL reconstruction.[25,26] Thus, enhancing our understanding of the factors involved in posttraumatic pain may be important in improving long-term results for the ACL-injured population. To further clarify the relationships between traumatic BMLs and knee pain and symptoms, we explored the cross-sectional associations between posttraumatic BML volume and self-reported knee pain and symptoms within the first 4 weeks after an ACL injury. We conducted the analyses on a sample of individuals with acute ACL injury, which is known to be highly associated with at least 1 traumatic BML. Our primary focus was the total BML volume of the injured knee, the secondary focus was the tibiofemoral compartments, and the separate condyles were of exploratory focus only. To address our primary focus, we also investigated the association between total BML volume and self-reported pain and symptoms among those with or without a depression fracture.

METHODS

Participants

We evaluated the cross-sectional association between traumatic BML volume and knee pain and symptoms among 121 young active adults (mean age = 26 ± 5 years, range = 18–35 years) with an acute ACL tear in a previously uninjured knee. All participants were included in a randomized clinical trial (knee anterior cruciate ligament nonoperative versus operative treatment [KANON] trial, ISRCTN84752559).[27–29] The median Tegner Activity Scale score was 9 (interquartile range, 7–9), and most patients were injured in sports (n = 119); the most common sports were soccer (64%), skiing (13%), and handball (7%).[28] The study sample is described in more detail in Table 1. Excluded were individuals who had a history of a previous injury to the index knee, a concurrent total collateral ligament rupture (grade 3 sprain verified by clinical examination and magnetic resonance imaging [MRI]), or a full-thickness cartilage lesion as visualized on MRI; details of the KANON study have been published previously.[27,28] The Lund University ethics committee approved the clinical trial, and all participants provided written informed consent.

Magnetic Resonance Imaging

The BML volume was automatically segmented on MR images obtained within 19 ± 6.5 days postinjury using a 1.5-T MR scanner (Gyroscan-Intera; Philips Healthcare, Eindhoven, The Netherlands) with a circular polarized surface coil. All participants were scanned with a standard protocol that consisted of (1) sagittal dual-echo turbo-spin-echo with recovery time (TR) = 2900 milliseconds, echo time (TE) = 15 milliseconds, time to inversion = 80 milliseconds, 15-cm field of view, 3-mm slice thickness with 0.6-mm gap, and 0.59-mm × 0.59-mm pixel size; (2) sagittal short tau inversion recovery with TR = 2900 milliseconds, TE = 15 milliseconds, time to inversion =160 milliseconds, 15-cm field of view, 3-mm slice thickness with 0.6-mm gap, and 0.29-mm × 0.29-mm pixel size; (3) sagittal 3-dimensional (3D) water-excitation fast low-angle shot with TR = 20 milliseconds, TE = 7.9 milliseconds, flip angle = 25°; and (4) sagittal 3D T2 weighted gradient echo with TR = 20 milliseconds, TE = 15 milliseconds, and flip angle = 50°. Both 3D series were acquired with a 15-cm field of view, 1.5-mm slice thickness, and 0.29-mm × 0.29-mm pixel size.[5,7]

Bone Marrow Lesion Quantification

Traumatic BML volume was quantified using methods previously reported (VirtualScopics Inc, Rochester, NY).[7] In short, the 3D sagittal MR image sets were fused into a dual-pulse sequence MRI data set.[7] This dual-pulse sequence was then automatically segmented using a proprietary computer algorithm, which identified the bones.[7] Next, the BML segmentation was completed by mapping the segmented bones into a 3-band composite data set made up of the 2 sagittal images from the dual echo and the inversion-recovery MRI data set from the sagittal short tau inversion-recovery acquisition. Finally, an expert radiologist reviewed the segmentation results before they were entered into a computer algorithm, which aggregated and reported the BML volume inside each region of interest.[7] Reproducibility was assessed through a random selection and reanalysis of 28 scans, which were read 2 weeks apart, with a mean intraclass correlation of 0.923 for

Table 2. Associations Between Baseline Bone Marrow Lesion (BML) Volume and Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain Subscale

Variable	Median (25%, 75% Percentiles, cm^3)	Unadjusted Parameter Estimate[a,c] (95% Confidence Interval)	Adjusted Model Parameter Estimate[b,c] (95% Confidence Interval)
BML volume			
Total knee (entire cohort, n = 121)	19.8 (13.5, 34.1)	–0.07 (–0.24, 0.09)	–0.09 (–0.26, 0.07)
Among individuals with depression fracture (n = 69)	28.5 (16.8, 41.7)	0.0 (–0.20, 0.20)	0.0 (–0.20, 0.21)
Among individuals without depression fracture (n = 52)	14.6 (8.0, 23.6)	–0.37 (–0.77, 0.03)	**–0.46 (–0.85, –0.06)**
Secondary analyses: BML volume of tibiofemoral compartments			
Lateral	14.8 (10.5, 25.3)	0.01 (–0.23, 0.23)	–0.03 (–0.26, 0.19)
Medial	3.7 (0.8, 11.0)	**–0.50 (–0.91, –0.10)**	**–0.48 (–0.88, –0.08)**
Exploratory analyses: BML volume of condyles			
Lateral tibia	10.4 (6.0, 15.2)	–0.08 (–0.48, 0.33)	–0.20 (–0.61, 0.21)
Lateral femur	3.8 (0.5, 10.2)	0.07 (–0.25, 0.40)	0.06 (–0.28, 0.40)
Medial tibia	2.6 (0.4, 8.9)	**–0.48 (–0.94, –0.02)**	–0.46 (–0.92, 0.00)
Medial femur	0.1 (0.0, 1.1)	–1.04 (–2.22, 0.14)	–1.09 (–2.30, 0.11)

[a] Parameter estimate = estimated difference in KOOS pain score per cm^3 of BML volume.
[b] Adjusted for time from injury to magnetic resonance imaging, age, body mass index, and sex.
[c] Bold = significant association ($P \leq .05$; precise P values are reported in the text). Body mass index was not recorded for 1 participant.

all 4 regions of interest.[7] Results are presented in centimeters^3.

Depression Fractures

Depression fractures were evaluated on the sagittal dual-echo turbo-spin-echo images by an expert radiologist and have been reported.[30] In brief, a *depression fracture* was defined as a trabecular fracture (a line with low signal and parallel to the cortex) combined with depressed cortical bone.

Patient-Reported Outcomes

Self-reported pain and symptoms of the injured knee were measured using the Knee Injury and Osteoarthritis Outcome Score (KOOS) on the same day as the MRI. We focused on 2 of the 5 subscales: pain and other symptoms.[31] Standardized response options are chosen from a Likert scale of 0 to 4, and a normalized score (range = 0–100, worst to best) is calculated for each subscale. The psychometric properties of the KOOS have been validated for the evaluation of knee injury.[32–34]

Data Analysis

A depression fracture as visualized on MRI has a strong relationship with traumatic BML volume,[7] but we hypothesized that it could also influence pain through other mechanisms; thus, we stratified our primary analysis for those with and those without a depression fracture. We used the Fisher exact test and independent-samples t tests to assess differences between participants with and participants without a depression fracture. We used multiple linear regression models to evaluate the cross-sectional association between KOOS pain (outcome variables) and total knee BML volume (primary aim), medial and lateral tibiofemoral BML volume (secondary aims), and regional BML volumes (exploratory aims) within 4 weeks of injury. We repeated these models to assess the association between KOOS symptoms (outcome variables) and the BML volumes previously described. For all analyses, we present crude results and results adjusted for 4 confounders: time from injury to MRI, age, body mass index, and sex. The study team selected these confounders a priori because they could be associated with KOOS pain (or symptoms) and BML volume. In the adjusted models, all confounders were entered into the model at once. We did not adjust for concomitant injuries (eg, meniscal injury, collateral ligament injury) because we hypothesized that traumatic BMLs during the first 4 weeks may relate to knee pain or symptoms because the BML volume is a proxy for the severity and mechanism of injury. We evaluated scatterplots, residual plots, DFFITS, and DFBETAS to determine if the assumptions for multiple linear regressions were satisfactory and to identify potential influential points. We then replicated the analyses without those potential influential points to assess if they changed the results. Statistical significance was defined as $P < .05$. We did not adjust for multiple comparisons because we defined a priori that the majority of analyses were secondary or exploratory in focus; thus, corrections would be overly conservative. All analyses were performed using SAS software (version 9.3; SAS Institute Inc, Cary, NC).

RESULTS

The majority of participants were men (74%), had at least 1 BML in the knee (96%), and had a depression fracture (57%; Table 1). Participants with a depression fracture were taller ($P = .005$), heavier ($P = .01$), and more likely to have a BML in the lateral or medial tibia ($P = .01$ and $P < .001$, respectively) than participants without a depression fracture. Almost every knee had a posttraumatic BML in the lateral tibia (96%). Additionally, posttraumatic BMLs were common in the lateral femur and medial tibia (83% of each) but not in the medial femur (53%).

The total knee BML volume was not related to self-reported knee pain in the entire cohort ($P = .25$; Table 2). Among those without a depression fracture, a larger total knee BML volume was associated with increased knee pain ($P = .02$); however, either no or a weak association was

Table 3. Associations Between Baseline Bone Marrow Lesion (BML) Volume and Knee Injury and Osteoarthritis Outcome Score (KOOS) Symptoms Subscale

Variable	Median (25%, 75% Percentiles, cm^3)	Unadjusted Parameter Estimate[a] (95% Confidence Interval)	Adjusted Model Parameter Estimate[b] (95% Confidence Interval)
BML volume			
Total knee (entire cohort, n = 121)	19.8 (13.5, 34.1)	0.06 (–0.09, 0.22)	0.03 (–0.12, 0.19)
Among individuals with depression fracture (n = 69)	28.5 (16.8, 41.7)	0.10 (–0.07, 0.27)	0.07 (–0.10, 0.25)
Among individuals without depression fracture (n = 52)	14.6 (8.0, 23.6)	–0.14 (–0.57, 0.29)	–0.25 (–0.67, 0.18)
Secondary analyses: BML volume of tibiofemoral compartments			
Lateral	14.8 (10.5, 25.3)	0.17 (–0.05, 0.38)	0.11 (–0.11, 0.32)
Medial	3.7 (0.8, 11.0)	–0.18 (–0.58, 0.22)	–0.16 (–0.55, 0.23)
Exploratory analyses: BML volume of condyles			
Lateral tibia	10.4 (6.0, 15.2)	0.08 (–0.30, 0.47)	–0.01 (–0.40, 0.38)
Lateral femur	3.8 (0.5, 10.2)	0.30 (–0.01, 0.61)	0.24 (–0.07, 0.56)
Medial tibia	2.6 (0.4, 8.9)	–0.32 (–0.76, 0.13)	–0.28 (–0.72, 0.16)
Medial femur	0.1 (0.0, 1.1)	0.59 (–0.55, 1.73)	0.49 (–0.66, 1.64)

[a] Parameter estimate = estimated difference in KOOS symptoms score per cm^3 of BML volume.
[b] Adjusted for time from injury to magnetic resonance imaging, age, body mass index, and sex. Body mass index was not recorded for 1 participant.

found for those with a depression fracture ($P = .96$). Greater volume in the medial tibiofemoral BML ($P = .02$), but not in the lateral tibiofemoral BML ($P = .77$), was associated with increased pain. No statistically significant associations with knee pain scores were present within individual regions (Table 2). We found no association between self-reported knee symptoms and BML volumes for the total knee, medial or lateral tibiofemoral compartment, or any individual region (Table 3).

DISCUSSION

This is, to our knowledge, the first study to assess the association between posttraumatic BML volume (total and regional) and knee pain or symptoms among a large sample of individuals with an acute ACL injury. We failed to identify a firm relationship between knee pain and symptoms and traumatic BML volume within 4 weeks of an acute ACL injury. Similarly, investigators[6] in the Multicenter Orthopaedic Outcomes Network (MOON) ACLR Cohort Study found that the presence of a posttraumatic BML was not associated with knee pain or symptoms as monitored by the KOOS. However, unlike us, they did not examine MR images within the first month after injury and did not assess pain and BML presence at the same visit. Kijowski et al[17] reported that traumatic BML volume of the total knee was not related to knee symptoms as monitored by International Knee Documentation Committee (IKDC) scores. However, unlike us, they did not evaluate knee symptoms and BMLs at the same time after injury.[17] Our findings confirm the absence of such overall relationships and extend them in suggesting that during the first 4 weeks after ACL injury, a larger total BML volume seems to be associated with more self-reported knee pain in patients without depression fractures. Other novel results suggest that larger posttraumatic BML volumes in the medial but not the lateral compartment were positively related to higher levels of pain. We failed to identify any association between BML volume and self-reported symptoms (on KOOS), and the relationships with pain were weak, albeit statistically significant. Thus, a large proportion of the pain after ACL injury may be caused by other mechanisms (such as inflammation or cartilage or meniscal injury), and further studies are needed to shed light on this complex problem.

Our novel strategy of stratifying for the presence of depression fracture was based on the hypothesis that fractured cortical bone may influence pain through mechanisms other than BML volume. Knees with depression fractures have posttraumatic BMLs of greater volumes; however, knees without such fractures are also affected by BMLs of various sizes.[30] Interestingly, we found that larger total knee BML volumes were related to higher levels of knee pain in knees without depression fractures but not in knees with depression fractures. This is not easily explained, although one possibility could be that impaction forces to subchondral bone produce more pain when the cortical bone remains intact than when it is depressed or even disrupted. An alternative explanation is that a depression fracture is a more predominant source of pain than BML volume.

Larger medial but not lateral compartment BML volumes were associated with higher self-reported pain scores in this study. In weight bearing, the majority of the load is typically transmitted through the medial compartment,[35] which may be an explanation for these findings. However, the minimal detectable change (ie, minimal amount of change, outside of error, that reflects true change over 2 time points) of KOOS pain is 6 points.[34] For every cubic centimeter increase in BML volume of the medial compartment, the average difference in KOOS pain score was –0.48. Of this subset, 95% had medial BML volumes between 0 and 11.0 cm^3 and, thus, we could anticipate a difference of only –5.28 KOOS pain score points at most.

The volume of a BML changes over time. Traumatic BML volume increases during the first 2 weeks after an ACL injury and then declines over the next 2 months.[10] Our study is unique because it was limited to the first 4 weeks after an ACL injury and assessed BML volume, location, knee pain, and symptoms at the same visit. Authors of the 2 other studies[10,16] that found an association between

traumatic BMLs and knee pain were the only researchers to perform all MRIs during the first month after an ACL injury and to obtain concurrent pain assessments. Another study,[17] which had null results, evaluated traumatic BML volume within the first 3 weeks after an ACL injury, but the authors assessed knee function (based on the IKDC knee evaluation questionnaire) within the first 12 weeks after the injury and 1 year later. It is challenging to interpret these results because we do not know how much time elapsed between MRI and when the participants reported knee function. Changes in BML volume over time also make it difficult to interpret data from the MOON cohort because BMLs were assessed on preoperative MRIs, which occurred 9 to 41 weeks after injury.[6] The timing of the BML volume measurements and pain assessments is important, so it may be helpful for future investigators to incorporate longitudinal assessments of BML volume and knee pain. Traumatic BML volume during the acute-subacute phase may be a proxy for the severity and mechanism of injury. However, traumatic BML volume after the first month may represent a healing response or how the bone is responding to activity (eg, rehabilitation, return to physical activity). It remains unknown how changes in traumatic BMLs relate to knee pain and symptoms and other landmark events in the recovery process (eg, return to physical activity).

Although our findings expand on previous studies[6,10,16,17] regarding traumatic BMLs and knee pain or symptoms, some important limitations were present. First, the cross-sectional design and weak relationships found here do not allow us to infer that larger traumatic BML volumes in the medial compartment and in those without a depression fracture caused pain. Despite the cross-sectional design, our results offer new information about the relationship between traumatic BML size and knee pain during an important period after ACL injury. Early symptoms predict postsurgical outcomes years after an ACL reconstruction.[24–26] Future longitudinal studies that assess whether baseline traumatic BML size can predict patient-reported outcomes years after surgery or that evaluate whether changes in traumatic BML size relate to changes in knee pain will help build on these findings. Second, it remains unclear if the associations presented here were confounded by inflammation or concurrent injuries (eg, meniscal injury or chondral lesions) that could have contributed to the development of both traumatic BML volumes and knee pain.[10] We opted to not adjust for concurrent injuries because we hypothesized that the relationship between BML volume and knee pain might reflect an association between the mechanism or severity of injury and knee pain. Our findings challenge this hypothesis. Even though BML size and location may indicate the severity or mechanism of injury,[4,10–15] these attributes failed to reflect the relationship between knee pain and injury severity. Hence, other factors probably better account for the relationship between knee pain and injury severity (eg, inflammation, effusion). Third, these are exploratory analyses from a randomized controlled trial that was not specifically designed and powered for these aims. However, the KANON trial provides a unique study population and the availability of a rich data set, which enabled us to expand the existing literature on a relevant topic.

In conclusion, this study confirmed the absence of a relationship between total knee BML volume as measured on MRI and self-reported pain and symptoms within 4 weeks of ACL injury. However, we extend previous reports in identifying associations between greater pain and larger BML volume in the medial compartment and greater pain among those without a depression fracture. Hence, although the location and size of a posttraumatic BML may help inform clinicians about the mechanism of injury or presence of concurrent injury,[4,10–15] they do not seem to explain the degree of pain reported by a patient. Future researchers should consider the influences of other potentially painful stimuli (eg, meniscal tear, collateral ligament injury, effusion), preferably using a longitudinal design.

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