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THE RELATIONSHIP OF TIBIAL BONE PERFUSION TO PAIN IN KNEE OSTEOARTHRITIS.

Authors

Stanley Seah[1], Diane Wheaton[2], Ling Li[2], Jonathan P. Dyke[3], Carl Talmo[2], William F Harvey[2], David J. Hunter[1,2].

Affiliations

1. Rheumatology Department, Royal North Shore Hospital and Northern Clinical School, University of Sydney, NSW Australia
2. Division of Research, New England Baptist Hospital, Boston, MA
3. Citigroup Biomedical Imaging Center, Weill Cornell Medical College, New York, NY

Corresponding Author

Dr. Hunter at Rheumatology Department, Royal North Shore Hospital and Northern Clinical School, University of Sydney, Sydney, NSW Australia.

Email: David.Hunter@sydney.edu.au

Phone: 61 2 9926 7379

Fax: 61 2 9906 1859

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Abstract

OBJECTIVE

To confirm altered perfusion within tibial bone marrow lesions (BMLs) and improve our understanding on the relationship between BMLs and pain in knee osteoarthritis (OA).

METHODS

Participants with moderate to severe knee OA were recruited and pain was assessed using the pain subscale of the WOMAC. Subchondral tibial BMLs were identified and graded on MRI PDW fat suppressed images. A pharmacokinetic model was used to analyse perfusion parameters on dynamic contrast enhanced MRI which represent transfer rates in and out of the BMLs. The relation between perfusion and pain was evaluated using multivariable linear regression after adjustment for BML grade, age, gender and BMI.

RESULTS

There were 37 participants (mean age 64.9 years, range 46 to 86) with radiographic Kellgren and Lawrence grades of 3 and 4 in the study knee; 75.6% had BMLs that were classified grades 1 and 2. The mean WOMAC pain score was 10.3 (0-20 scale). There was a significant correlation between BML Kel (rate of contrast elimination) and BML grade ($p=0.001$ univariate, $p=0.002$ multivariate analyses), although we did not demonstrate any significant multivariate association between BML perfusion and pain. We also found an inverse relationship between pain at sleep and BML grade ($p<0.05$).

CONCLUSIONS

The absence of any significant association between bone perfusion and pain implies that the relationship of tibial BMLs to pain in OA is still incompletely understood. BMLs are just one component of the whole knee joint and are formed from various causes, all of which interact and collectively contribute to the genesis of pain in OA.

INTRODUCTION

Osteoarthritis (OA) is the most common joint disease in modern, aging societies and causes substantial physical and psychosocial disability(1). The risk for disability (defined as needing help walking or climbing stairs) attributable to knee OA is as great as that attributable to cardiovascular disease and greater than that due to any other medical condition in elderly persons (1). OA occurs when the dynamic equilibrium between the breakdown and repair of joint tissues is overwhelmed by a combination of genetic, metabolic and hormonal factors interacting with local biomechanical forces (2). This progressive joint failure may cause pain, physical disability, and psychological distress (1), although many persons with structural and radiological changes consistent with OA are asymptomatic (3). The reasons why there is this disconnect between disease severity and the level of reported pain and disability is unknown. In advanced OA, pain can be present with progressively less activity eventually occurring at rest or nocturnally.

The source of pain in OA is best framed in a biopsychosocial framework (posits that biological, psychological and social factors all play a significant role in pain in OA) (4). The structural determinants (part of the biological determinants) of pain and mechanical dysfunction in OA are also not well understood, but are believed to involve multiple interactive pathways. One important source of nociceptive input is the subchondral bone. During the initiation and progression of OA, subchondral bone is the site of numerous dynamic morphological transformations due to an altered osteoblast metabolism, which is part of the pathological process (5). These in situ structural changes in subchondral bone can be readily observed using imaging techniques such as MRI during the course of OA.

On MRI, subchondral bone marrow signal alterations are characterized by ill-defined subchondral areas of high signal intensity on T2 (T2w)- or proton density-weighted (PDw) fat suppressed (FS) fast spin echo (FSE) or short tau inversion recovery (STIR) images (5). These bone marrow lesions (BMLs) play an integral if not pivotal role in the symptoms that emanate from knee OA and its structural progression (6). More recently their relation to pain severity was also demonstrated (7). These oedema-like lesions gradually increase in size over time and their presence in subchondral bone marrow has been associated with increased bone turnover indices as well as structural deterioration in knee OA (8;9). After intravenous administration of contrast agents, enhancement of these signal alterations is evident, indicating hypervascularity and repair activity (10;11). Contrast kinetics of small molecular agents in bone result from a combination of both perfusion and permeability effects (12). These combined effects shall be referred to as properties of bone perfusion in this study.

Another bone-related cause of pain is bone angina due to decreased blood flow and elevated intraosseous pressure (13). It has been suggested that OA has early vascular components that change underlying bone perfusion in the affected bone(14).The pathophysiology of this change remains unclear, although phlebographic studies in OA indicate impaired vascular clearance from bone and raised intraosseous pressure in the bone marrow near the painful joint(13;15-17). These prior studies demonstrated elevated intraosseous pressures in hip and knee OA whilst patients without OA or pain had normal intraosseous pressures. Furthermore, osteotomy of the proximal femur reduced both intraosseous pressure and the subsequent pain in patients with hip OA (13;15-17). These studies collectively suggest that BMLs may lead

to changes in fluid dynamics which result in the intraosseous hypertension that is associated with bone pain in OA.

Interestingly, limited analysis of BMLs appear to correspond to thrombi, diffuse fibrinoid necrosis, myxoedematous degeneration and cellular infiltrate of the bone marrow – all indicative of infarction-like pathology (18;19). These findings strengthen the association that subchondral bone changes contribute to the pain, bone remodeling and bone necrosis that occurs in patients with OA.

Although the presence of BMLs is strongly associated with the progression and pain in OA, the particular bone pathology most responsible for pain remains elusive. Identifying this would be a major advance in delineating appropriate therapeutic targets.

The aims of this study are to confirm our preliminary data demonstrating altered perfusion within tibial BMLs (20) and to improve our mechanistic understanding of why tibial BMLs are related to pain by examining the relationship between tibial BML size and perfusion as well the association between tibial BML perfusion to pain severity and pain at rest or sleep.

METHODS

Study Sample

We conducted a pilot study to examine the objectives. We recruited 37 participants (age range: 46 to 86 years, BMI range 21.4 to 35.2) with knee OA who were on a waiting list for total knee replacement (TKR). Participants had skyline and bilateral standing AP radiographs during the screening phase. The radiographic Kellgren and Lawrence grade in the knees of participants ranged from grades 3 to 4. Exclusion criteria included pregnant women, those who were having a revision knee replacement instead of a primary knee replacement, a contraindication for MRI scans and those with an allergy to the contrast agent gadolinium. Any patient with an underlying pathophysiology that could possible influence pain beyond the impact of OA alone (such as RA, infection, gout, or neuropathic disorders) was also excluded. The institutional review board of New England Baptist Hospital approved the study. Informed consent was obtained from all study participants.

Assessment of symptoms

Pain was assessed using the pain subscale of the Likert version of the Western Ontario and McMaster Universities Arthritis Index (WOMAC) (21). This disease-specific measure is reliable, valid and responsive and consists of 5 pain items, 17 function items and 2 stiffness items using a 5- point scale to score each item, where higher scores indicate worse symptoms. Five categories of pain (walking on flat surface, going up or down stairs, pain present at night while in bed, sitting or lying or standing upright) were assessed separately with a 5-point scale from 0 (no pain) to 4 (most severe pain). Each score was then summed to create a total pain score (range 0 to 20).Pain scores at night while sleeping range from 0 (none) to 3 (severe).

MRI Acquisition

Subjects had an MRI performed of their study knee prior to TKR (within 2 weeks of their surgery date) on a 1.5 Tesla scanner with a dedicated 8-channel extremity coil (1.5T Twin Speed Excite scanner (GE Healthcare, Waukesha, WI)). The MR exam consisted of an axial and sagittal proton density weighted (PDW) fat suppressed series and a high resolution coronal T1-Weighted 3D spoiled gradient echo (SPGR) acquisition with water excitation. The following imaging sequences were used for BML localization on each patient: both Axial and Sagittal PDW fat suppressed with TR/TE (echo time) of approximately 3550 ms and 20-30 ms respectively. Acquisition parameters of 3 mm slices, no skip/gap, 320 X 224 matrix, flip angle 90 degrees, receiver bandwidth (RCV BW) 31.25, 15 cm FOV (for distal femur and proximal tibia) for a total acquisition time of 4.5 minutes.

Gd-DTPA was injected at a peripheral intravenous site at a standard concentration of 0.1 mmol per kilogram using a power injector followed by a saline flush. Dynamic contrast enhanced (DCE) MRI was performed using a sagittal 3D T1-weighted fast spoiled gradient echo (FSPGR) sequence with 20 sagittal slices of 3 mm thickness over 7 minutes with a 7.5 second time resolution. During data acquisition, the TR was 6.6 and TE was 1.7 with a 12 degree flip angle, RCV BW 50, a 12 cm field of view and a 256 x 128 matrix.

MRI Analysis

Subchondral BMLs were initially identified on both axial and sagittal PDW fat suppressed images. As the focus of this analysis is on tibial BMLs the largest tibial BML was scored. This region was utilized for DCE-MRI perfusion analysis and defined as discrete areas of increased signal adjacent to subcortical bone. Each BML was graded from 0-3 on the basis of lesion size according to the BLOKS scoring system (22). One region of interest (ROI) in each knee was defined that circumscribed the outline of the BML. This ROI was defined on multiple slices and averaged to create a single time intensity curve representative of the primary BML lesion in each subject. The grading for size of BML for BLOKS includes the cystic component. Similarly the ROI for BML incorporated the cystic component.Each patient underwent a DCE-MRI scan while dynamic perfusion data was extracted using mathematical modelling based on the Brix two-compartment pharmacokinetic model(23;24). Analysis was performed using in-house software [JD] written in IDL 7.0 [ITT Visual, Boulder CO]. Briefly, the Brix two-compartment model is capable of producing perfusion parameters such as transfer rates into and out of a region of interest.

Some of the predictors/parameters that were used in this study are

i. Slope (%/min) – Initial uptake of Gd into the region found by finding the fastest uptake in the first few minutes after injection

ii. A (unitless) – corresponds to the size of the EES (extravascular extracellular space) or area the Gd can leak into outside the plasma and not internal to the cells

iii. K_{ep} (1/min) – efflux rate constant from EES to plasma which provides an index of venous hypertension and represents the ratio of the permeability surface area product over the extravascular extracellular space (K_{trans}/v_e). The smaller the $k_{ep}$the more delayed the enhancement.

iv. K_{el} (1/min) – represents the washout or clearance of Gd out of the region of interest. A more positive k_{el} indicates a more rapid washout.

v. $A.k_{ep}$ (1/min) – initial uptake of Gd in the region of interest that models the slope but is found via fitting of the entire curve by the model.

Statistical Analysis

We assessed the relation between perfusion parameters in BML with WOMAC pain and night pain (dependent variable-one item from WOMAC pain subscale). These were adjusted with their respective muscle variables as internal control. The relation between perfusion and WOMAC pain was assessed using a linear regression model, assuming the normal distribution of WOMAC pain score. Pain score at night while sleeping was categorized into three levels from none (0 or 1), to moderate (2), to moderate or more (3), and ordinal logistic regression model was performed to test its relationship with BML perfusion. The proportional odds assumption inherent in the ordinal logistic regression model will was tested first. A non-significant test result was taken as the evidence that this assumption was met and the odds ratios from the model was interpreted as the odds of being "lower" or "higher" on the response variable across the entire range of the outcome. The relation of BML grade to perfusion and pain at night were also assessed, with linear regression for the former and ordinal logistic regression for the latter, respectively.

For each model, the unadjusted and adjusted estimated values, along with 95% confidence interval (95%CI) and p-values were reported. Analyses were conducted with SAS v9.2, SAS Institute, Cary, NC.$P<0.05$ with two-sided test was considered statistically significant.

RESULTS

The characteristics of the participants in this study are shown in Table 1. A total of 37 subjects (21 females and 16 males) with a mean age of 64.9 years and a mean BMI in the overweight category of 28.9 kg/m^2. The mean WOMAC pain score was 10.2 (0-20 scale) which indicates a study population with moderate pain severity. The majority (75.6%) had BMLs that were classified grades 1 and 2 according to lesion size. The median no. of tibial bone marrow lesions was 2 (range 1-5). The largest BML (maximum grade) was selected for DCE analysis.

Table 2 shows the relationship between BML grade and the five perfusion parameters. There was a significant correlation in the bivariable and multivariable analyses between BML K_{el} and BML grade, after adjusting for age, gender and BMI. There was no significant association between BML grade and the other four perfusion parameters. Figure 1 reflects the negative relationship between BML K_{el} and BML grades

(p=0.002) consistent with a hypothesis of venous obstruction. Examples of the DCE-MRI acquisition and measurement are included as Figure 2.

The relationship between BML perfusion and WOMAC pain is presented in Table 3. Bivariable analysis showed the significant positive relationships between BML A, BML A.K_{ep} and WOMAC pain (for BML A, p=0.038 (95%CI 0.021 to 0.690); for BML A.K_{ep}, p=0.024 (95% CI 0.020 to 0.276)). However, when adjusting the effects of BML grade, age, gender and BMI, neither of them remained significant (for BML A, p=0.231 (95%CI (-0.138 to 0.551); for BMLA K_{ep}, p=0.088 (95%CI -0.018 to 0.246)).

We also assessed the relation between BML perfusion and pain at night (Table 4). A statistically non-significant test means that the proportional odds assumption of each ordinal logistic regression was not violated (p>0.05). The significant association was tested between BML K_{ep} and pain at night while sleeping after controlling for the effects of BML grade, age, gender and BMI. With BML K_{ep} increase, patients are more likely to have moderate pain at sleep (OR=1.65, 95%CI: 1.03-2.65, P=0.039).

Finally, figure3 depicts the relationship between pain at night with BML grade (Fisher's exact test p=0.715). It is noteworthy that the vast majority of participants (90%) in the BML grade 3 group had none or mild pain at sleep compared to 79% and 69% in the BML grades 1 and 2 groups respectively, suggesting that larger BMLs do not result in more pain at night, although this difference is not significant. The patients with BML grade=3 are less likely to have pain at night than those with BML grade 1 or 2 (Compared to grade1: OR=0.38, 95% CI: 0.07-2.01; compared to grade2: OR=0.44, 95%CI: 0.08-2.58).

DISCUSSION

The relationship of bone marrow perfusion to pain in knee OA remains an enigma. Data in the OA literature regarding this have also proved conflicting. Whilst some studies, albeit small ones do not suggest any association between BMLs to pain (23), the balance of data however, supports a strong relationship between BMLs and pain in OA (5). Their presence can potentially alter fluid dynamics and perfusion in subchondral bone which can result in intraosseous hypertension, bone necrosis and cartilage breakdown (24). Whilst previous studies in the OA literature support a link between BMLs and knee pain, few have evaluated bone perfusion in relation to knee pain in OA. Our study used dynamic contrast-enhanced MRI with Gd-DTPA to extract kinetic information on bone perfusion in association with these lesions. In this population of participants with symptomatic knee OA, our study yielded three main findings in relation to bone perfusion and pain.

- There was a correlation with BML size and rate of contrast elimination (k_{el}).

Contrast elimination reflects venous stasis and intraosseous hypertension as a consequence of venous outflow obstruction. The finding of a significant association with BML size and the rate of contrast elimination is consistent with previous work on perfusion parameters that point to outflow obstruction as the primary change in kinetic parameters (25). These authors demonstrated that perfusion out of the region of interest was significantly lower in BMLs when compared with normal bone. It would have been expected that the rate of perfusion between extracellular space and plasma (k_{ep}) would also increase with BML size due to intraosseous hypertension.

Some of the vascular changes associated with BMLs have been recognised as replacement of the normal subchondral marrow with fibrovascular granulation tissue. Saadat *et al*(26) assessed patients with advanced knee OA and reported that there was a correlation of BMLs with fibrovascular tissue ingrowth of bone as a result of angiogenesis which leads to new increased blood flow to the area. This fibrovascular tissue is continuous with the vascular channels which invade the articular cartilage in BMLs and are associated with knee pain (27). The contribution of angiogenesis to pain enables the innervation of tissues and may synergise with inflammation to exacerbate pain (28).

- BML perfusion is not associated with pain after adjusting for important covariates.

The failure to find an association of bone perfusion with pain is of interest and suggests that perfusion of BMLs does not contribute to their pain genesis. Other studies also allude that knee pain stems from many other causes and even though BMLs are associated with pain in OA, this association with pain is significant only in the presence of other abnormal articular changes. Torres *et al*(29) agreed that BMLs alone were not sufficient to account for pain and its contribution to pain severity appeared to require the presence of other modifications such as capsular distention and bone attrition. Attrition of bone is a more common finding in people with knee pain and OA than those with OA without knee pain (30). By the time a patient experiences pain and has evidence of OA on MRI, many other pathologic features such as synovitis, synovial effusions and cysts coexist which makes it challenging to identify the single feature that causes the most pain (31).

There have also been studies that did not find any association between BML size and pain in OA (32;33). An attempt to reconcile these data could be that the presence of BML and altered perfusion may only signal an element of susceptibility for the induction of pain whose expression still required additional structural abnormalities within the knee (34). Moreover, BMLs Grades 1 and 2 had small volumes compared to the total joint volume and may not contribute to the overall knee pain.

We did find a positive association of BML K_{ep} and pain at night suggesting a potential relationship between the permeability of the BMLs and nocturnal pain. The underlying mechanism for this relationship is unclear and would be worth investigating in future studies to see if this can be replicated.

- Trend to inverse correlation between pain at night and BML Grade

Larger BMLs have been shown to be associated with higher grades of cartilage defects (9) and one would again expect increasing BML size to be associated with greater pain scores. This was therefore a result that was contrary to what we hypothesised.

There are two possible explanations for this unexpected finding. Firstly, it is not clear if BMLs exhibit a homogenous expression in all patients. Previous histopathological studies have demonstrated that the BMLs themselves consist of a mixed pathology including granulation, diffuse necrosis, fibrinoid deposition and blood vessel wall hyperplasia (19). In addition, histologically it has also been reported that only 4% of BMLs contained edema and that they consisted of other irregularities such as marrow fibrosis and trabecular remodeling (18;35). Pain initiation from BML abnormalities emanate from the fact that necrotic cells release neuromediators(34). It will therefore also be of interest to ascertain the degree and amount of

necrosis within these BMLs to determine if size does also correlate with necrosis. In light of these, the BMLs in our study participants may not have been homogeneously edematous and that other characteristics within the whole knee joint may also be responsible for the induction of pain.

There are several limitations of the study that require mentioning. Firstly, we evaluated the association of BMLs and pain of the entire knee. Differences in the compartmental BMLs and their relation to pain at their respective anatomical sites were therefore not examined. The second limitation was that we did not take into account that in addition to BMLs and altered perfusion, there are multiple joint structures within the knee such as subchondral bone cysts and synovitis that could also have contributed to knee pain. Future research into this area could include patient subgroups with other subchondral bone pathology that may shed more light on their relationship with bone perfusion and pain in OA. Another limitation was the lack of concomitant information regarding OA treatments the participants may currently be receiving or have received previously such as chondroitin, hyaluronate and physiotherapy which could have affected the size of BML, pain, fluid dynamics and bone perfusion. In future studies it would also be important to have histologic correlation and a broader sample representing different stages of disease severity and not just those with end-stage disease. It is possible that the central region on which the DCE MRI was assessed may have different angiogenic activity and contrast uptake to the rim of enhancement in the periphery seen on the fat suppressed sequence. Future studies should extend our findings to include the whole BML and other regions of the joint including the femur.

To conclude, osteoarthritis is a dynamic disease process with interconnecting symptoms and structural changes. Even though there is increasing evidence that BMLs play an important part in the pathogenesis of knee OA, BMLs are formed from various causes, all of which may be interacting and complex and comprise of biomechanical, genetic and inflammatory components, of which bone perfusion is only one aspect. The mixed results in our study imply that the pathological and functional significance of tibial BMLs in relation to pain is still a matter of debate. Ascertaining which structures in the knee with OA are associated with pain will aid our understanding of the pathophysiology of OA and lead to the development of more effective therapeutic options to delay disease progression.

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Conflict of interest statement

Nothing to declare. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Author contributions

DJH conceived and designed the study, drafted the manuscript and takes responsibility for the integrity of the work as a whole, from inception to finished article. JPD was also involved in the design of the study. All authors contributed to acquisition of the data. All authors critically revised the manuscript and gave final approval of the article for submission.

Table 1 Baseline demographics of study population (n=37)

M:F ratio	21:16
Age, mean (years)	64.9 (range 46 to 86)
Body Mass Index, mean (kg/m^2)	28.9 (range 21.4 to 35.2)
Pain score at night while sleeping (n, %)	
1	15 (40.5)
2	16 (43.3)
3	6 (16.2)
WOMAC Pain, 0-20 scale	10.2 (range 3 to 15)
BML Grade (n, %)	
1	14 (37.8)
2	14 (37.8)
3	9 (24.4)

Table 2. The relation of BML grade to perfusion

Perfusion Parameters	Bivariable estimate effect- β coefficient (95%CI)	Multivariable estimate effect- β coefficient (95%CI)
BML slope/Muscle slope	-1.911 (-4.430, 0.607)	-1.794 (-4.127, 0.540)
BML A/ Muscle A	-0.303 (-1.707, 1.102)	-0.331 (-1.634, 1.011)
BML K_{ep}/ Muscle K_{ep}	-0.423 (-1.173, 0.326)	-0.404 (-1.172, 0.364)
BML K_{el}/ Muscle K_{el}	0.380 (0.161, 0.599)*	0.361 (0.143, 0.579)*
BML AK_{ep}/ Muscle AK_{ep}	-2.256 (-5.819, 1.306)	-2.288 (-5.656, 1.079)

* $p < 0.005$

Multivariable model adjusted for age, BMI and gender

Fig 1. Chart of BML K_{el} with BML Grade. Kel decreases with increasing BML size showing delayed outflow postulated to represent venous obstruction.

BML kel

Overall, p=0.002

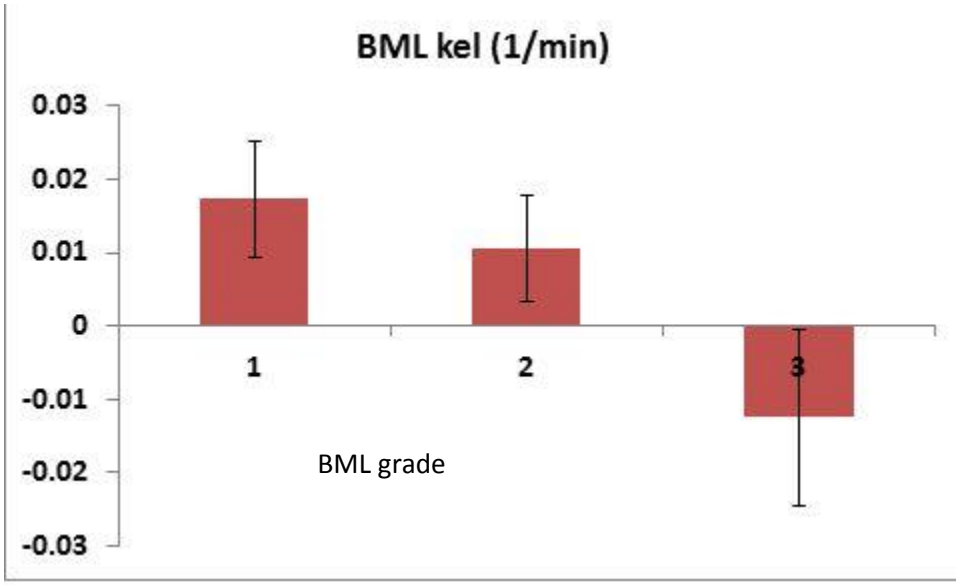
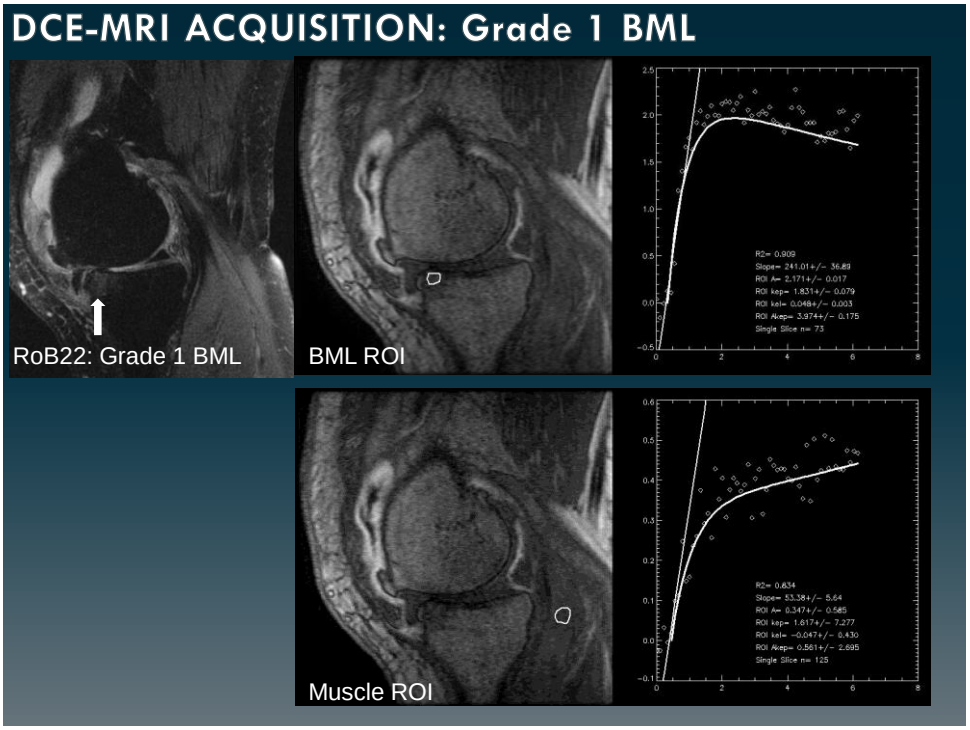


Figure 2. Representative images of DCE-MRI acquisition . Notice that there is more rapid washout or clearance of the Gd compared to muscle in the lower grade 1 BML's. This implies more normal elimination and proper venous outflow. Our findings indicated that the larger BMLs (See Grade 3 lesion) had a more negative Kel (more delayed clearance) indicating more delayed venous outflow.



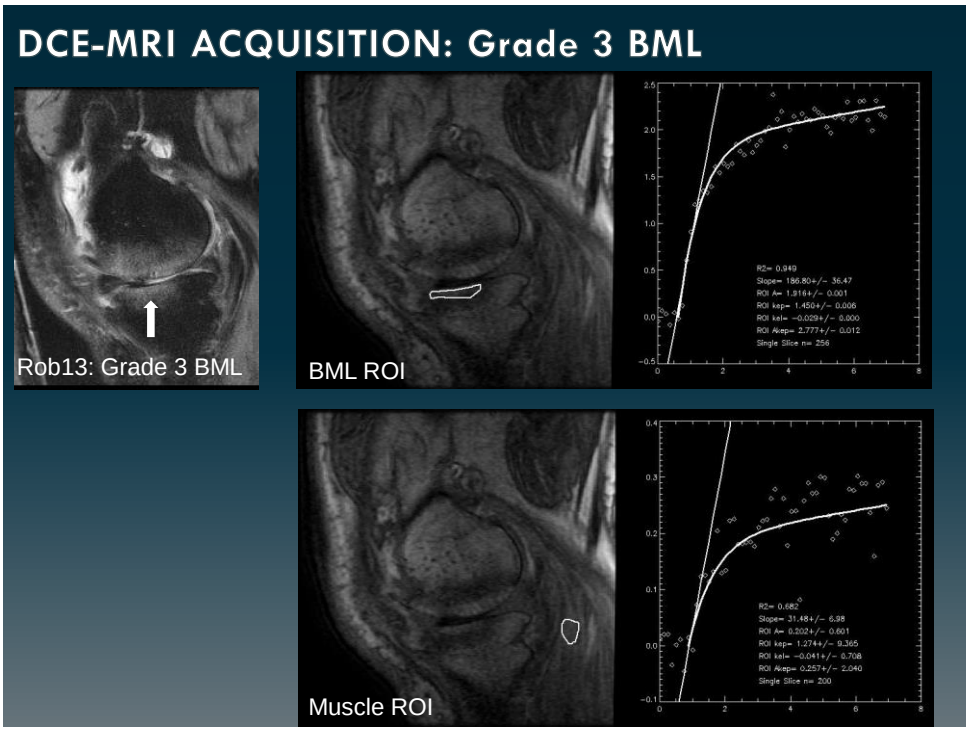


Table 3. Relation between BML perfusion and pain

Perfusion Parameters	Model 1		Model 2	
	Estimate effect (95%CI)	p-value	Estimate effect (95%CI)	p-value
BML slope/Muscle slope	0.124(-0.064, 0.312)	0.190	0.112(-0.084, 0.308)	0.253
BML A/ Muscle A	*0.355(0.021, 0.690)*	*0.038*	0.207(-0.138, 0.551)	0.231
BML K_{ep}/ Muscle K_{ep}	0.168(-0.487, 0.823)	0.606	0.163(-0.442, 0.768)	0.588
BML K_{el}/ Muscle K_{el}	-0.550(-2.507, 1.408)	0.572	-0.524(-2.657, 1.608)	0.620
BML A.K_{ep}/ Muscle A.K_{ep}	*0.148(0.020, 0.276)*	*0.024*	0.114(-0.018, 0.246)	0.088

Model 1. Relation between WOMAC Pain scores and BML perfusion and muscle

Model 2. Relation between WOMAC Pain scores with BML perfusion and muscle, adjusted for BML grade, age, gender and BMI

Table 4. Relation between BML perfusion and pain at sleeping

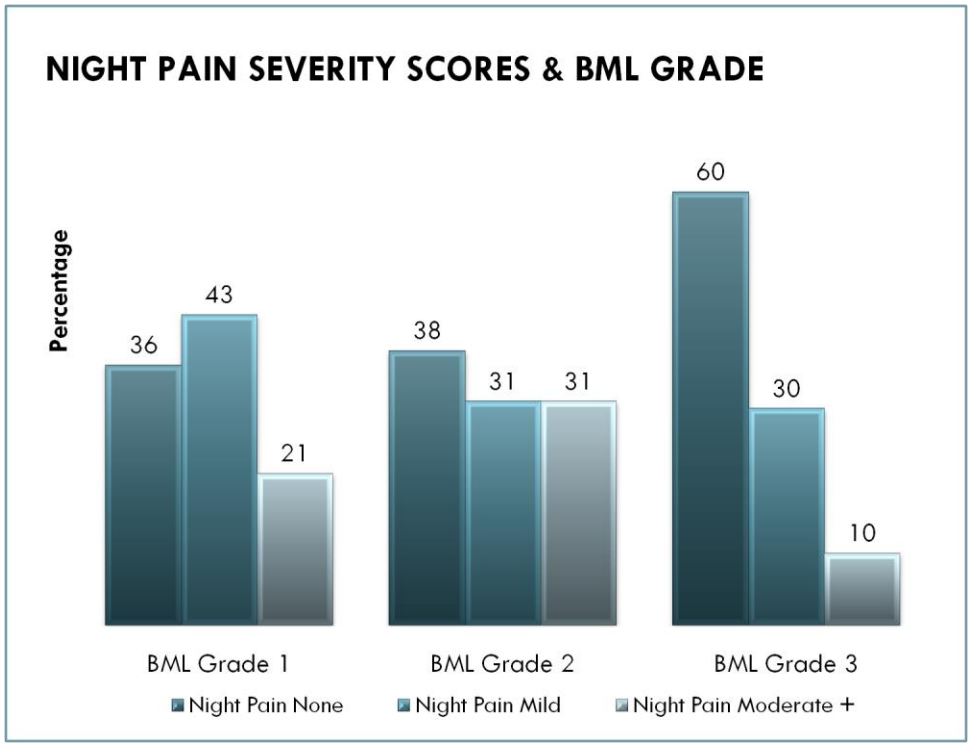
Perfusion Parameters	Model 1		Model 2	
	OR(95% CI)	Proportional odds assumption p-value*	OR(95% CI)	Proportional odds assumption p-value*
BML slope/Muscle slope	1.10(0.99, 1.23)	0.713	1.13(0.99, 1.29)	0.989
BML A/ Muscle A	1.08(0.90, 1.30)	0.832	0.97(0.79, 1.20)	0.976
BML K_{ep}/ Muscle K_{ep}	1.52(0.99, 2.34)	0.222	*1.65(1.03, 2.65)*	*0.887*
BML K_{el}/ Muscle K_{el}	0.73(0.27, 2.01)	0.583	1.00(0.28, 3.62)	0.965
BML AK_{ep}/ Muscle AK_{ep}	1.06(0.99, 1.14)	0.669	1.04(0.96, 1.13)	0.986

Model 1.Relation between WOMAC Pain with sleeping scores and BML perfusion and muscle

Model 2.Relation between WOMAC Pain with sleeping scores with BML perfusion and muscle, also adjusts for BML grade, age, gender and BMI.

* Score test for proportional odds assumption

Fig 3.Relationship between pain at night while sleeping and BML Grade.



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