Bone marrow lesions are related to dynamic knee loading in medial knee osteoarthritis

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ABSTRACT

Objectives: To evaluate the relationship between mechanical loading, as indicated by the external knee adduction moment (KAM) during walking, and BML on MRI in people with medial knee osteoarthritis.
Methods: Measures were taken in 91 individuals with medial knee osteoarthritis. Logistic regression analyses were performed with the presence/absence of medial tibial or medial femoral BML as the outcome and either peak KAM or KAM impulse as the independent variable. Analyses were also adjusted for age, gender, body mass index, alignment and walking speed.
Results: In adjusted analyses, peak KAM was significantly related to medial tibial (OR 2.3; 95%CI 1.07 to 4.7), but not medial femoral (OR 1.85; 95%CI 0.93 to 3.7) BML. KAM impulse was significantly related to both medial tibial (OR 9.4; 95%CI 1.53 to 57.2) and medial femoral (OR 14.4; 95%CI 2.3 to 89.8) BML.
Conclusions: The findings support the hypothesis that greater mechanical loading of the medial compartment plays a role in the pathogenesis of BML in medial tibiofemoral osteoarthritis.

Bone marrow lesions (BML) in the subchondral trabecular bone are ill-defined areas of high signal intensity on T2-weighted fat-suppressed magnetic resonance imaging. A characteristic feature of knee osteoarthritis, BML are associated with pain[1 2] and disease progression.[3 4] Despite the importance and frequency of BML, their aetiopathogenesis is poorly understood.

There is some evidence that BML are related to mechanical loading. Static knee alignment, a local mechanical factor from which increased knee load can be inferred, is related to BML location and frequency.[3] BML are more prevalent in the medial compartment of people with varus malalignment, compared with those with neutral alignment.[3] BML are also more prevalent in regions of relatively higher apparent subchondral bone density,[5] which in itself is related to greater mechanical loading.[6] While these support a relationship between BML and knee loading, no study has evaluated this association to date.

Although measurement of knee mechanical load is difficult in vivo, the external knee adduction moment (KAM) derived from gait analysis provides a valid and reliable indicator of compressive load in the medial tibiofemoral compartment.[7] The KAM has time-varying characteristics over the stance phase of walking gait (figure 1). The peak KAM is of particular importance in knee osteoarthritis as it has been related to disease severity[8 9] and to the risk of radiographic disease progression.[10] KAM impulse, which is the positive area under the KAM–time curve, is also important as it indicates total mechanical loading of the medial compartment of the knee during walking.[6]

The aim of this study was to determine the relationship between mechanical loading (as indicated by KAM measures) and medial BML. We hypothesised that the peak KAM and the KAM impulse would be related to the presence of BML in the medial tibiofemoral compartment in people with medial knee osteoarthritis.

PATIENTS AND METHODS

Setting and participants

Ninety-one community volunteers with radiographic medial tibiofemoral osteoarthritis were recruited. Diagnosis of knee osteoarthritis was based on American College of Rheumatology criteria[11] of age over 50 years and knee pain on most days of the previous month. Other inclusion criteria were pain/tenderness mainly over the medial knee and medial tibiofemoral radiographic osteoarthritis defined as at least grade 1 medial joint space narrowing (medial>lateral) or grade 1 medial tibial or femoral osteophytes.[12] Exclusion criteria were: (1) Kellgren and Lawrence (K&L) grades 1 and 4; (2) knee surery or intra-articular injection within 6 months; (3) current or past (within 4 weeks) oral corticosteroid use; (4) systemic arthritis; (5) history of knee joint replacement or tibial osteotomy; (6) medication or condition that could affect bone density.

The research was approved by the University of Melbourne Human Research Ethics Committee. Participants provided written informed consent.

Radiographs

Standardised standing semiflexed posteroanterior knee x-rays were taken. The radiographic severity of tibiofemoral osteoarthritis was assessed with the K&L system[12] by an experienced musculoskeletal researcher (KLB) whose intrarater reliability was 0.87 (weighted kappa).

Anatomical knee alignment was measured from the x-rays and is reliable in our hands (intraclass coefficient 0.95). A prediction equation was used for conversion to mechanical axis[13] with a lower value representing greater varus malalignment.

Gait analysis

A 120 Hz, eight-camera, motion analysis system (Vicon, Oxford, UK) was used to measure the external KAM. The plug-in-gait lower limb marker set was used. Ground reaction forces were measured with force plates (AMTI, Watertown, Massachusetts, USA) embedded in the floor of a 10 m walkway at 1080 Hz, in synchrony with the

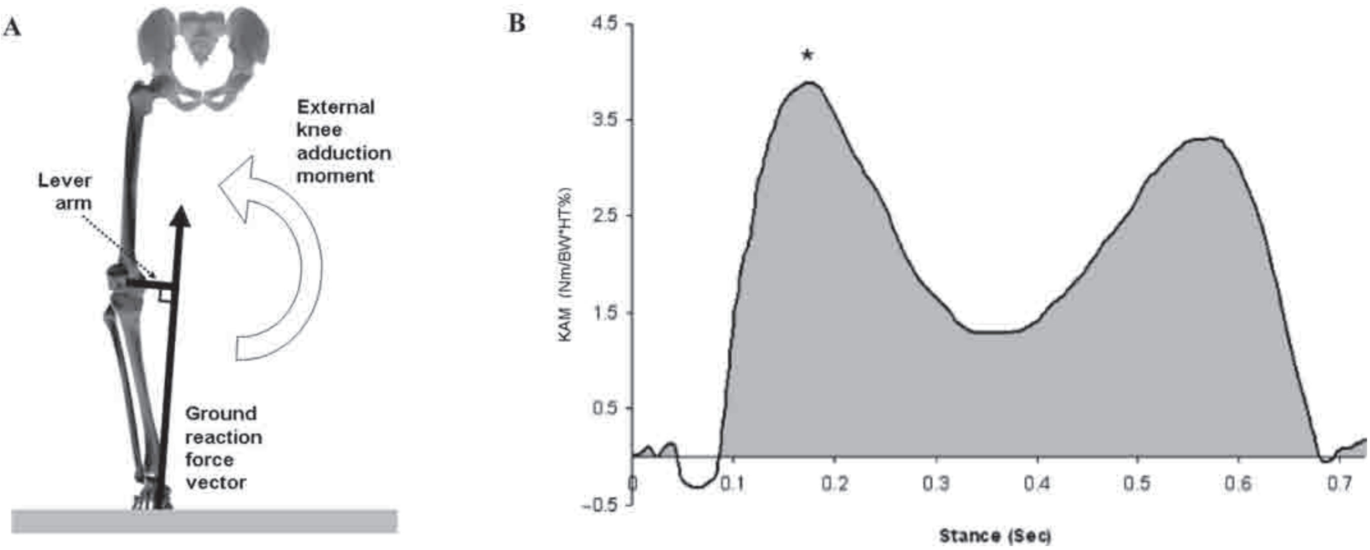

Figure 1 (A) Diagram of the knee adduction moment (KAM), which forces the knee into varus, loading the medial compartment. The KAM is primarily the product of the ground reaction force and the length of the lever arm, defined as the perpendicular distance from the centre of the knee joint to the line of action of the ground reaction force. (B) Tracing of a typical KAM over the stance phase of walking showing the peak KAM (*) and the KAM impulse representing the positive area under the curve (shaded region).

cameras. Participants walked in their usual, low-heeled footwear at a self-selected pace.

KAM was calculated using inverse dynamics (Vicon Plug-in-Gait version 1.9) and normalised for body weight and height.[14] The variables of interest were peak KAM (Nm/BW*HT%) and positive KAM impulse (Nm.s/BW*HT%) (figure 1). Variables were calculated for each trial, then averaged over five trials. Our test–retest reliability for peak KAM and KAM impulse is excellent; intraclass coefficients[3 5] of 0.98 and 0.96, respectively.

Bone marrow lesions

The knee was imaged in the sagittal plane on a 1.5-T whole body magnetic resonance imaging unit with a commercial transmit–receive extremity coil (Philips Medical Systems, Eindhoven, The Netherlands). Image sequence for BML was a coronal T2-weighted fat-saturated acquisition, repetition time 3500–3800 ms, echo time 50 ms, slice thickness 3.0 mm, interslice gap 1.0 mm, one excitation, 13 cm field of view and 256 × 192 pixel matrix.

The presence of BML in the medial and lateral compartments was assessed using the BLOKS semiquantitative scoring system[15] by an experienced reader (DJH) blinded to participant measurements (intrarater reliability 0.88 (weighted kappa)).

Statistical analysis

We performed binary logistic regression analyses with presence/absence of medial tibial or medial weight-bearing femoral BML as the outcome and peak KAM or KAM impulse as the predictor variable. The analysis was repeated adjusting for the covariates of age, gender, body mass index, static knee alignment and walking speed. Statistics were computed using SAS version 9.0.

RESULTS

Table 1 Participant characteristics given as the mean (95% CI) or the number (percentage)

		Medial tibial BML		Medial femoral BML	
Characteristics	**Total cohort (n=91)**	**Absent (n=33)**	**Present (n=58)**	**Absent (n=36)**	**Present (n=55)**
Age (years)	64.5 (62.9 to 66.1)	66.1 (63.7 to 68.6)	63.6 (61.5 to 65.6)	66.2 (63.9 to 68.6)	63.4 (61.3 to 65.5)
Height (m)	1.67 (1.65 to 1.69)	1.67 (1.64 to 1.70)	1.67 (1.65 to 1.70)	1.67 (1.64 to 1.70)	1.67 (1.65 to 1.70)
Mass (kg)	81.1 (77.9 to 84.4)	77.8 (73.0 to 82.6)	83.0 (78.7 to 87.3)	81.0 (76.8 to 85.5)	81.2 (76.8 to 85.5)
Body mass index (kg/m^2)	28.9 (28.0 to 29.8)	27.8 (26.5 to 29.2)	29.5 (26.5 to 29.2)	29.0 (27.4 to 30.7)	28.8 (27.7 to 29.9)
Gender (n (%))					
Female	46 (51%)	20 (61%)	26 (45%)	20 (56%)	26 (47%)
Male	45 (49%)	13 (39%)	32 (55%)	16 (44%)	29 (53%)
K&L grade (n (%))					
2	48 (53%)	26 (79%)	22 (38%)	26 (72%)	22 (40%)
3	43 (47%)	7 (21%)	36 (62%)	10 (28%)	33 (60%)
Static knee alignment (°)†	178.3 (177.9 to 178.7)	179.3 (178.7 to 179.9)	177.7 (177.2 to 178.3)	179.1 (178.5 to 179.7)	177.8 (177.2 to 178.3)
Walking speed (m/s)	1.27 (1.23 to 1.32)	1.27 (1.20 to 1.34)	1.28 (1.23 to 1.33)	1.26 (1.20 to 1.33)	1.28 (1.23 to 1.34)
Peak KAM (Nm/BW*HT%)	3.72 (3.54 to 3.90)	3.43 (3.10 to 3.75)	3.89 (3.67 to 4.10)	3.44 (3.10 to 3.78)	3.90 (3.70 to 4.10)
KAM impulse (Nm.s/BW*HT%)	1.25 (1.18 to 1.32)	1.09 (0.98 to 1.20)	1.34 (1.25 to 1.43)	1.09 (0.99 to 1.19)	1.36 (1.27 to 1.45)

†Static knee alignment of 180° equates to a neutral mechanical axis with lower values indicating greater varus.
BML, bone marrow lesion; BW, body weight; HT, height; KAM, knee adduction moment; K&L, Kellgren and Lawrence.

A description of the cohort is provided in table 1. Most knees displayed medial greater than lateral joint space narrowing (89/91). Medial compartment BML were present in approximately 60% of knees but were uncommon in the lateral compartment (<7% of knees).

Unadjusted logistic regression analyses revealed that a higher peak KAM and a higher KAM impulse were significantly related to the presence of BML at the medial tibia and medial femur (table 2). When adjusted for covariates, a higher peak KAM increased the odds of having BML at the medial tibia while a higher KAM impulse increasing the odds of having BML at the medial tibia and at the medial femur. Static alignment independently predicted BML presence as a covariate in the adjusted logistic regression model, with peak KAM at the medial tibia and medial femur. Peak KAM and KAM impulse were equally accurate in predicting BML presence as shown by similar C-statistics for the unadjusted and adjusted models.

DISCUSSION

Mechanical factors are believed to play a role in the progression of knee osteoarthritis. To date the mechanism underpinning the relationship between increased medial tibiofemoral loading and progression of cartilage loss in the same compartment has been unclear. This study suggests an independent relationship between KAM measures and the presence of medial compartment BML in people with mild-to-moderate medial knee osteoarthritis. Our results support the hypothesis that greater mechanical loading is related to the aetiopathogenesis of BML. As subchondral BML are strongly associated with pain and structural disease progression, understanding the aetiopathogenesis of subchondral BML will facilitate the development of targeted treatments.

This study provides important insights into the genesis of BML. Earlier studies had suggest that BML may be related to mechanical loading. Static knee load, as indicated by knee malalignment measured on x-ray, is related to BML prevalence.[3 4] Static knee alignment shows weak to moderate correlations with the KAM;[8 16] in our study greater varus malalignment was modestly associated with a higher peak KAM ($r=-0.29$, $p<0.01$) and higher KAM impulse ($r=-0.43$, $p<0.01$). This indicates that alignment and KAM-based loading parameters are not necessarily measuring the same construct. Moreover, our results showed that static alignment was no longer an independent predictor of BML when included in the regression model with KAM impulse. The higher prevalence of medial tibiofemoral compartment BML (60% and 64%) compared with lateral compartment BML (2% and 7%) in our cohort is also consistent with higher medial compartment loading.[7] Taken together our results suggest that the repetitive loading experienced by the medial tibiofemoral compartment during walking is related to BML in people with knee osteoarthritis.

Our results and other evidence in the literature support the contention that BML are an imaging biomarker of greater knee loading. Examination of bone specimens exhibiting BML taken from people undergoing total knee joint replacement reveals reduced mineralisation and increased bone volume fraction consistent with increased remodeling.[17] It is feasible that these areas of bone architecture pathology are caused by focally increased loading. This temporal sequence is supported by an animal study in which the development of BML followed load-altering cruciate-ligament transection.[18] It remains unclear whether cartilage changes precede or follow the development of BML.

Mechanical loading and BML have been separately related to pain[1 19] and to disease progression.[3 10] The relationship between loading and pain may be via BML stimulating nociceptive fibres in the affected bone region.[20] Similarly, the link between loading and cartilage degeneration may be mediated via BML altering the stresses experienced by subchondral bone and overlying cartilage, as BML are less well mineralised than unaffected bone.[17] Alternatively, loading may cause cartilage degeneration by other mechanisms.

Our study has limitations. First, given the relatively small sample size it was not possible to evaluate the relationship of mechanical loading to BML size and also to lateral compartment BML. Further study is recommended to establish this. Second, as the cohort included only those with mild to moderate radiographic disease, results cannot necessarily be generalised to those with severe osteoarthritis or to those at risk of developing osteoarthritis. Third, as the study was cross-sectional in design, the temporal relationship between mechanical loading and the development of BML cannot be confirmed. Longitudinal studies will help clarify this sequence of events.

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Table 2 Relationship between mechanical loading as indicated by knee adduction moment parameters and medial compartment BML

	Medial femoral BML						Medial tibial BML					
Variables	**β**	**SE**	**OR**	**95% CI**	**p Value**	**C**	**β**	**SE**	**OR**	**95% CI**	**p Value**	**C**
Peak KAM†	0.68	0.28	1.97	1.13 to 3.5	0.0171	0.70	0.68	0.29	1.97	1.11–3.5	0.0202	0.67
Peak KAM	0.61	0.35	1.85	0.93 to 3.7	0.0440	0.77	0.81	0.38	2.23	1.07 to 4.7	0.0167	0.80
Age	−0.06	0.03	0.94	0.88 to 1.00			−0.06	0.04	0.94	0.88 to 1.01		
Gender M vs F	0.22	0.25	1.55	0.58 to 4.1			0.31	0.26	1.86	0.67 to 5.2		
BMI	−0.05	0.06	0.95	0.84 to 1.07			0.07	0.06	1.07	0.95 to 1.21		
Alignment	−0.34	0.15	0.71	0.53 to 0.94			−0.38	0.16	0.69	0.50 to 0.93		
Walking speed	−1.40	1.47	0.25	0.01 to 3.7			−1.33	1.54	0.26	0.01 to 5.4		
KAM impulse†	2.71	0.80	15.0	3.1 to 73.0	0.0008	0.72	2.53	0.80	12.5	2.6 to 59.7	0.0015	0.70
KAM impulse	2.67	0.93	14.4	2.3 to 89.8	0.0106	0.78	2.54	0.92	9.4	1.53 to 57.2	0.0097	0.80
Age	−0.07	0.04	0.93	0.87 to 1.00			−0.07	0.04	0.94	0.87 to 1.01		
Gender M vs F	0.08	0.26	1.18	0.42 to 3.3			0.17	0.27	1.42	0.50 to 4.0		
BMI	−0.06	0.06	0.95	0.83 to 1.07			0.06	0.06	1.07	0.94 to 1.21		
Alignment	−0.25	0.15	0.78	0.58 to 1.05			−0.31	0.16	0.73	0.54 to 1.01		
Walking speed	0.58	1.41	1.79	0.11 to 28.4			0.76	1.46	2.2	0.12 to 37.6		

Results of the unadjusted and adjusted logistic regression analyses with † indicating the unadjusted results.
BMI, body mass index; BML, bone marrow lesion; F, female; KAM, knee adduction moment; M, male; OR, odds ratio.

Competing interests None.

Ethics approval This study was conducted with the approval of the University of Melbourne, Human Research Ethics Committee.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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