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Review

Osteoarthritis Bone Marrow Lesions

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SUMMARY

Assessment and treatment of Bone Marrow Lesions (BMLs) could ultimately make step changes to the lives of people with osteoarthritis (OA). We here review the imaging and pathological characteristics of OA-BMLs, their differential diagnosis and measurement, and cross-sectional and longitudinal associations with pain and OA structural progression. We discuss how biomechanical and cellular factors may contribute to BML pathogenesis, and how pharmacological and non-pharmacological interventions that target BMLs might reduce pain and OA structural progression. We critically appraise semiquantitative and quantitative methods for assessing BMLs, and their potential utilities for identifying people at risk of symptomatic and structural OA progression, and evaluating treatment responses. New interventions that target OA-BMLs should both confirm their importance, and reduce the unacceptable burden of OA.

Introduction

A pre-conference workshop at Osteoarthritis Research Society International (OARSI) in Berlin 2022 highlighted that assessment and treatment of Bone Marrow Lesions (BMLs) could ultimately make step changes to the lives of people with osteoarthritis (OA). Subchondral BMLs are associated with other OA pathological features, and found in up to 66% of symptomatic OA knees[1]. They may fluctuate in size[2], but more than a third will not have resolved within 2 years[3]. There is often remark on the discordance between OA structural change and pain. However, OA structural change is not just about cartilage, and reflects disease of the whole joint, including subchondral bone. BMLs are associated with and fluctuate with pain, might in part drive OA pain, and predict prognosis and treatment outcomes. Targeting BMLs is a novel treatment approach that might both reduce symptoms and modify OA structural progression.

What are BMLs?

BMLs are invisible to radiography and ultrasound, and have been defined through magnetic resonance imaging (MRI) (Fig. 1)[4]. They have been most studied in knees or hips, but are well described in other OA joints[5,6]. BMLs are characterized on MRI by ill-defined hypointensity on T1-weighted non fat-suppressed images, and hyperintensity on fluid-sensitive, T2-, proton density-, and intermediate-weighted fat-suppressed and short tau inversion recovery (STIR) images. They enhance after intravenous administration of contrast agents. BMLs are not exclusive to OA. Not all BMLs in OA are OA-BMLs (i.e., not all are due to OA), and other non-OA pathology should be excluded (Fig. 1). OA-BMLs are defined by being adjacent to articular cartilage (subchondral) in a joint with structural OA and without any visible fracture line. Adjacent cartilage lesions are often of high grade.

Although originally described as bone marrow edema, the specific histological, gene and protein signatures of OA-BMLs reflect diverse, inter-related pathological processes, including active

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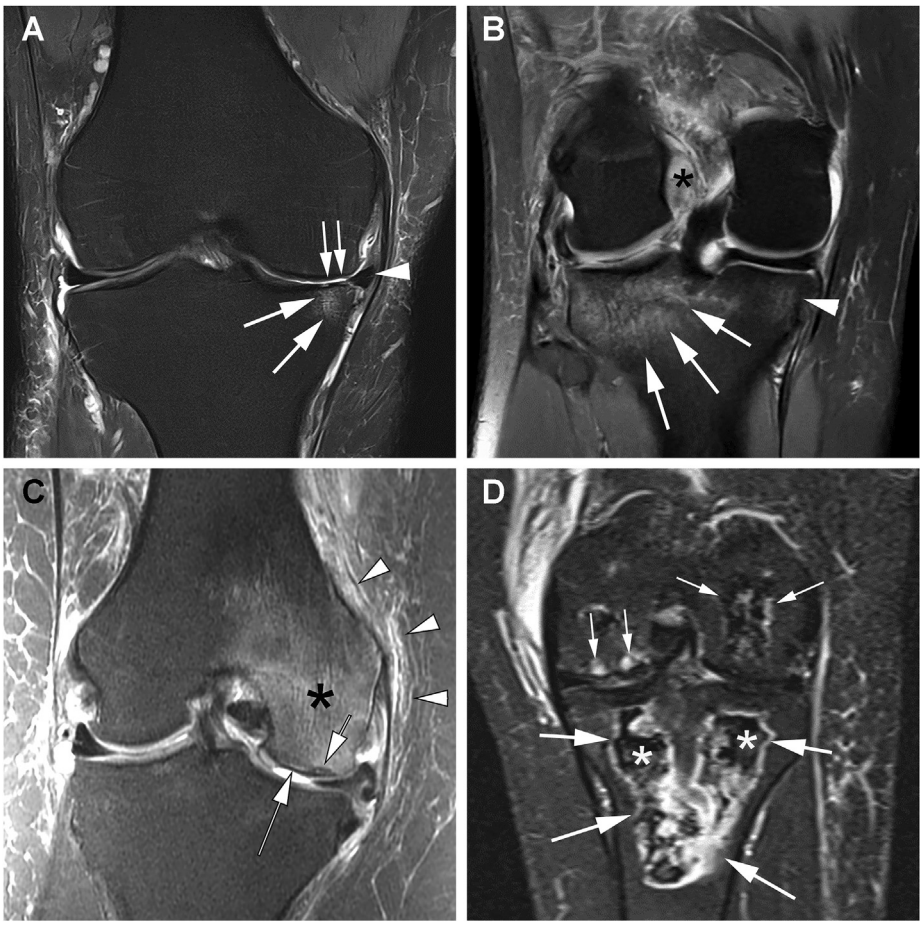

Fig. 1

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Osteoarthritis bone marrow lesion (OA-BML) and differential diagnoses. BMLs occur in OA (OA-BMLs) (A), or might result from trauma (B) resulting from contusion ('bone bruises'), stress reaction or fracture, or from non-traumatic pathology such as subchondral insufficiency fracture (SIF) (C) or subsequent spontaneous osteonecrosis of the knee (SONK), bone infarcts/avascular necrosis/osteonecrosis (D). Other causes of BMLs are osteochondritis dissecans, infection, haematologic or metastatic malignancy. Some BMLs may be idiopathic and transient, or reflect physiological red marrow reconversion. They may be associated with rheumatoid arthritis, enthesopathy or tendinopathy. ***A. Osteoarthritis*** (OA): Coronal fat-suppressed proton density-weighted MRI shows ill-defined subchondral hyperintensity without a visible fracture line at the medial tibial plateau (large arrows) representing a typical OA-BML. In addition, there is severe medial meniscus extrusion (arrowhead) and diffuse superficial loss of cartilage at the central medial femur and tibia (small arrows). ***B. Trauma***: Coronal fat-suppressed intermediate-weighted MRI shows ill-defined hyperintensity of the posterior lateral tibial plateau with no fracture line (arrows). A second, smaller hyperintense lesion is visible at the posterior medial tibia (arrowhead). These findings represent bone contusions in the context of a traumatic anterior cruciate ligament tear (asterisk). In contrast to OA-BMLs, bone contusions are usually larger, have a more geographic appearance and have not necessarily only subchondral location. ***C. Subchondral Insufficiency Fracture*** (SIF): Coronal fat-suppressed proton density-weighted MRI shows a subchondral linear hypointensity zone directly adjacent to the normal subchondral plate (short arrow) at the medial femoral condyle. In addition, there is extensive bone marrow hyperintensity of the femoral condyle ('bone marrow edema', asterisk) and soft tissue hyperintensity ('inflammation') at the medial joint line (arrowheads). Subchondral linear hypointensity is pathognomonic for subchondral insufficiency fracture (SIF). There is full-thickness cartilage loss at the central medial femur (long arrow) and moderate meniscal extrusion due to a posterior medial meniscus root tear, which is commonly associated with SIF. ***D. Avascular osteonecrosis***: Coronal fat-suppressed proton density-weighted MRI shows a large well-defined hyperintense lesion in the epi-metaphyseal tibia (arrows) with a fat-equivalent center (asterisks) pathognomonic for bone infarcts or avascular necrosis. Smaller hyperintense lesions in the medial and lateral epiphyseal femur also represent bone infarcts (small arrows).

cellular pathology, more than plasma extravasation. Non-OA BMLs might have their own specific signatures. For example, fibrovascular infiltrates in bone marrow spaces in rheumatoid arthritis contain specific immune cells resembling synovial pannus[7]. OA-BMLs display high metabolic activity, inflammation, angiogenesis, and bone turnover (Fig. 2)[8]. They are associated with structural change; lost osteochondral integrity, fibrosis, cysts, and *de novo* cartilage within subchondral bone. While non-BML regions of

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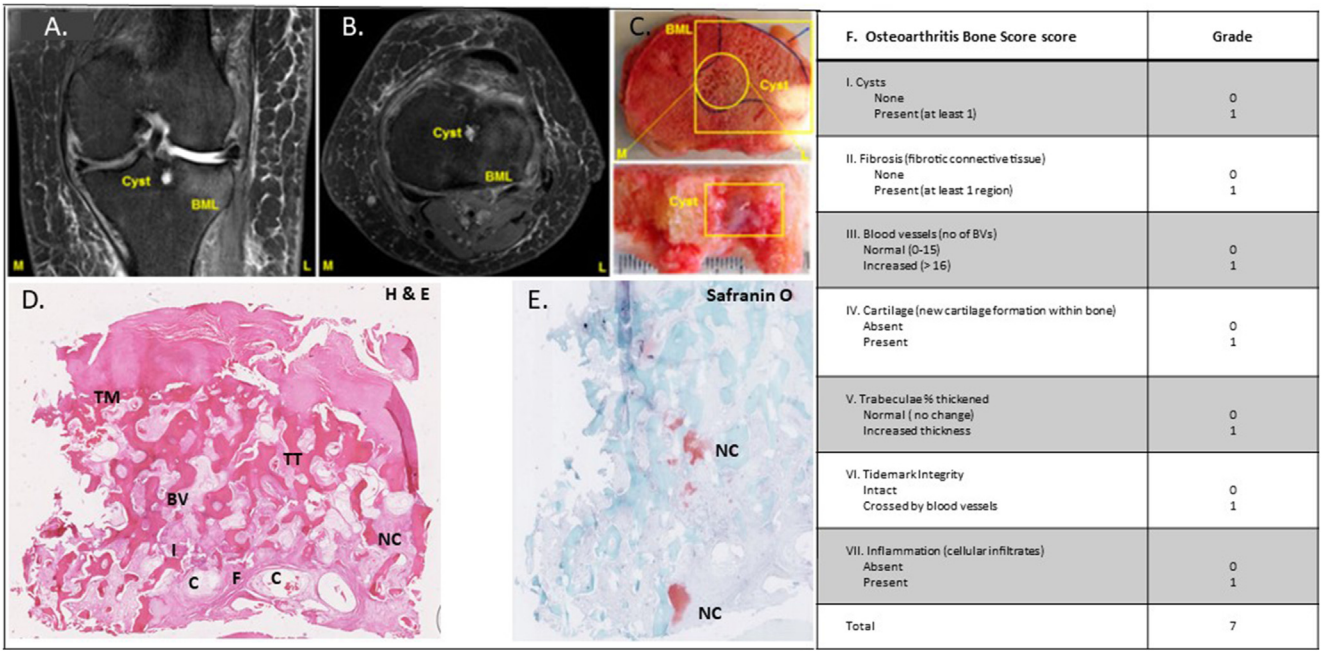

F. Osteoarthritis Bone Score score	Grade
I. Cysts	
None	0
Present (at least 1)	1
II. Fibrosis (fibrotic connective tissue)	
None	0
Present (at least 1 region)	1
III. Blood vessels (no of BVs)	
Normal (0-15)	0
Increased (> 16)	1
IV. Cartilage (new cartilage formation within bone)	
Absent	0
Present	1
V. Trabeculae % thickened	
Normal (no change)	0
Increased thickness	1
VI. Tidemark Integrity	
Intact	0
Crossed by blood vessels	1
VII. Inflammation (cellular infiltrates)	
Absent	0
Present	1
Total	7

Fig. 2 Osteoarthritis and Cartilage

Histological characteristics of OA-BMLs. Coronal (A) and axial (B) MRI views of someone with advanced knee OA prior to total knee arthroplasty, with tissue harvested at surgery (C). BML tissue identified by MRI in A and B was analysed histologically using haematoxylin and eosin (D) and Safranin O (E) staining. The samples show characteristic features of cysts (C), fibrosis (F), increased blood vessels (BV), new cartilage (NC) within bone (pink in E), trabecular thickening (TT), loss of tidemark integrity (TM) and subchondral inflammatory cell infiltration (I), giving total Osteoarthritis Bone Score (OABS) (F) of 7.

subchondral bone display bone attrition in moderate to advanced OA, BMLs display trabecular thickening (albeit with reduced mineralisation). Associations between BMLs and increased trabecular thickness[8], disruption of the osteochondral junction[8] and subchondral microfracture[8,9] point to increased bone turnover. BML-like histopathology is associated with increased numbers of tartrate-resistant acid phosphatase (TRAP)-positive osteoclasts and circulating biomarkers such as TRAP-5b[10]. Treatments that suppress bone turnover may reduce BML size[6,11]. Microarray analysis of gene expression in BML tissues reflects high metabolic activity, with 166 genes identified as up- or down-regulated, from 59 identified pathways known to regulate processes as diverse as angiogenesis, inflammation and neurodegeneration[12].

Some of the pathological changes in BMLs might contribute to pain and progressive structural damage. Cellular products such as nerve growth factor (NGF), which are increased in subchondral bone with histological characteristics of BMLs[7], might sensitise nerves, increasing their activation by biomechanical forces or leading to spontaneous activity. Subchondral fibrovascular infiltration is associated with fibrovascular channels crossing the osteochondral junction, possibly breaching the barrier that the junction normally poses, permitting passage of sensitising factors in synovial fluid into subchondral bone[13]. Increased perivascular sensory innervation in subchondral bone affected by BMLs might further increase sensitivity to biomechanical or chemical activation[8].

Associations of BMLs with osteochondral structural damage might be bidirectional. Breaches in the osteochondral junction due to progressive OA pathology might permit extrusion of synovial fluid, or diffusion of soluble factors into the subchondral bone[13], establishing a cellular response that on MRI is apparent as BML. Reciprocally, changes in subchondral bone architecture can increase biomechanical forces sustained by articular cartilage[14], overcoming homeostatic reserve and exacerbating OA joint damage. New bone formation in the OA joint might lead to both trabecular thickening and osteophyte growth.

The precise causes of OA-BMLs are uncertain, but several risk factors for their presence or progression have been identified. Biomechanical factors might be critical. Varus tibiofemoral alignment predisposes to increased BML presence and size in the medial tibiofemoral joint[15]. This longitudinal association suggests mediation by increased compartmental loads and adduction moment. Interventions that redistribute these stresses by orthoses or high tibial wedge osteotomy may reduce BML size[16,17]. Obesity or dietary lipid intake[18] and high physical activity[15] each might contribute to the genesis of BMLs, although interventions addressing these factors have not, to date, definitively reduced BMLs[19,20]. Shared factors, perhaps genetic, might contribute both to BML genesis and, for example, to obesity, and some observed associations of BMLs might reflect shared pathogenesis rather than direct causation.

How are BMLs measured?

BML measurement is essential if we are to show that interventions target and modify BMLs. Optimal measurement tools will indicate those pathological processes that explain symptoms or

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structural progression. For BML measurement to be reliable, MRI protocols must use optimal pulse sequences[21,22]. Research using only non-fat-suppressed sequences provides limited data, and fluid-sensitive sequences are required. Gradient echo sequences are unsuitable due to insensitivity to diffuse marrow abnormalities caused by trabecular magnetic susceptibility (T2* effects), leading to missing or underestimation of the extent of a lesion. Metal-induced artifacts make assessment of BML signals very difficult. MRI reading also requires validated training and calibration between multiple readers to ensure that OA-BMLs are distinguished from other pathologies.

OA-BMLs can be semiquantitatively graded using the MRI OA Knee Score (MOAKS)[23] or Rapid OA MRI Eligibility Score (ROAMES)[24]. MOAKS includes detailed subregional grading of areas of presumed BML together with associated cysts containing fluid equivalent signal directly adjacent to the subchondral plate. MOAKS has been used in several clinical trials and epidemiological studies[23,25,26]. ROAMES is a simplified instrument for defining structural eligibility of patients for inclusion in clinical trials. Quantitative measurement of BMLs using image segmentation is possible, for example using the Knee Inflammation MRI Scoring System (KIMRISS)[27,28]. Even though the ill-defined boundaries of BMLs and the coexistence of cystic and non-cystic regions within a single lesion can compromise machine-read quantitative measurement, KIMRISS has shown good reliability and association with pain severity.

For clinical applications, semiquantitative scoring might have advantages of feasibility in different healthcare settings, although validation against more quantitative methods would be valuable. Small changes in BMLs might herald further improvement with time, and therefore detailed measurement might prove useful as an early biomarker of response, or in short-term developmental studies of novel treatments. Quantitative methods might be sensitive to detect longitudinal BML changes, while assessing within-grade changes can increase the sensitivity of semiquantitative methods[29]. Confidence for use of BML measures in future evaluations of BML-targeted disease-modifying interventions requires their validation as surrogate markers for the disease progression that leads to symptoms. The inherent natural variability of BMLs over time suggests potential to improve, but that same variability can produce background noise that makes benefits from treatment difficult to detect. Reliable tools that measure clinically and pathologically relevant characteristics should be selected for future research and clinical use. Different tools might be appropriate for different questions or treatment modalities.

MRI detection of BMLs is both feasible and acceptable in clinical trials[25,30], whereas histological measurement can aid *ex vivo* dissection of multiple pathological processes. BMLs have been identified in animal OA models, where histological measurement might have advantages due to the small size of the joints of rodents that are often used for preclinical testing of novel pharmacological agents. The recently described OA Bone Score grades 7 BML-associated histopathological characteristics, and displayed good reliability, effectively discriminated between OA and non-OA medial tibial osteochondral samples, and was better able to distinguish BML from non-BML bone than was Mankin's chondropathy grade[8]. Rasch analysis suggested two inter-related pathological processes, respectively affecting trabecular and non-trabecular structures.

Symptoms that are specifically associated with BMLs, rather than other aspects of OA pathology, might reveal benefit in clinical trials of OA-BML-targeted treatments more than do more general outcome measures. BMLs are associated more strongly with weight-bearing than with rest pain[31,32]. However, reported outcome measures for weight-bearing pain are subscales of global pain scores, comprising small numbers of items, and might benefit from further development to ensure adequate sensitivity to change. Clinical trials aiming to reduce current symptoms by targeting BMLs might measure both patient-relevant outcomes such as global pain, but also those aspects of pain that are mediated by BMLs.

How clinically relevant are BMLs?

OA-BML presence and size are associated with pain[33]. People with knee OA who have BMLs are 2–5 times more likely to have knee pain than those without[34]. The presence or size of BMLs can predict future incident and progressive pain[35], and BMLs can change concurrently with changing symptoms; pain resolution occurs more frequently when BMLs become smaller[36]. While also being associated with other structural, cellular and biochemical features of OA that in turn might cause pain, BMLs might contribute directly to OA pain. Osteoclasts and inflammatory cells within BMLs can produce nerve sensitising factors, including cytokines and NGF, sensory nerves within BMLs might transduce nociceptive signals, and altered subchondral bone quality might increase mechanosensitivity.

Despite statistically significant associations, the extent to which BMLs contribute to OA knee pain remains uncertain, and likely varies between patient subgroups and across time. Associations between changing BMLs and pain have not reached statistical significance in all studies[2,37,38]. Other factors, both in the knee (e.g., cartilage damage or synovitis)[31], and in the central nervous system[39] may contribute to OA pain, independent of, or interacting with any effects of BMLs. Current knee pain might depend more on current BML size, number and distribution, rather than on changes to BMLs over the preceding 2 years[2]. The strength of associations might depend on how both BMLs and pain are assessed. The strength of detected association between BMLs and pain might in part be dependent on MRI technique[40], and OA-BMLs may be particularly associated with weight-bearing rather than non-weight-bearing pain[31]. Associations might be dependent on therapeutic context, and some studies embedded within randomised controlled trials of zoledronate or licofelone did not find significant associations between changing BMLs and pain[37,38].

BMLs predict structural and radiographic progression, particularly cartilage loss[41–43]. There is a strong association between BMLs and structural progression in the same compartment[42], and 81% of knees with medial compartment progression have colocalised BMLs. Increasing medial BML size is associated with progressive adjacent cartilage loss[41], and medial compartment BMLs are strongly predictive of total knee replacement[29,43]. BMLs might contribute directly to radiographic progression through aberrant bone turnover, remodelling and quality, and pathological bone:-cartilage molecular crosstalk.

OA is a disease of the whole joint, and BMLs are associated with OA pathology in different compartments. Confounding by other OA pathology might therefore contribute to apparent associations between BMLs and OA pain or structural progression. The presence of BMLs is strongly associated with articular cartilage defects in OA in the same joint compartment, although 17–57% of knee compartments with BMLs >1 cm did not have cartilage defects more severe than irregularities on the articular surface nor loss of cartilage thickness >50%[44,45]. Prediction of joint space narrowing by baseline BMLs might be at least partly explained by associations with baseline cartilage damage[43]. OA pain is also associated with synovitis[31,46], and synovitis is associated with more severe cartilage pathology[47]. Synovitis therefore might partly explain observed associations between BMLs and pain[46]. Tibiofemoral alignment might contribute to the association between BMLs and progressive knee cartilage loss, since varus alignment is associated with both medial compartment BMLs and articular cartilage loss[41].

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Multivariable regression models have attempted to establish the extent to which associations between BMLs and symptoms or structural damage might be explained by their correlations with other OA pathology. In multivariable models that included measures of cartilage pathology and of BMLs, BMLs remained significantly associated with OA pain[31]. In another study, synovitis explained less than one quarter of the observed association between measures of BMLs and OA pain[46]. Together these data point to possibly direct effects of BMLs on OA pain, but interventions that specifically and directly change BML pathology will be required in order to prove their direct effects. The development of such inverventions requires more detailed understanding of BML pathogenesis.

What is the clinical utility of BMLs?

Pharmacological and non-pharmacological targeting of OA-BMLs might constitute a novel treatment class to rapidly improve symptoms, retard structural and symptom progression, and reduce the currently high need for joint replacement surgery. Clinical trials should cautiously consider differential diagnoses. Some BMLs might be inappropriate for OA-BML treatment, for example BMLs representing subchondral insufficiency fracture. Attempts to date to reduce OA-BMLs have targeted subchondral bone turnover (bisphosphonates[6,11], strontium ranelate[48]), or reducing biomechanical stresses thought to mediate BML formation or pain (patellofemoral bracing[17], high tibial osteotomy[16]). Other treatments might remove or replace BMLs (subchondroplasty[49], arthroplasty), or more generally restore normal cellular function (Bone Marrow Concentrate and Platelet Product injections[50]). Treatments targeting sensitising molecules (e.g., NGF) might, in part, reduce pain by acting on factors produced within BMLs. Not all treatments that reduce BMLs have been found to reduce pain[48], and treatments that can reduce pain associated with BMLs, such as exercise, analgesics and weight loss, might do so without reducing BMLs[19,20]. The Golden Chalice would achieve both.

OA-BMLs might help to identify people at risk of symptomatic and structural OA progression who stand to gain most from treatment. BMLs might identify either a subtype or phase of OA that could benefit from specific treatment. Further research is required to determine whether some individuals, perhaps differing in genetic constitution, joint structure or OA aetiology, are at high risk of developing BMLs, or whether a 'BML phenotype' reflects a disease phase that might affect anyone with OA. Pain and structural progression might result from interactions between BMLs and other factors such as joint malalignment or cartilage defects, and BML measurement might need to be combined with other risk factors in order to predict outcomes with sufficient accuracy to permit changes to clinical practice.

Clinical response to BML-targeted interventions might be most expected in the subgroup of individuals for whom BMLs are the predominant cause of pain or structural disease progression. OA-BML assessment might enable stratification by identifying a treatment-responsive OA patient subgroup. MRI evidence of BMLs has been used as an eligibility criterion in clinical trials of bisphosphonates for knee OA[30], although evidence of their efficacy remains uncertain, even in people with BMLs[51]. If BML assessment is to enter clinical practice for stratified or personalised medicine, future studies must demonstrate that a treatment is more effective for or better tolerated by individuals with BMLs than those without BMLs.

BMLs have the potential to serve as biomarkers that detect early response to interventions that target BML pathology. If pain improvement accompanies BML reduction, then pain assessment might itself be an early index of response. However, retardation of structural progression might require RCTs to be continued for several years, and future studies should determine whether early pain relief or resolution of BMLs might predict subsequent OA structural disease modification. Evidence early after initiating treatment of a lack of expected BML response might usefully indicate a need for early treatment discontinuation, in order to reduce costs and potential adverse events from prolonged interventions that are likely to not help that particular individual.

What are the next steps in exploiting OA-BMLs?

BMLs are not the only osteochondral pathology in OA, but current evidence strongly indicates their key linkage with OA structure and symptoms. More research is urgently needed to better understand the mechanisms by which BMLs form, regress, and cause symptoms or structural progression. Measurement tools require refinement and their properties compared. New interventions must be developed that target key biochemical or structural aspects of OA-BMLs, both to prove their importance, and to reduce the unacceptable burden of OA.

Contributions

All persons designated as authors qualify for authorship, and all those who qualify are listed as authors. Each author has participated sufficiently in the work to take public responsibility for appropriate parts of the content. All authors have made substantial contributions to all three of (1) the conception and design of the commentary, (2) drafting the article and revising it critically for important intellectual content, and (3) final approval of the version to be submitted. All authors take responsibility for the integrity of the work as a whole, from inception to finished article.

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Conflcit of interest

David Andrew Walsh (DAW) declares that he has undertaken consultancy through the University of Nottingham to GlaxoSmithKline plc, AbbVie Ltd, Pfizer Ltd, Eli Lilly and Company, AKL Research & Development Limited, Galapagos, and Reckitt Benckiser Health Limited (each non-personal, pecuniary). He has contributed to educational materials through the University of Nottingham, supported by Medscape Education, New York, International Association for the Study of Pain and OARSI, each of which received financial support from commercial and non-commercial entities (each non-personal, pecuniary). He has been responsible for research funded by Pfizer Ltd, Eli Lilly and UCB Pharma (non-personal, pecuniary). He receives salary from the University of Nottingham, who have received funding for that purpose directly or indirectly from Sherwood Forest Hospitals NHS Foundation Trust, and UKRI/Versus Arthritis (personal, pecuniary). All DAW's commercial relationships are non-personal pecuniary or non-pecuniary.

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NS's commercial relationships are non-personal pecuniary or non-pecuniary.

Ali Guermazi (AG) declares that he has undertaken consultancy to Pfizer, Novartis, TissueGene, MerckSerono, Regeneron and AstraZeneca (personal, pecuniary). He is shareholder of Boston Imaging Core Lab, LLC, a company specialized in reading radiological images for epidemiological studies and clinical trials. He is Director of the Quantitative Imaging Center (QIC) at Boston University School of Medicine. AG is the co-Editor-in-Chief of Skeletal Radiology.

David Hunter (DJH) declares that he has undertaken consultancy through the University of Sydney to Pfizer, Lilly, TLCBio, Novartis, Tissuegene, and Biobone. He has been responsible for research funded by Pfizer Ltd, Eli Lilly, Novartis and TLCBio (non-personal, pecuniary). DJH receives salary support from the University of Sydney and Royal North Shore Hospital. His salary support for the University of Sydney is supported by Arthritis Australia and an NHMRC Investigator Grant Leadership 2 (#1194737). DJH is the co-director of the Sydney Musculoskeletal Health Flagship at the University of Sydney. In addition, DJH is the editor of the osteoarthritis section for UpToDate and co-Editor in Chief of Osteoarthritis and Cartilage.

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