Definitions, pathogenesis, and pharmacological options for bone marrow lesions: an updated review

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ABSTRACT

The term "Bone Marrow Lesions" (BMLs) identifies a pathological state characterized by a structural degeneration of the osteochondral unit (OCU) and by an alteration of the biochemical balance existing between articular cartilage and subchondral bone. These lesions, if they are not resolved spontaneously and if not adequately treated, can give rise to chronic degenerative diseases such as osteoarthritis and, in the most serious cases, evolve into stress fractures. The technique considered to be the gold standard for the detection of BMLs is Magnetic Resonance Imaging (MRI), to which BMLs appear as an area of ill-defined hyperintensity (high signal) in subchondral bone in fat-suppressed T2-weighted sequences, and hypointense areas (low signal) in T1-weighted sequences. There are several pharmacological intervention strategies for the treatment of BMLs, primarily the administration of bisphosphonates, but in recent years Iloprost treatment is also proving to be an effective therapeutic strategy. The aim of this review is to provide further evidence on the sequence of clinical-biological events leading to the appearance of these lesions, and on the current treatment strategies with the best outcome, in order to shed light on the importance of conducting further research in this field, since BMLs are part of a pathological picture characterised by numerous variables.

KEYWORDS

Bone marrow lesions, magnetic resonance imaging, osteochondral unit, clinical symptoms, pharmacological treatment.

Introduction

The increasing use of Magnetic Resonance Imaging (MRI) in clinical practice has led to the recognition of a new entity, Bone Marrow Lesions (BMLs), which are characterised by excessive water signals in the medullary space [1]. Initially, such signals on MRI were identified as Bone Marrow Edema (BME) [2]. However, since histological analysis showed the absence of edematous changes in many cases, the term "bone marrow lesion" was adopted [3]. Then, BLMs has been associated with a wide variety of inflammatory and non-inflammatory rheumatologic conditions, being closely related to the presence of pain, disease progression and worsening patient prognosis [4]. Furthermore, these pathological MRI signals involve bone marrow and bone tissue and are implicated in several musculoskeletal disorders. For example, the presence of BMLs is considered a determinant of pain and progression in osteoarthritis [5-7].

Osteoarthritis is known to be characterised by the degeneration of Osteochondral Unit (OCU) and altered bone remodeling [8,9]; in fact, it can be considered as a group of overlapping disorders that result in a functional joint failure. It is now clear that multiple factors, in joint tissues, contribute to this degeneration; of these, BMLs are a relatively recent discovery [10,11]. In this regard, several researchers have associated BMLs with histological evidence of microscopic bone microdamage, correlating their presence with misalignment, pain, and disease progression [5,6,12,13]. Noteworthy, it has been observed that the appearance of BMLs often precedes joint degeneration, suggesting a role for BMLs as a possible candidate to prevent the onset of osteoarthritis before irreversible cartilage degeneration occurs [14].

In recent years, it has also been suggested that BMLs size may be an important imaging biomarker for knee osteoarthritis and that reducing its width may be an important therapeutic target to modify the progression of osteoarthritis, e.g. by preventing or slowing joint-space narrowing [15-17]. However, most of the studies conducted to date to investigate the histopathology of BMLs mainly concern qualitative descriptions [18-20]. Knowledge of the relationship between the BLMs formation and the increase in clinical symptoms is crucial in understanding the pathophysiology of associated musculoskeletal disorders and limiting the rapid disease progression that follows. Therefore, we have provided a concise review of articles in the literature describing the clinical and pathophysiological significance of MRI-identified BMLs, with the aim of (i) describing their main aetiological, histo-pathological and clinical features, and (ii) summarizing current diagnostic and pharmacological treatment strategies.

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The osteochondral unit (OCU)

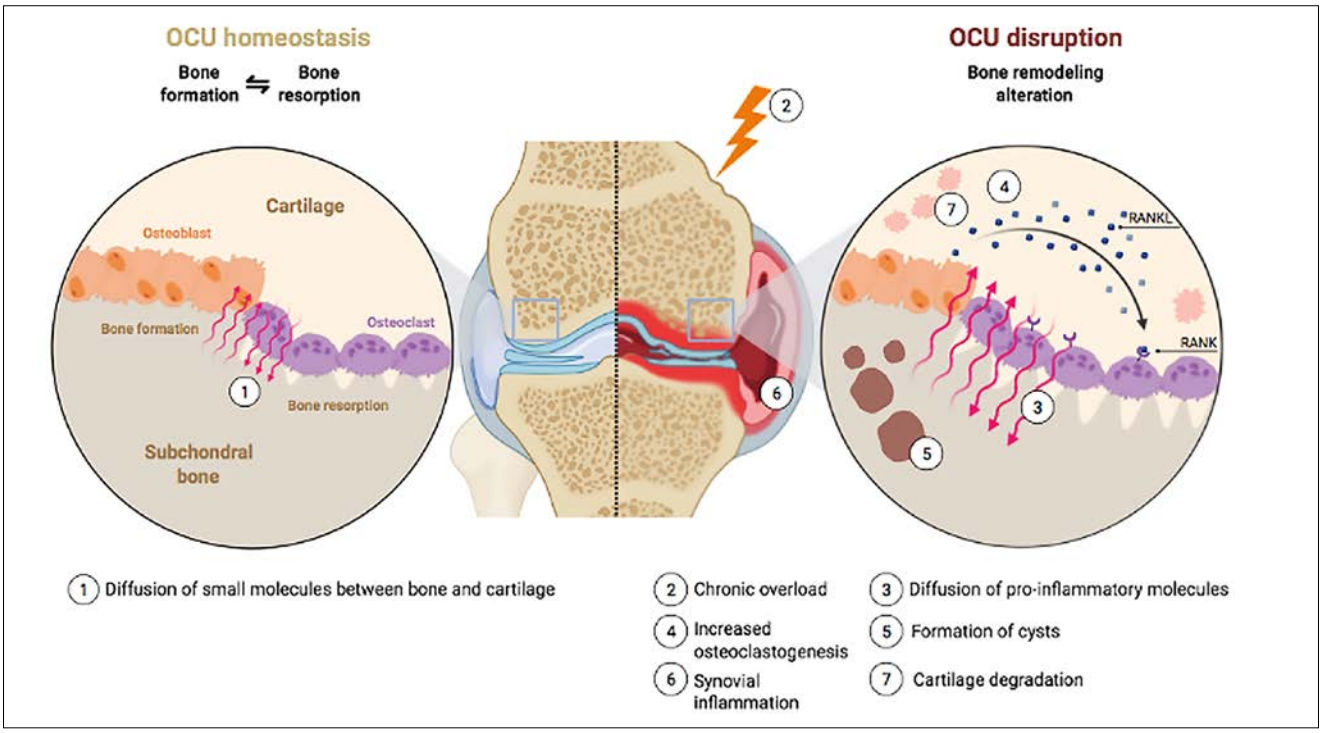
The homeostasis of joint tissues is important for maintaining the integrity and function of the joint itself. Articular hyaline cartilage, calcified cartilage, and subchondral bone, which gradually evolves into trabecular bone, together make up the OCU: the histological boundary between the articular and calcified cartilage layer is called tidemark [21]. The OCU is the end product of enchondral ossification process, that occurs after birth in the fetal cartilage, making way for the layer of articular cartilage that covers the ends of the adult long bones [22]. There is both a biomechanical and a biochemical crosstalk between the components of the OCU. Biomechanically, the subchondral bone adapts its morphology to the load exerted, to support the overlying cartilage to distribute forces over the joint. Biochemically, the canalicular/lacunar network and the vascularisation that characterise the subchondral bone allows the passage of small molecules from and to the articular cartilage [23]. The deterioration of any of the components of the OCU, usually of a traumatic nature, leads to the appearance of BMLs that, if unable to heal, evolve into chronic degenerative diseases such as osteoarthritis. Regardless of the cause, an altered process of bone remodeling is triggered in these regions, leading to a loss of subchondral bone and long-term effects that alter the health and function of the entire joint (Fig.1) [24,25].

Histo-pathological features

BMLs are regions characterised by a high metabolic activity, increased cell turnover and bone remodeling, and have a typical neuronal and inflammatory gene expression pattern. To date, not many studies in the literature have investigated the histo-pathological features of BMLs. In general, the various studies agree that BMLs are characterised by increased bone turnover and progressive destruction of the OCU. The main macroscopic feature of BMLs is the cystic areas; histological analysis following haematoxylin-eosin staining also revealed additional anatomo-pathological features, such as concomitant thickening and thinning of trabecular bone, inflammatory cell infiltrates, soft tissue infiltrate and cartilage ossifications at the tidemark [26]. The progressive damage to the OCU leads to the appearance of fissuring and microcracks in the subchondral bone, which allow the exchange of pro-inflammatory molecules between bone and cartilage: the cytokines and prostaglandins that manage to reach the overlying cartilage, in this way lead to its catabolism, which further compromises joint integrity [27]. According to Shabestari *et al*., the water signal that characterises BMLs on MRI appears to be determined by an increase in vascularisation in the affected area. In their study, they found that subchondral bone with BMLs was characterised by a four-fold increase in vascularisation and angiogenesis compared to control tissue. In addition, this was correlated with increased Vascular Endothelial Growth Factor (VEGF) expression by chondrocytes in the cartilage overlying the lesions. These results suggest that BMLs may occur as a result of a chronic bone healing process, due to repeated microdamage in the affected bone tissue [28].

The increased angiogenesis that occurs in the subchondral bone not only facilitates an increase in biochemical crosstalk with consequent damage to the articular cartilage, but also enables its innervation [29]. In fact, angiogenesis is known to be a pathway closely related to neurogenesis: the increase in VEGF expression, reported in several studies to occur in regions af-

Figure 1 Osteochondral Unit: homeostasis and disruption.

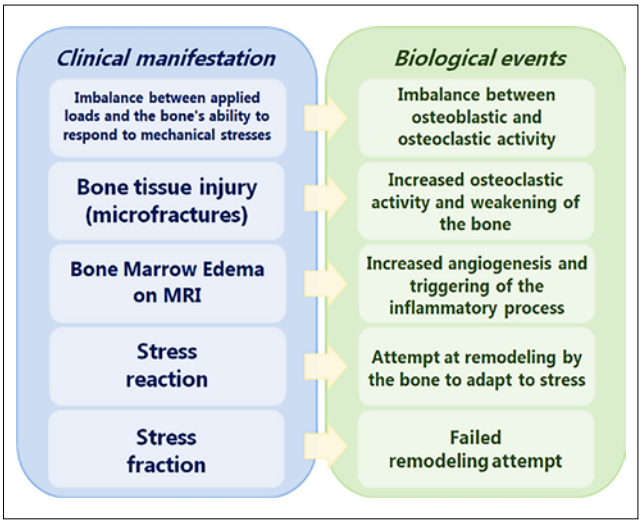


fected by BMLs, is accompanied by nociceptor growth through Nerve Growth Factor (NGF). Since NGF is an important mediator of pain perception, increased NGF expression in the OCU is considered the main cause of joint pain [30]. In an interesting study carried out by Kuttapitiya *et al*., a transcriptomic analysis of BMLs was performed using a microarray technique, which showed that these regions are characterised by up-regulation of genes related to pain perception. These include Stathmin 2 (STMN2), which is involved in responsiveness to NGF and neuronal growth, Thrombospondin 4 (THBS4), implicated in the inflammatory response to Central Nervous system injury and neuropathic pain states, and other genes involved in neuronal morphogenesis. These results provide further evidence that BMLs may represent a potential new diagnostic tool and therapeutic target for joint damage and pain [31].

Clinical-biological sequence of events

BMLs can be associated with stress fractures: repetitive cyclic loading and/or submaximal stress of a bone, as mentioned, causes microdamages which, if not repaired, can evolve into a stress reaction by the bone and in the most severe cases, a stress fracture. When the bone is exposed to chronic stress, a remodeling process is triggered: an imbalance between the activity of osteoblasts and osteoclasts in favor of bone resorption occurs, resulting in weakening of the bone at the sites where the stress is applied. In addition, levels of endosteal and periosteal proliferation increase, to counteract the weakening of the bone at these sites. Finally, if the source of mechanical stress persists, this results in an accumulation of microdamage to the trabecular bone, that can lead to a complete fracture [32]. This cascade of events is also accompanied by the appearance on MRI of bone edema which, according to some studies in the literature, appears to be a consequence of the increased angiogenesis occurring in BMLs; this event, together with the increased bone turnover, represents a persistent attempt at healing performed by the OCU (Fig.2) [33].

Figure 2 Clinical-biological sequence of events determining the evolution of BMLs in stress fracture.



Diagnostic techniques

BMLs evaluation is generally performed using fat-suppressed or proton-dense T2-weighted MRI, although other MRI sequences may also be used. For example, BMLs appear as area of ill-defined hyperintensity (high signal) in subchondral bone in fat-suppressed T2-weighted sequences, whereas they appear as hypointense areas (low signal) in T1-weighted sequences [34-38]. It has recently been proposed that to assess the extent of osteoarthritis progression, it would be preferable to use a combination of the two sequences: in fact, although T2-weighted sequences are recommended for the assessment of BMLs as they depict lesions in their maximum extent, T1-weighted sequences are mainly used for the assessment of cartilage [39-41].

There is currently considerable debate about the optimal way to visualize BMLs, but it is unclear whether BMLs detected by different MRI sequences differ at the tissue level. Indeed, it is possible that among BMLs identified by conventional T2-weighted images, some may also be detectable using another MRI sequence, but others may not, suggesting that the underlying tissues in these groups are not the same and may be related to different clinical outcomes [42]. In this regard, Muratovic *et al*. investigated histological changes that, depending on the presence or absence of BMLs, may occur in all components of the OCU in tibial plateaus obtained from 60 patients undergoing knee arthroplasty for osteoarthritis [42]. BMLs were identified by MRI performed *ex vivo* with T1 and PDSF-weighted sequences. Their results showed that the presence of BMLs detected by specific MRI sequences is strongly associated with the degree of structural change in the OCU in knee osteoarthritis. Furthermore, different MRI sequences appear to be able to differentiate several degrees of structural damage in knee osteoarthritis. Thus, the authors concluded that BMLs detected with specific sequences could act as potential MRI biomarkers for the identification of individuals at high risk of progressive osteoarthritis or for the development and monitoring of new therapies for this condition [42].

Pharmacological intervention strategies

Two main drugs have been proposed for the BMLs treatment, prostacyclin and bisphosphonates, which act on different bone targets and can interact with different steps in the etiopathological pattern of BMLs [43]. Undoubtedly, the most studied drug is Iloprost, a prostacyclin analogue known to induce vasodilation, reduce capillary permeability, inhibit platelet aggregation, and decrease the concentration of oxygen free radicals and leukotrienes [44,45].

Although its pharmacokinetic actions are well documented, to date the pharmacological effects of Iloprost responsible for pain relief and decreased BMLs size are not yet known.

It is unclear whether pain relief and BMLs reduction during and after Iloprost application are primarily based on normalization of intraosseous pressure or interactions with local leukotrienes and cytokines [46]. However, several investigators agree on the short-term effects of Iloprost in the BMLs treatment, in-

cluding lesion regression and symptom improvement, whether with poorer results in the advanced stages of the disease [47,48].

Other drugs suggested for the BMLs treatment are bisphosphonates, which are known to inhibit osteoclast activity and thus reduce bone resorption. Their use is intended to prevent the collapse of subchondral bone resulting from local bone resorption caused by the reaction to the failure fracture healing; thus, they provide better structural support until the local regeneration process creates a new bone structure sufficient to support load [49]. However, clinical results of bisphosphonate treatment for BMLs are controversial. In the only randomised, double-blind, placebo-controlled study on knee osteonecrosis, Meier *et al*. found no significant differences between ibandronate and placebo [50]. On the other hand, other studies have shown clinical and radiological benefits from treatment with bisphosphonates [51].

In addition, Laslett *et al*. tested the use of zoledronic acid for the BMLs treatment in patients with osteoarthritis in a randomised clinical trial. Improvement in pain was observed in patients on the medication at 6 months follow-up but not at 3 and 12 months follow-up, while no significant difference in the Knee Injury and Osteoarthritis Outcome Score (KOOS) was observed [16].

Finally, in the only study comparing the effect of prostacyclin and bisphosphonate in the BMLs treatments of the knee and foot, Baier *et al*. found that both treatments have a therapeutic benefit, allowing symptoms relief and BMLs reduction on MRI, with a faster and greater effect for prostacyclin [52].

Conclusions

BMLs are not only a considerable pain generator, but also an entity linked to worsening patient prognosis in many musculoskeletal disorders. In this regard, the aim of our review was to summarise the current knowledge on the role of BMLs in pathological conditions of bone, specifically in osteoarthritis, through a detailed analysis of its clinical and histo-pathological features, as well as diagnostic techniques and pharmacological treatment strategies.

Little is known about the role of BMLs in the etiopathological processes of the many conditions in which they are involved, but also in terms of their clinical impact and treatment. MRI undoubtedly plays a fundamental role, allowing a correct and adequate diagnosis, based on recognisable typical patterns that must be considered together with any abnormalities present, the patient's age, and clinical history. In addition, various forms of treatment have been proposed with promising results. Future studies on BMLs will be needed to better define specific disease patterns, with the aim of allowing a more accurate differential diagnosis and providing precise indications for available and new therapies, also adapted to the specific pathology and stage of the disease.

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