Pathophysiology and treatment of bone edema: focus on the knee

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ABSTRACT

Bone edema is a frequent condition that can involve several joints, especially the hip and knee. The radiological signal patterns for knee bone marrow edema are typically nonspecific. In recent literature, the general term "bone edema" has been replaced with the expressions "bone edema syndrome" or "bone edema lesions". The causes of this condition can be traumatic, metabolic, inflammatory or micro-vascular, and may determine blood stasis, increased intra-bone pressure and, consequently, bone ischemia. The outcome of bone edema syndrome is variable, ranging from complete healing to osteonecrosis (ON), depending on the repair response. Pain is the main symptom; the most important differential diagnoses in bone edema syndrome are traumatic injuries, bone tumors or neurosensory changes. At the level of the knee, lesions can be distinguished into traumatic versus atraumatic, reversible versus irreversible, and subchondral versus joint-extended. Traumatic cases are the consequence of impact with bony surfaces impact and the most frequent mechanisms are pivot-shift, hyper-extension or varus-valgus stress; patellar luxation may contribute too. In contrast, atraumatic lesions are divided into reversible (regional migratory osteoporosis or algo-dystrophic syndrome) or irreversible such as avascular necrosis or spontaneous osteonecrosis of the knee (SONK). In recent literature, a spontaneous trabecular bone insufficiency fracture pattern (spontaneous insufficiency fracture of the knee, SIFK) has also been identified. This can self-limit and resolve spontaneously or degenerate into more severe forms of necrosis. Conservative treatment is considered in small lesions (< 3.5 cm2) or early cases of SONK and SIFK. It consists of partial load bearing, physical therapy, painkillers and treatment with bisphosphonate/prostacyclin. Surgical treatment, on the other hand, is reserved for patients with persistent pain after conservative treatment, meniscal extrusions or clear signs of marked ON. We here aim to provide a review of the current literature on bone edema injuries of the knee, focusing on the different clinical features and most recent effective treatments..

KEYWORDS

Bone marrow edema, Knee, SONK, SIFK, AVN.

Introduction

Bone marrow edema (BME) was first described in 1988 by Wilson *et al*. [1] who reported magnetic resonance imaging (MRI) patterns consisting of low or intermediate signal intensity on T1-weighted sequences (T1w) and high signal on fluid-sensitive T2-weighted (T2w) and short T1 inversion recovery (STIR) sequences [2]. Indeed, BME is a radiological definition that can be related to a variety of clinical and pathological conditions. The significance of the histopathological findings in BME is still partially unclear; BME is an expression of multiple histological abnormalities including true edema, bon e marrow necrosis, bone marrow fibrosis, trabecular bone fracture, and lymphocytic infiltration [3,4]. For this reason, in recent literature the term BME has been replaced by the more appropriate "bone marrow lesions" (BMLs) [5]. The aim of our article is to provide a detailed review of the literature on BMLs, focusing on the knee joint.

Pathophysiology

The pathogenesis of BMLs is poorly understood considering the different clinical entities underlying these conditions.

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The MRI signal patterns for BME are typically non-specific. Traumatic, metabolic, inflammatory or vascular injuries may cause bone impairment, increased turnover, intraosseous pressure and, ultimately, ischemia. If the repair mechanisms are adequate, gradual resolution of BMLs is possible; otherwise, they may lead to osteonecrosis (ON) or stress fractures [4-6].

As proposed by Eustace *et al*. [7], alteration of the drainage mechanism of intra-osseous capillaries may determine an increase in the volume of extracellular marrow fluids, as in the case of infectious and rheumatic conditions or inflammatory processes in general. Edema may also be the result of blood congestion, as in capillary thrombosis or compartment syndrome. Moreover, a single bone trauma (fracture, bone bruise) or multiple repeated stresses, as in the presence of altered biomechanics (e.g., varus knee malalignment), may determine

capillary damage.

Zubler *et al*. [8] observed two distinct MRI patterns in BMLs: one termed "edema-like" and the other "necrosis-like". "Edema-like" lesions are undefined areas with low signal intensity on T1w images and high signal intensity on T2 fat-suppressed sequences; they show homogeneous gadolinium uptake after intravenous injection. On the other hand, "necrosis-like" lesions show up as well-defined areas with low signal intensity on T1w scans and high signal intensity on T2 fat-suppressed sequences, with inhomogeneous gadolinium enhancement. "Edema-like" lesions are consistently found at the periphery of "necrosis-like" lesions, and histologically they correspond to edema. "Necrosis-like" lesions mainly correspond to marrow necrosis and fibrosis (Fig. 1) [9].

Pain is the main symptom of BMLs and its development is multifactorial and linked to the underlying cause of the edema. Traumatic injuries, destruction of bone marrow sensory neurovascular bundles, tumor growth, and increased intra-osseous pressure are some of the possible causes of the irritative symptoms that patients report.

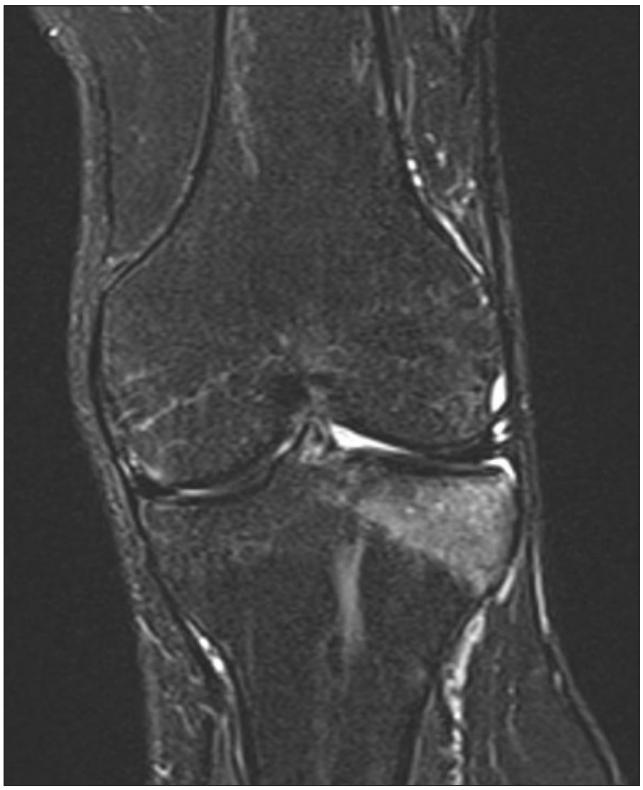
Classification

Hofmann *et al*. in 2005 published a meticulous article categorizing knee BME. Their classification, based on etiopathogenesis, identifies three groups: ischemic, mechanical and reactive BMLs [4].

Imaging

MRI allows accurate evaluation of BMLs [1], and the appearance of the lesions is influenced by the MRI sequences. The T1w sequence with fat suppression (CE T1W FS) has been demonstrated to be the best MRI sequence for assessing BMLs, showing a larger extension of the edema. Two other sequences, STIR and proton density fat-suppressed, showed good reliability in assessing bone edema, comparable to that of CE T1W FS.

Figure 1 STIR MRI sequence of a tibial BML.



Instead, in the 3D gradient echo T1w fast field echo sequence the BML volume was significantly smaller [10].

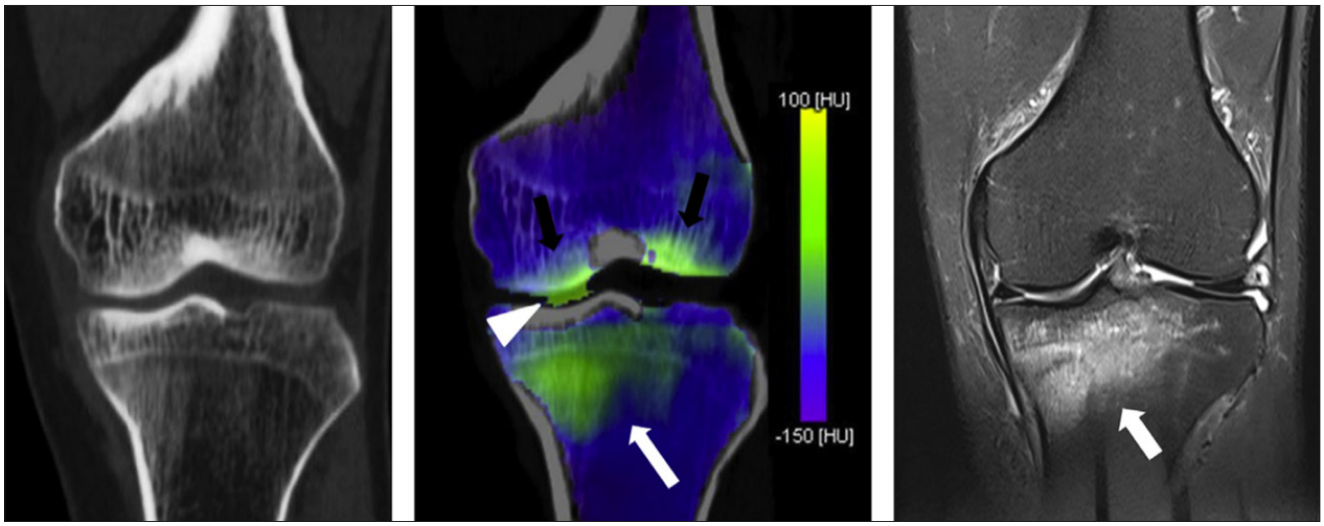
Dual-energy CT (DECT) is specific (96%) and accurate (84%) for detecting knee BMLs and can be used as an alternative to MRI, particularly when MRI is contraindicated or unavailable (Fig. 2) [11].

Specific patterns

BMLs in osteoarthritis

Subchondral BMLs are commonly found in osteoarthritis (OA)

Figure 2 Correlation between CT, DECT and MRI scans in knee BML.



and they are a radiological hallmark of this pathology. The correlation between BMLs and cartilage loss has been well underlined in the literature [12].

The pathogenetic mechanism and its correlation with OA is not completely clear: repeated trauma may favor the development of BMLs with progression related to limb malalignment [13]. Despite this, histological studies have shown a lack of true edema and the presence of fibrosis and/or necrosis of subchondral bone marrow. BMLs progress to OA is extremely variable: complete resolution is possible, but structural progression to ON may also happen [14].

Bone marrow edema syndromes

The term "bone marrow edema syndromes" (BMEs) refers to a series of transient clinical conditions characterized by BME with relatively unknown etiopathogenesis. Different diseases described in the literature are part of this definition: transient osteoporosis of the hip (TOH), regional migratory osteoporosis (RMO), complex regional pain syndrome (CRPS), and transient post-traumatic BMEs.

Many hypotheses have been proposed to explain BME etiology during the past few years. First of all, a possible correlation between atraumatic reflex sympathetic dystrophy [15] and hyperemia caused by the obstruction of venous circulation return was considered [16].

BMLs of the knee

BMLs of the knee can be classified into traumatic or non-traumatic, reversible or irreversible sub-chondral lesions or non-sub-chondral lesions with secondary extension to the joint, according to Kon *et al*. [17]. A new topographic classification of BMLs of the knee has been proposed by Compagnoni *et al*. [18] and it is useful for physicians, helping to guide the treatment.

Traumatic BMLs

A traumatic BML is the bone print of a trauma [19]. It can be the consequence of a direct or indirect impact force, or the result of a traction mechanism during an avulsion injury [20]. Five principal mechanisms have been described in knee lesions: pivot shift stress, dashboard mechanism, hyperextension stress, clip injury, and lateral patellar dislocation.

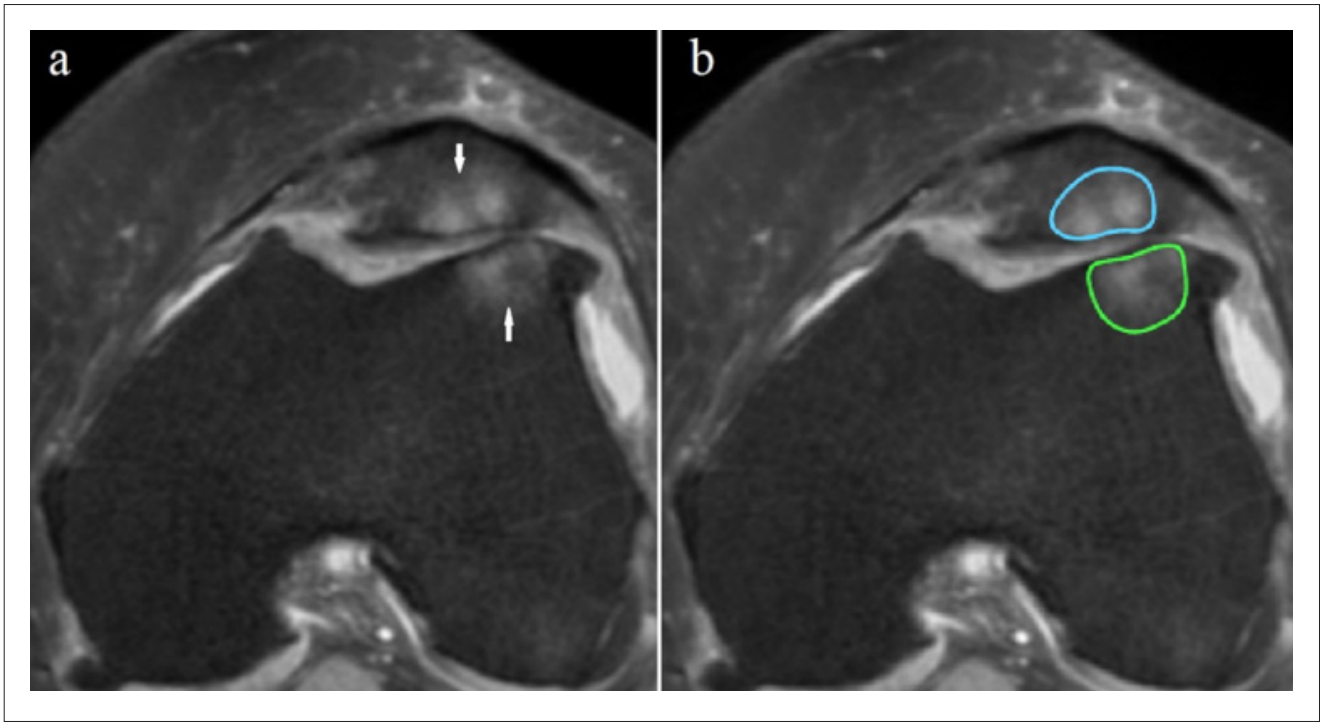
Pivot shift injury is the most common. It occurs when an external rotation of the tibia or an internal rotation of the femur is combined with a valgus stress. This kind of mechanism usually determines a reversible subchondral contusion that can be a secondary marker of an anterior cruciate ligament (ACL) rupture. Eighty-six percent of lateral femoral condyle (LFC) bone bruises have been found to be associated with a partial or complete rupture of the ACL. Posterolateral tibial bruising is considered pathognomonic for ACL rupture [21,22]. As regards its distribution, the BML usually involves the posterior aspect of the lateral tibial plateau and the lateral femoral condyle around the sulcus because of the impaction between these two structures.

A dashboard injury is the result of an impact with the anterior aspect of the proximal tibia on a flexed knee. This traumatic mechanism can lead to rupture of the posterior cruciate ligament. In this case, the BML will involve the anterior aspect of the tibia and, occasionally, the posterior surface of the patella (Fig. 3).

Hyperextension injury can occur when an impact force is applied to the anterior aspect of the proximal tibia with the foot firmly planted on the ground. The BML will affect both the anterior tibial plateau and the anterior femoral condyles as a consequence of their impaction, and will show the typical "kissing" contusion pattern.

Clip injury develops after a pure valgus or varus stress and is a result of the compression of the femoral condyle against

Figure 3 Bone bruise in MPFL lesion.



the tibial plateau.

Lateral patellar dislocation and patellar instability are typically and pathognomonically linked to bone bruises of the anterolateral aspect of the LFC and the inferomedial patellar facet. In this situation it is important to check the integrity of the medial patellofemoral ligament (MPFL) [23]. The BML signal caused by traumatic subchondral lesions is usually reversible. In cases of lateral patellar dislocation, a fracture is a reversible event only if there is no avulsed osteo-chondral fragment or secondary deformity.

Non-traumatic BMLs

A non-traumatic BML may be the expression of reversible conditions (TOH, RMO, CRPS and insufficiency fractures) or irreversible ones such as avascular necrosis (AVN) and spontaneous osteonecrosis of the knee (SONK).

Spontaneous insufficiency fracture of the knee (SIFK) is a peculiar condition: it is the consequence of a physiologic force applied to weakened bone trabeculae. It leads to a fracture of the subchondral bone that can stabilize itself or progress to a collapse of the articular surface with evolution towards OA [24]. For that reason, SIFK is considered a borderline condition that can be reversible or irreversible. On MRI, SIFK is characteristically observed as a diffuse area of BML on the loading areas of the femoral condyle with possible extension to the central zone of the tibial plateau [25].

SONK is a focal superficial and subchondral necrosis mainly seen in the medial femoral condyle (MFC). The typical involvement of the MFC could be linked to its subchondral vascularization, sustained by a single nutritious branch with an apparent watershed area of limited supply.

The specific etiology of SONK is not clear: it may probably be related to SIFK progression to ischemia and ON [26,27].

SIFK and SONK most commonly affect middle-aged women (over 50 years). The typical symptom is peculiar night pain with an acute onset and no history of recent trauma. The true prevalence of these conditions is probably underestimated (due to lack of initial diagnosis and subsequent development of severe arthrosis) [28]. Because of the increased pressure and mechanical stress across the joint, there is also a positive correlation between SIFK/SONK and medial meniscal root tears (MRTs)/meniscal extrusions and grade III-IV chondral lesions [26-30].

Plain radiographs are usually negative in the initial stages. MRI shows BMLs: an extension greater than 4 mm in thickness or 14 mm in length is indicative of early irreversible ON. Focal epiphyseal contour depressions and low signal lines are other signs of an irreversible process [31]. MRI timing is fundamental: it is always difficult to make differential diagnosis between SIFK and meniscal lesions acutely. An early MRI could be negative or show only soft tissue edema; therefore, when a SIFK/SONK is suspected, it is better to wait 6–8 weeks after the acute symptoms or repeat the MRI exam after 2 months.

Early diagnosis and early correct conservative treatment of SIFK can stop its progression into irreversible SONK [26].

Spontaneous or avascular osteonecrosis (SO) most frequently affects female patients under the age of 45. It is usually bilateral. It has numerous triggering causes that can classically be distinguished into direct and indirect [32]. Conditions directly associated with SO are sickle cell disease, decompression syndrome, Gaucher's disease, and myeloproliferative and coagulation disorders. Indirect risk factors are alcohol and tobacco consumption, use of corticosteroids, and obesity. Alcohol abuse and intake of corticosteroids are the main risk factors (90% of cases) and they are associated with possible enlargement of the intraosseous fat cells with increased bone marrow pressure and secondary ischemia. Smoking is associated with vasoconstriction and atherosclerosis and it could determine SO [33,34]. SO is clinically characterized by gradual onset of pain. The medial femoral condyle is more involved, but an extension to the tibial plateau is also possible.

There can also be simultaneous involvement of other joints such as the contralateral knee (80% of cases), hip or shoulder. MRI shows multiple foci of involvement with a typical serpentine pattern and well-demarcated edges [28].

Treatment

Correct differential diagnosis of BMLs is mandatory for correct treatment. The management of the single patient should be based on symptoms and disease staging.

Conservative treatment

Patients suffering from small BMLs (small lesions <3.5 cm^2) without signs of ON, reversible SIFK, or early-stage SONK (small lesions <3.5 cm^2) should be treated conservatively [32]. Partial weightbearing is the first therapeutic step and it should be associated with other treatment strategies such as physical, hyperbaric and shockwave therapy.

Pulsed electromagnetic fields have an anabolic effect on bone tissue [35]. Marcheggiani Muccioli *et al*. [36] analyzed the long-term result of 28 patients suffering from symptomatic SONK confirmed by MRI. The cohort was treated with local pulsed electromagnetic field therapy, 6 hours/day, for 3 months. The authors observed a significant improvement in algic symptoms and Knee Society Score in the first 6 months of follow up: this physical therapy first reduced knee pain and necrosis, sparing 86% of knees from prosthetic surgery at 24-month follow-up.

There are three categories of drugs that can be used for the medical treatment of BMLs: prostacycline derivatives, bisphosphonates, and biological therapy using TNF-inhibitors.

Baier *et al*. [37] demonstrated that intravenous injection of both prostacycline and bisphosphonate led to significant improvements in symptoms 3 months and 1 year after therapeutic intervention. The pharmaceutical treatment determined a distinct reduction of BMLs on MRI scans in more than 40% of cases. Iloprost is a prostacycline analog that induces vasodilation, reduces capillary permeability, inhibits platelet aggregation, and decreases the concentration of oxygen free radicals and leukotrienes [38].

Disch *et al*. [39] reported side effects in 57% of patients treated with intravenously administered iloprost. These occurred during the first 30 minutes of the first infusion and none of them required treatment. Side effects were less marked during

subsequent administrations.

Bisphosphonates inhibit osteoclastic activity and act on bone resorption [40]. The use of bisphosphonates in the treatment of early ON is based on the assumption that the structural bone failure is the result of resorption of necrotic bone during revascularization before new bone has been formed. It can be hypothesized that if accelerated bone resorption can be reduced during the revascularization process until sufficient new bone has been formed, then structural failure might be avoided. In animal studies, bisphosphonates have been shown to prevent resorption of necrotic bone during revascularization and ischemic necrosis with preservation of bone structure [41]. In humans, bisphosphonate treatment has been used in bone marrow edema [42] or AVN of the femoral head and favorable results have been reported in terms of diminishing the pain, improving mobility, and lowering the incidence of articular collapse in AVN [43].

Zoledronic acid is a bisphosphonate that also has very good bone affinity: it gave good results in terms of knee pain control and reduction in BMLs size at 6-month follow up, but it showed poor specificity [44].

Neridronate (100 mg administered intravenously four times, once every third day) has been identified as the treatment of choice in CRPS showing clinically relevant and persistent benefits right from the first 20 days after administration. On the basis of this evidence, in 2015 neridronate was used in a randomized double-blind placebo-controlled study to assess its efficacy in controlling pain in acute painful knee OA (< 3 months) with MRI showing BMLs. In patients with acute painful knee OA, four infusions of neridronate led to a clinically relevant pain benefit and a regression of BMLs on MRI after 2 months of follow up, avoiding progression of SIFK and BMLs [45].

These results suggest an important role for conservative and pharmacological treatment with prostacyclin or bisphosphonates for early-stage BMLs.

Surgical treatment

Persistent knee pain and/or edema after conservative treatment, substantial meniscal extrusion or MRTs, and irreversible ON are indications for surgical treatment.

Subchondroplasty (SCP) involves the localized injection of flowable calcium pyrophosphate (CaP) substitute into symptomatic BMLs of subchondral trabecular knee bone. This synthetic substitute provides mechanical support and promotes bone turnover thanks to its osteoconductive characteristics [46]. SCP can be performed safely after a correct MRI planning with intra-operative fluoroscopic evaluation to reach the BML and arthroscopic control to exclude intra-articular leakage of the CaP. Early results report improvements in pain relief and functional outcome scores for at least one year, with total knee replacement (TKR) conversion rate reduced by 70% [47,48] according to the topographic classification of Compagnoni *et al*. [18], SCP is indicated in a grade C lesion, with no significant ON, OA or malalignment.

Evidence about SCP is still scarce: it is a young surgical technique and there is no EBM literature making it possible to evaluate and confirm its efficacy. Neither unicompartmental knee replacement (UKR) nor TKR are contraindicated after SCP with calcium phosphate.

Biological SCP using bone marrow aspirate concentrate (BMAC) is becoming a treatment strategy for knee OA, with promising early findings. Kon *et al*. [48] described combined BMAC SCP and intra-articular injection in 30 patients with unicompartmental degeneration and subchondral bone alterations on MRI. They found an improvement from basal scores 3, 6 and 12 months after the procedures.

A persistent painful knee after conservative treatment and bone edema resorption may need surgical treatment, especially in the presence of associated type 4–5 MRTs. Non-operative treatment of medial meniscus posterior horn root tears is associated with poor clinical outcomes, worsening arthritis, and a relatively high rate of arthroplasty at 5-year follow-up [49]. Conservative treatment in those cases could be proposed only for older patients with major comorbidities and/or advanced OA. Many different techniques have been proposed according to the type and severity of MRTs. Sometimes surgical meniscal root reinsertion is not sufficient to solve the meniscal extrusion: in those cases, it may be necessary to perform an arthroscopic centralization of the extruded medial meniscus as described by Leafblad *et al*. [50].

When conservative treatment and early surgery strategies fail, UKR or TKR are the last options for the orthopedic surgeon in cases of irreversible symptomatic ON and osteochondral lesions.

Conclusion

BML corresponds to a pathological MRI presentation found in a wide spectrum of different pathological conditions. This presentation, although partially variable, is not specific and does not allow characterization of the different BML types.

Little is still known about the role of BMLs in the pathogenetic processes of the many conditions in which they are involved. A detailed analysis of clinical and histopathological features is crucial and will pave the way for future studies that may better define specific BML patterns [51]. This, in turn, will lead to more accurate differential diagnosis making it possible to arrive at a better clinical-diagnostic framework allowing accurate and specific treatments.

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LIST OF ABBREVIATIONS

Bone marrow edema (BME)
Bone marrow lesions (BMLs)
Bone marrow edema syndromes (BMEs)
Magnetic resonance imaging (MRI)
T1-weighted sequences (T1w)
High signal on fluid-sensitive T2-weighted (T2w)
Short T1 inversion recovery (STIR)
T1w sequence with fat suppression (CE T1W FS)
Osteonecrosis (ON)
Dual-energy CT (DECT)
Osteoarthritis (OA)
Transient osteoporosis of the hip (TOH)
Regional migratory osteoporosis (RMO)
Complex regional pain syndrome (CRPS)
Anterior cruciate ligament (ACL)
Lateral femoral condyle (LFC)
Medial patellofemoral ligament (MPFL)
Avascular necrosis (AVN)
Spontaneous osteonecrosis of the knee (SONK)
Spontaneous insufficiency fracture of the knee (SIFK)
Medial femoral condyle (MFC)
Subchondroplasty (SCP)
Calcium pyrophosphate (CaP)
Unicompartimental knee replacement (UKR)
Total knee replacement (TKR)
Bone marrow aspirate concentrate (BMAC)

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