Acta Clin Croat (Suppl. 3) 2023; 62:106-114
doi: 10.20471/acc.2023.62.s3.14

Review

BONE MARROW LESIONS: TWO PILLARS CONCEPT

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SUMMARY – A common magnetic resonance imaging pattern of bone marrow lesion has been described in numerous pathological entities. However, despite intensive research, its etiopathological pathways and repercussions on disease progression remain controversial. From our current knowledge, subchondral bone represents an active site of remodelling fulfilling both mechanical and biological joint requirements. Alteration of bone remodelling activity, as one of the major characteristics of bone marrow lesions, can potentially lead to biological and structural impairment of the affected tissue and consequently the entire joint. The discovered close connection between subchondral bone biology and its structural changes together with parallel changes in overlying cartilage is setting the scene for a potentially new concept. In this "Two Pillar" concept both structure and biology of subchondral bone (and its biomechanical and biochemical interference with the layer above) represent the foundations of the structure and function of articular cartilage. In light of the proposed concept, we will review current knowledge on aetiology, pathogenesis, and clinical presentation of BML and correlate it to existing and emerging treatment options.

Keywords: *Bone marrow lesions, subchondral bone pathology, MRI, bone remodelling*

Introduction

Bone marrow lesion (BML) is a generic term characterising the specific magnetic resonance imaging (MRI) pattern originating from subchondral or non-subchondral bone. From the radiological point of view it is described as a high signal on fluid-sensitive (T2) sequences, with or without intermediate to low T1 signal intensity compared to normal bone marrow[1]. This MRI pattern may occur in a number of clinical entities with a broad range of symptoms.

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Moreover, BMLs can be found in asymptomatic, middle-aged population, with an incidence of 14%, and are associated with a higher risk of developing osteoarthritis (OA)[2]. Interestingly, this MRI abnormality was first described back in 1986 in patients affected by rheumatoid arthritis and afterward in 1988 in patients with transient osteoporosis of the hip or knee[3]. Although these alterations were ascribed to local edema, little evidence has been found in that direction. In fact, the majority of histological samples demonstrate a set of rather nonspecific changes involving lymphocytic infiltration, increased vascularization, fibrosis, poor mineralization, and trabecular bone microfractures[4]. Therefore, the previously used term "bone marrow edema" has been replaced with the more appropriate term "bone marrow lesion"[5]. Despite that, the bone layer immediately below it -

"the subchondral bone"- has only recently received more attention[6].

Moreover, even the meaning of the adjective "subchondral" is equivocal, being differently described in previous literature[6]. From the current view, the subchondral bone plate represents an active site of remodelling fulfilling both mechanical and biological joint requirements. As an adaptation to joint biomechanics alterations or microdamage repair, the bone remodelling cycle is activated, thus leading to changes in the subchondral cortical bone plate and trabeculae[7]. High cellular activity and remodelling in the subchondral bone can potentially lead to biological and structural impairment of the affected tissue. What's more, changes in the thickness and stiffness of the subchondral bone make the overlying cartilage more susceptible to damage from shear force[7]. The arising evidence of the close connection between subchondral bone biology and its structural changes together with parallel changes in overlying cartilage are setting the scene for a potentially new concept. In this "Two Pillar" concept both the structure and biology of the subchondral bone (and its biomechanical and biochemical interference with the layer above) represent the foundations of structural and functional integrity of the articular cartilage (Figure 1). We aimed to provide a systematic synthesis of the current knowledge on aetiology, pathogenesis, clinical manifestations, and treatment options of BML within the scope of the "Two Pillar" concept.

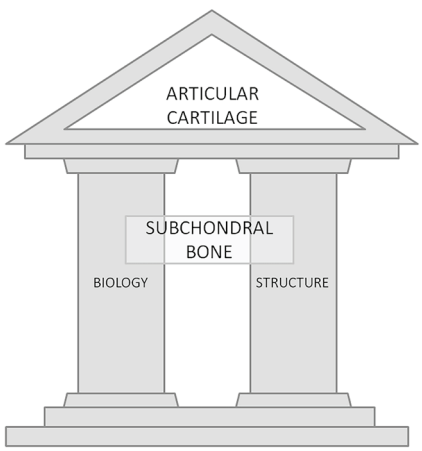

Figure 1. Schematic representation of the Two Pillars concept. Both structural integrity and biological activity are necessary to support the functionality of articular cartilage. If any of the pillars (or both) are affected, there is an imminent danger of cartilage deterioration and collapse.

Aetiology and pathogenesis

Numerous and diverse pathogenetic mechanisms of the subchondral bone marrow lesions could be simplified into traumatic or non-traumatic (Table 1), and with respect to the evolution of disease, into reversible and irreversible[6]. However, in certain conditions such as spontaneous insufficiency fracture of the knee (SIFK), spontaneous osteonecrosis of the knee (SONK), and avascular necrosis (AVN), an overlap between etiological events is also likely. For a correct diagnosis, it is of utmost importance to contextualise the observed MRI patterns with coexisting abnormalities, age, physical examination, and clinical history.

Table 1. Etiological classification of the bone marrow lesions (modified from Kon et al. (6)).

Traumatic	**Non-traumatic**
acute/stress fracture	degenerative lesion (OA)
bone contusion (bruise)	inflammatory lesion (RA)
chronic/repetitive stress	transient osteoporosis (TPO)
osteochondral injury	regional migratory osteoporosis (RMO)
iatrogenic/post-surgery lesion	transient bone marrow oedema syndrome
spontaneous insufficiency fracture (SIFK)	
spontaneous osteonecrosis of the knee (SONK)	
avascular necrosis (AVN)	

Trauma is the main etiological factor in a large portion of BML cases. BML associated with trauma can be further divided into acute findings or a result of chronic repetitive stress due to overload (Figure 2)[8]. The most common BML MRI patterns are observed in acute anterior cruciate ligament (ACL) injuries and are thought to be a consequence of the impact between the femoral and tibial cartilage that is transferred to the subchondral bone. Typical locations are the lateral femoral condyle and the posterior aspect of the lateral tibial plateau[9]. Furthermore, it is known that the extent of lesion changes over the course of repeated MR imaging[10]. However, only a few authors have investigated its long-term evolution after injury. It has been

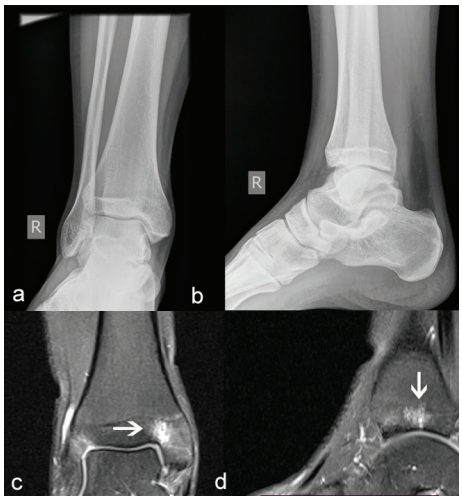

Figure 2. A 20-year-old professional football player 6 months after an ankle sprain, presented with chronic pain on the medial side. Plain AP (a) and LL (b) radiographs revealed no significant pathology, but coronal (c) and sagittal (d) proton density with fat suppression images revealed edema-like signals in the medial malleolus.

reported that tear complexity and multiple ligament involvement correlate with BML resolution time[11]. The site of BML was also reported to have an influence, as with ACL injury femoral lesions had a shorter resolution time than tibial BMLs[12]. Nevertheless, the spatial distribution of the lesion signal associated with ACL rupture may predict a progression in osteochondral damage[13].

Repetitive microtrauma can induce a disruption of subchondral bone components forming communication with the joint space, increased marrow blood flow, or impaired/congestive drainage[14]. All could potentially cause an increase in intraosseous pressure and subchondral bone perfusion abnormalities associated with BML.

Although it is well understood that OA is a disease of the whole joint, a common perception is that it generally starts in the articular cartilage. Recently accumulated evidence has shifted this paradigm[4,6-7], and accumulating evidence demonstrates connection between BML on MRI and pain and structural deterioration of the overlying cartilage. It has been suggested that subchondral bone pathology may lead to cartilage disruption by altering the biomechanical force distribution across the cartilage, or disruption of the osteochondral junction and release of biomediators affecting the cartilage[15]. There is evidence that in early OA, the homeostatic subchondral bone remodelling fails and increases, resulting in a reduced thickness of the subchondral plate[16]. As pathology advances, it ultimately leads to subchondral bone sclerosis, thickening of calcified cartilage and trabeculae, together with decreased trabecular number[16]. Moreover, there is a clear correlation between increased bone remodelling and cartilage degeneration[17]. In 1988, Brown *et al.* associated the elevated angiogenic factor in synovial fluid with cartilage degeneration[18]. In the course of the disease, chondrocytes, near the structurally changed tidemark, present with hypertrophic phenotype and expression of the vascular endothelial growth factor (VEGF) increases[19]. As increased, unhealthy vascularization presents one of the eminent features of a dysregulated subchondral bone remodeling[20] it seems logical not to overlook the impact of BML on both the bone structure and biology in OA joints.

Just as OA has long been regarded as a disease of cartilage alone, rheumatoid arthritis (RA) has been considered as a condition mainly affecting the synovium. With advancements in imaging, observations of bone marrow lesions in patients with RA became more frequent[1,8]. The prognostic value of the MRI pattern was confirmed in numerous studies, regardless of the presence of synovitis[8,21]. It has even been suggested that inflammation present in BML could precede synovial inflammation[22]. Recent studies have proposed that not only the presence of BML, but also the severity/extent of these lesions is relevant[6,23].

A number of clinical conditions characterised by a BML pattern, commonly defined as „bone marrow edema syndromes", have a self-limiting course. The essential tools for distinguishing between the entities are age, gender, and clinical history. One of the most frequently described conditions is transient osteoporosis (TOP). Spontaneous resolution usually occurs in 4 to 24 months, however, TOP can progress to regional migratory osteoporosis or even to an insufficiency fracture[3]. As we mentioned, the clinical presentation of RMO distinguishes this condition from TOP. Irreversible conditions, such as AVN and SONK stand on the other side of the spectrum. Their aetiology is still not completely understood. Initially suggested, the (micro)vascular origin of necrosis remains limited to histological evidence from only a couple of studies[24]. Consequently, the spontaneous osteonecrosis of the knee, described by Ahlback et al.[25] in 1968, is currently being related to subchondral fractures where unstable

osteochondral portions fail to heal and subsequently undergo necrosis.

BML is commonly seen in surgical procedures involving cartilage or the whole osteochondral unit, with reports ranging up to 80%[6]. Such findings have been described early after autologous chondrocyte implantation (ACI)[6]. However, understanding of the correlation with clinical outcome is still controversial. Some regard the persistence of BML findings for over 12 months as a predictor of inferior clinical outcome, whereas others ascribe it as an abnormal tissue reaction, but not severe enough to have impact on the clinical outcome[6]. However, further effort is needed to better elucidate its pathologic pathways, evolution over time, impact on patient outcome and potential treatment.

Histopathology

BMLs histologically represent an increased bone turnover[26]. Distinct etiologies of BMLs affecting the subchondral bone result in different histopathological findings. However, these findings could overlap and coexist in the same clinical entity.

Pathognomonic histopathological signs of subchondral bone injury can be found in acute trauma or repetitive microtrauma cases. In some cases of trauma, with progression of bone remodelling, changes in subchondral bone stiffness and early signs of OA may appear. Together with subchondral structural and biological changes, chondrocyte apoptosis, necrosis and loss of superficial proteoglycans may occur[27]. Compared with isolated defects of cartilage, defects forming access to the bone marrow have much more efficient spontaneous repair[28]. Pluripotent undifferentiated mesenchymal cells from the blood clot differentiate into chondrocytes and osteoblasts, forming an osteochondral repair tissue[29]. The likelihood of complete repair of an osteochondral defect depends on the size of the defect. Another factor that plays an important role is malalignment. Long-term studies have proven that incongruencies followed by an increase in joint contact pressure have a poor prognosis[30]. The restoration of subchondral bone is essential to allow new cartilage formation[31]. Finally, the restoration of subchondral bone may prevent secondary changes in the surrounding tissue and prolong the durability of the new repair tissue[32].

Early structural changes of the subchondral bone in OA are followed by alterations of the cell-mediated bone remodelling process[30]. The key cellular players in bone remodelling are osteoclasts and mesenchymal stem/stromal cells (MSCs), and their descendants, osteoblasts and osteocytes[31]. Intriguingly, MSC abnormalities have been found to be the most confined to the bone marrow lesions sites of the OA bone[31]. Abnormal behaviour and phenotype were found to affect osteoblasts, as well[32]. As the disease progresses, so does the phenotype of chondrocytes, followed by an increase in VEGF expression[18]. Potentially, this could all lead to induced vascularization and be responsible for delivering osteoclast precursors to already structurally altered remodelling sites. Microcracks, another typical finding in OA, result in an influx of synovial fluid, increased intraosseous pressure, local necrosis and the formation of intraosseous pseudocysts[29].

In the case of rheumatoid arthritis, bone marrow lesions are probably more related to the inflammatory infiltrate[22]. McQueen et al. confirmed the presence of osteitis only in areas corresponding to characteristic MR pattern[33]. However, histopathology studies have not yet defined the link between marrow infiltration and bone resorption[22].

Histology is simpler in self-limiting conditions which consist of a real edema and a reduced mineralization. Irreversible damage with ischemic events and/or microcracks may result in necrosis of the subchondral bone, as seen in AVN and SONK. The entire subchondral region may be affected and may collapse on the initially intact articular surface. Specific subchondral bone alterations have been reported after reconstructive cartilage repair procedures[34]. Evaluations after cartilage surgery showed that such procedures can affect the entire osteochondral unit. Changes have been shown in bone mineral density, bone volume, and trabecular thickness over an extended postoperative period[35].

Diagnosis

MRI has a leading role in diagnosing bone marrow lesions. Recognizable typical patterns might be sometimes seen even at the early stages of the disease (Figure 3). However, normal marrow appearance does not absolutely exclude the presence of bone marrow infiltration. The signal intensity of the BML alone is generally not specific to a disease process[25]. Attention to the location and pattern of bone marrow signal abnormality, evolution, and change over the course of time, along with the help of age, gender, and clinical history, could serve to differentiate several etiologies with BML findings. Future research should aim to delineate

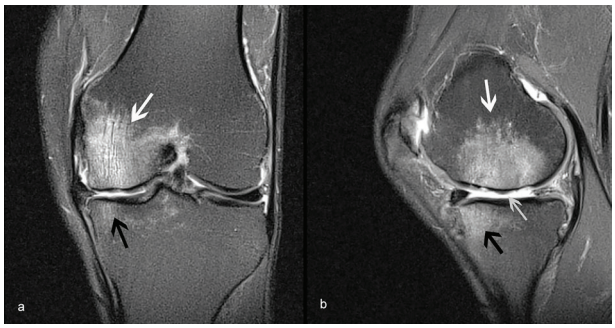

Figure 3. Osteoarthritis-related bone-marrow edema-like signal. Sagittal (a) and coronal (b) proton density with fat suppression show high signals in the femoral (white arrows) and tibial (black arrow) subchondral bone. Moderate osteoarthritic changes of the medial compartment affecting both the cartilage and the meniscus (grey arrow),

MRI findings for greater specificity among etiologies with BML findings. The most common, and for the patients the most important clinical feature of BML is pain. The nerve endings in the subchondral bone are most likely to be the cause of this pain[36]. Potentially, nerve endings can be affected from various sides and causes. Pain may arise from irritation induced by an increased intraosseous pressure[3]. Raised intramedullary pressure could potentially lead to diminished perfusion, inducing hypoxia and acidosis which can act as an additional mechanism of pain. The inflammatory infiltrate in the bone marrow lesions, as in RA[22], has been documented to be a source of proinflammatory cytokines and the production of prostaglandins[37].

There is evidence that the presence of BML, particularly 3 months after the injury, may negatively influence functional recovery and return to the previous physical level[38]. What remains an open question is whether or not the presence of BML has a direct impact on a patient's long-term function and development of degenerative joint changes.

There is a clear association between BML and pain in patients affected by OA. A higher prevalence of BML was proven in patients with symptomatic knee OA than in asymptomatic patients [39]. Sowers et al. demonstrated a significant association between the size of BML>1cm and symptom development[40]. A more recent study showed that the increase in the size of BML is a negative prognostic factor for pain and cartilage loss and that it is predictive of total knee replacement (TKR)[7]. Conclusively, these results suggest that the presence and the enlargement of BML might be independently and strongly associated with the progression of disease toward the need for TKR.

Interestingly, BML may be present in patients with no clinical knee OA where it is associated with increased BMI and the development of pain[2]. In such cases, lesions are reversible and may provide a target for early detection or even prevention of knee OA. Moreover, BML of the subchondral bone presents a marker of disease activity and it is currently being set in clinical trials to assess early treatment response[22].

Treatment

It is becoming evident, and confirmed from recent studies, that without restoration of the subchondral bone, any treatment of surrounding tissue is likely to fail. For this reason, there is considerable ongoing interest in targeted therapies aiming at the subchondral bone in order to preserve the whole joint. Considering the aetiology, size, and grading of the lesion, treatments of subchondral bone marrow lesions may be divided into *conservative* and *surgical*. We emphasise that the biology and/or structure of the subchondral bone should be taken into account, as these are the two pillars holding the foundation of the cartilage above.

Smaller lesions (<3,5 cm^2) without signs of osteonecrosis usually regress and do not require surgical treatment[23]. Based on the course of symptoms and radiological findings, the treatment often includes non-steroidal anti-inflammatory drugs, analgesics, and protected weight-bearing[23]. However, there are some cases where the early stages and signs of osteonecrosis have been proven to regress with physical treatment. Case series of patients diagnosed with SONK in the early stage proved pain and lesion size improvement after pulsed electromagnetic fields therapy[41]. The proposed pharmacological treatment can be classified into two main groups: prostacyclin (the most studied prostacyclin analogue is iloprost) and bisphosphonates (ibandronate sodium, alendronate sodium, and strontium ranelate). The effect of prostacyclin in treating BML has shown a positive effect on lesion size and symptoms[2]. What remains unclear is if the pain reduction is primarily based on the reduction of increased intraosseous pressure or on the anti-inflammatory effect. As mentioned, mesenchymal stem/stromal cells play a central role in bone remodelling and the formation of bone marrow lesions. Therefore, it is conceivable to believe that new-generation antiresorptives

such as ibandronate and ranelate might have a bigger impact on the pathology of lesions[43], by both reducing osteoclast activity and promoting mineralization. Two recent studies have shown positive effects of these agents, one with improving the joint space narrowing[44] and reducing the loss of cartilage volumes together with the decrease of lesion size[45] (Figure 4). Baier et al. were the first to compare the effect of prostacyclin and bisphosphonate i.v., and demonstrated that both treatments offer symptom relief and lesion reduction, however, prostacyclin had a quicker and greater effect[46]. Clearly, further studies are needed to clarify and differentiate the mechanisms of action of these agents in order to gain a better understanding of the optimal ways of their use.

When conservative treatment of bone marrow lesions fails, surgical treatment is needed. Surgical treatments include less invasive options such as stimulation of a healing response with or without intraosseous delivery of orthobiologics/cells or stabilisation of microtrabecular fractures, and more invasive procedures include bone grafting, corrective osteotomy, or even joint replacement. In a pre-collapse stage where the subchondral bone structure is still intact, stimulation of healing response and biological enhancement with an injection of orthobiologics/cells might be sufficient to stop or even reverse the process. Core decompression consists of intraosseous drilling which decreases intraosseous pressure and creates "vitality" channels that bring blood supply and replace the necrotic bone with the new one. Future trends may include adding bone marrow concentrate or platelet-rich plasma (PRP) to the drilling procedure. Hernigou et al.[47] demonstrated a successful application of an autologous bone marrow graft, and interesting new development has been pioneered for the treatment of BMLs and cartilage defects in OA[48].

They combined intra-articular injections with intraosseous infiltrations of PRP with promising results[48]. This direct, intraosseous administration of PRP might enable a direct effect on cells that play a central role in bone remodelling (Figure 5). Prelim-

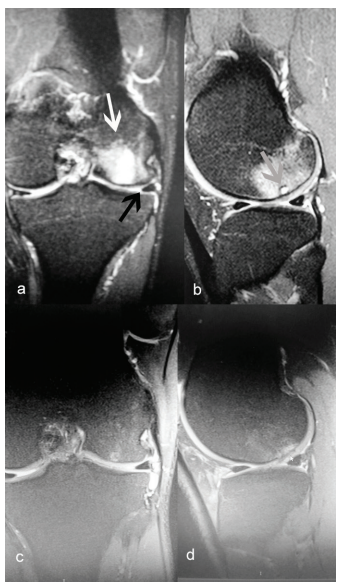

Figure 4. A 30 years old professional football player with pain across the medial side of the knee. Coronal (a) and sagittal (b) T2-weight images revealed a massive oedema-like signal (white arrow) of the medial condyle with a subchondral cyst (grey arrow), as well as partially removed medial meniscus (black arrow). The patient was treated conservatively with ibandronate (according to the protocol described by Bartl et al. (46)) and physical therapy. At the 3-month follow-up, control MRIs (c) and (d) showed nearly complete regression of oedema-like signals and a significant decrease in pain and disability.

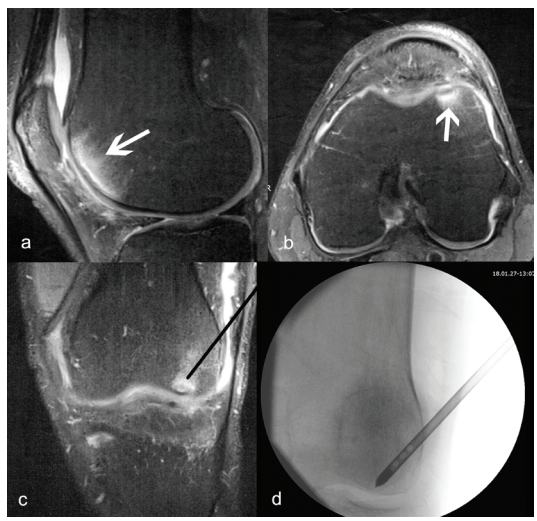

Figure 5. Spontaneous insufficiency fracture of the lateral femoral condyle in a 28-year-old professional football player. Saggital (a) and axial (b) proton-density with fat suppression images demonstrate subchondral fracture in the lateral femoral condyle (white arrows) with surrounding oedema. The patient was treated with intraosseous core decompression (stimulation of healing response) and instillation of autologous conditioned plasma (biological enhancement). Coronal (c) PD fat suppression image with preoperative planning of cannula positioning (black line). Intraoperative fluoroscopy view (d) of cannula insertion prior to autologous conditioned plasma injection.

inary results from the most recent study suggest that targeting articular cartilage and subchondral bone with intra-articular injections and intraosseous infiltrations of PRP reduces pain and significantly improves knee joint function in patients with OA[49]. If the microtrabecular fractures of the subchondral bone are present, stabilisation is warranted. Cohen et al.[50] proposed the injection of synthetic bone substitute calcium phosphate under fluoroscopic guidance into the bone marrow lesion. The initial results in the treatment of OA show potential in terms of pain reduction, functional recovery, or even delay of TKR[50]. However, if the microtrabecular fractures progress to bone collapse, the treatment should include bone grafting followed by osteochondral restoration techniques.

Conclusions

Subchondral bone marrow lesions can be detected in a vast number of different pathological entities, and are characterised by spatial and temporal alterations in bone remodelling activity and represent sites where both bone biology and structure are affected. MRI plays a crucial role in diagnosis, but it is of utmost importance to correlate these findings with age, clinical history, and coexisting abnormalities (cartilage, ligaments, etc.). Several different conservative and surgical approaches have been proposed, but current data is insufficient to construct a valid treatment algorithm. Considering the repercussions on the surrounding tissue, future strategies should not only aim at the damaged cartilage but also at the discovered abnormalities of the layer below, aiming for both biology and structure restoration. Future studies should focus on a better understanding of different BML patterns and how to link them to optimal treatment choices. Also, new and emerging therapies that include the application of orthobiologics, different cell types, and innovative carriers can significantly improve the efforts in optimising the management of BML.

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Sažetak

LEZIJE KOŠTANE SRŽI: KONCEPT DVAJU STUPOVA

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Uobičajeni prikaz lezija koštane srži na magnetskoj rezonanciji opisan je u brojnim patološkim entitetima. Međutim, unatoč intenzivnim istraživanjima, njegovi etiopatološki putevi i posljedice na progresiju bolesti ostaju kontroverzni. Prema našim trenutnim spoznajama, subhondralna kost predstavlja aktivno mjesto remodeliranja s važnom mehaničkom i biološkom ulogom u održavanju homeostaze zglobova. Promjene remodeliranja kosti, kao jedna od glavnih karakteristika lezije koštane srži, može potencijalno dovesti do biološkog i strukturnog oštećenja zahvaćenog tkiva i posljedično cijelog zgloba. Otkrivena bliska veza između biologije subhondralne kosti i njezinih strukturnih promjena, zajedno s paralelnim promjenama u hrskavici koja se nalazi iznad, postavljaju scenu za potencijalno novi koncept. U ovom konceptu "Dva nosiva stupa" i struktura i biologija subhondralne kosti (i njezina biomehanička i biokemijska interferencija sa slojem iznad) predstavljaju temelje strukture i funkcije zglobne hrskavice. U svjetlu predloženog koncepta osvrnuti ćemo se na trenutne spoznaje o etiologiji, patogenezi i kliničkoj prezentaciji lezija koštane srže te ih povezati s postojećim i novim mogućnostima liječenja.

Ključne riječi: *Lezije koštane srži, patologija subhondralne kosti, MR, koštano remodeliranje*