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Narrative Review

A review of bone marrow lesions in the arthritic knee and description of a technique for treatment

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ABSTRACT

Introduction: Subchondral bone pathology includes a wide range of pathologies, such as osteoarthritis, spontaneous insufficiency fractures, osteonecrosis, transient bone marrow lesions syndromes, and trauma. They show typical magnetic resonance imaging (MRI) findings termed bone marrow lesions (BMLs). However, the etiology and evolution of BMLs in multiple conditions remains unclear. There is still no gold standard treatment protocol in treating BMLs in the knee, and a variety of treatment modalities have been tested in the hope that they might reduce pain and stop disease progression.
Objectives: To review the treatment options for BMLs of the knee.
Methods: A literature review was performed that included searches of PubMed, Cochrane, and Medline databases using the following keywords: Bone marrow lesions, sub chondroplasty, bone marrow concentrate, platelet-rich plasma (PRP), subchondral bone augmentation.
Results: The use of novel biologic techniques to treat BMLs in the knee, such as PRP and Bone Marrow Cells, has yielded promising clinical outcomes.
Conclusions: Future research of BMLs will be mandatory to address the different pathologies better and determining appropriate treatment strategies. There is still a need for high-quality RCTs studies and systematic reviews in the future to enhance further treatment strategy in preventing or treating BMLs of the knee.

Introduction

The subchondral bone is a structure present underneath articular cartilage consisting of two major parts: the bone plate and the spongiosa. It is responsible for cartilage nutrition and plays an essential role in the healing of chondral lesions.[1] Focal changes in the subchondral bone, termed bone marrow lesions (BMLs), are features detected by magnetic resonance imaging (MRI). In patients with knee osteoarthritis (OA), BMLs can correlate with faster joint degeneration[2,3] and increased pain.[4-6] Recent research has focused on using biologic therapeutics to help maintain and improve cartilage health[7-10] however, treatment options taking into account the subchondral bone are still limited. Osteo-core plasty is a new, minimally invasive procedure for treating subchondral pathologies to prevent the progression of osteoarthritis.[11]

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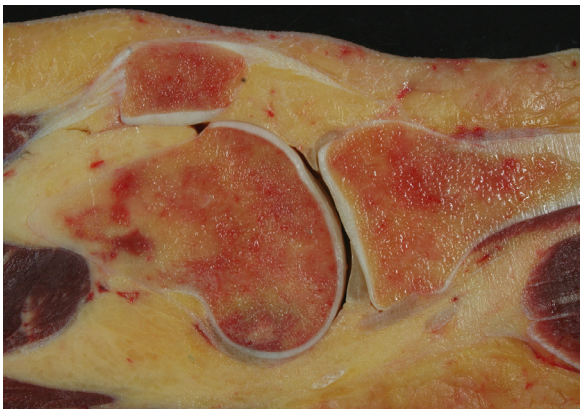

Fig. 1. Sagittal section of fresh frozen knee specimen (less than 40 years old) showing the patella, medial femoral condyle, and tibial plateau with the integrity of chondral surfaces and subchondral bone.

Fig. 2. Sagittal section of the lateral femoral condyle showing a cartilage lesion that involves the subchondral bone.

The osteochondral unit and bone marrow lesions

Articular cartilage and subchondral bone act as a functional unit, the osteochondral unit (OCU), to maintain joint homeostasis (Fig. 1). Numerous research efforts have focused on articular cartilage damage, while relatively few are focused on subchondral bone pathology. (Fig. 2) BMLs represent an alteration of bone marrow signal intensity, with high signal on fluid-sensitive sequences (T2/proton density with fat suppression and short tau inversion recovery (STIR) with or without low T1WI signal by magnetic resonance imaging (MRI). BMLs are present in a wide range of pathologies, including traumatic contusions and fractures, post-cartilage surgery, OA, transient BML syndromes, spontaneous insufficiency fractures (SIFK), osteonecrosis (ON), and conditions associated with Complex Regional Pain Syndrome (CRPS). These MRI alterations may correspond histologically to edema and trabecular necrosis, cysts, fibrosis, and cartilage fragments. Thus, instead of the commonly used term “bone marrow edema,” the terms “bone marrow edema-like signal” or “BMLs” are potentially more appropriate. MRI plays a fundamental role in guiding the diagnosis of BMLs based on recognizable typical patterns even at the early stages. BMLs remain controversial for their still unidentified role in pathological processes, clinical impact, and treatment.

Classification of bone marrow lesions

A classification of BMLs based on etiology (ischemic, mechanical, and reactive) has been proposed. However, as BML etiology is poorly understood, subchondral bone marrow edema-like lesions around the knee can alternatively be classified as traumatic/non-traumatic and reversible/irreversible.[2] The reversibility of the BML depends on its etiology and whether there is an alteration to the structure of the osteochondral unit. There are distinctive features on MRI that can help to predict if the BML is reversible. Prognostic criteria that appear to indicate a benign course are no changes on plain radiographs, the lack of additional subchondral changes other than BML and the absence of focal epiphyseal contour depression. Conversely, the presence on MRI of low signal intensity lines deep in the condyles,[3,4] or a subchondral area of low signal thicker than 4 mm, strongly predict irreversibility.[5,12]

Traumatic bone marrow lesions

Trauma-induced BMLs can be associated with acute direct (ie, contusion, knee ligament tear) or indirect (subacute lesions resulting from overload) trauma.,[2,5,13] However, there is a subset of asymptomatic patients subject to repetitive microtrauma, with subchondral edema-like signal(s) on MRI.[14,15] These types of lesions have been shown in up to 41% of collegiate basketball players.[16] Osseous injuries can be caused by a direct strike, applied shear forces, multiple bones impacting one another, or from traction forces in the context of avulsion injuries.[17] These mechanisms and their associated soft-tissue injuries can be revealed by studying their associated marrow edema-like signal distribution.[18] Pivot shift injuries, often related to ACL tears, are the most common cause of subchondral contusions.[13,19,20]

The damage to the osteochondral unit plays a significant role in the evolution of BMLs. While edema-like signal in ACL lesions without cortical involvement tend to resolve spontaneously in 95% of cases,[21] BMLs are still present at three years in lesions associated with a disruption of the femoral cortical surface. With respect to ACL injury mechanism, it has been suggested that noncontact injuries appear to cause more severe BMLs in both the medial and lateral compartments than contact injuries.[13] The location of the lesion is another factor that may affect the evolution of BML. In the setting of an ACL tear, BMLs located on the femoral condyle tend to resolve at three months versus six months for lateral tibial BMLs.[5] Moreover, 67% of lateral femoral condyle ACL injury-associated bone bruises have been related to osteochondral damage. In contrast, no cartilage defects were found in cases of BML of the posterolateral tibial plateau.[22]

There is no agreement in the literature regarding a correlation at short-term follow-up between BMLs and functional status, even though it has been reported that patients with an ACL tear and BML have increased pain scores and longer rehabilitation time,[23] mainly if the alteration is still detectable three months after the injury.[24] It is still under debate if the initial joint injury and BML are directly correlated to long-term function and OA development.[13]

Atraumatic bone marrow lesions

Subchondral insufficiency fractures

Spontaneous Insufficiency Fractures of the Knee (SIFK) are non-traumatic fractures without histological evidence of necrosis, usually occurring in overweight, elderly female patients. SIFK involves a physiologic force applied to weakened trabeculae, which leads to a fracture along the subchondral area of the bone.[25] SIFK can be reversible, but also can progress to a permanent collapse of the articular surface, resulting in rapidly destructive OA.[5,26]

On MRI, SIFK is best shown on T2-weighted and proton density-weighted images associated with marked bone marrow edema. Other MRI findings include a hypointense line that is irregular, sometimes discontinuous, in the subarticular marrow, and an area of low signal intensity immediately subjacent to and creating the appearance of a thickened subchondral bone plate. These localized abnormalities represent the fracture line and the granulation tissue.[25] The low signal intensity area has prognostic relevance, if it is thicker than 4 mm or longer than 14 mm, the lesion may be irreversible and evolve into irreparable epiphyseal collapse and articular destruction.[12,27] Edema-like signals present in SIFK extend from the subchondral region over large areas, often involving the entire femoral condyle and reaching the metaphysis.[28] This differs from the more localized BMLs subjacent to cartilage loss in osteoarthritis. However, the extent of the lesion has no known prognostic significance.[25] SIFK typically is observed along the central weight-bearing aspect of the femoral condyle (60%-90%) and is commonly associated with meniscus pathology.[29,30] Notably, it has been suggested that over 50% of patients demonstrate radial or posterior root tears.[31] These findings support the proposed role of mechanical stress in the development of SIFK and emphasize the rationale for meniscal conservation.

The clinical course of SIFK can be unpredictable, and does not necessarily progress in every patient.[5] Typically, the initial phase consists of severe pain with functional impairment for at least three to six months, followed by spontaneous resolution with functional and radiographic improvement.[32] While subtle contour deformities occasionally can be observed in self-resolving lesions, prominent contour deformity and the collapse of the subchondral bone plate are poor prognostic factors.[25] On the contrary, the lack of additional subchondral changes other than BML is 100% predictive of reversibility.[12] Markers of high-grade BMLs include medial meniscus posterior root tears with associated moderate to severe extrusion, high-grade chondrosis, larger lesion sizes, and articular surface collapse.[30]

Osteonecrosis

Ahlback first described osteonecrosis (ON) of the knee in 1968.[33] Since then, the improvement of knowledge in this field has led to the identification of three distinct categories of ON: spontaneous osteonecrosis of the knee (SONK or SPONK), avascular osteonecrosis (AVN), and post-arthroscopic ON. SONK was recognized early as a distinct form of epiphyseal osteonecrosis. This condition typically is seen in patients after the 6th decade of life and more frequently in women. Patients usually report a sudden onset of knee joint pain related to minimal or no trauma, and often recall a precise moment when the symptoms started.[25] SONK is the most common form of osteonecrosis of the knee.[34]

The etiology of SONK is not completely understood, but two hypotheses have been proposed. Avascular origin was initially suggested as the underlying etiology; however, the evidence in favor of this theory is limited. More recently, SONK has been associated with subchondral insufficiency fractures of the knee (SIFK). A study by Yamamoto and Bullough,[35] which was supported by results of later studies,[36,37] showed that the first event is a SIFK, which progresses into collapse followed by secondary necrosis limited to the

area between the fracture line and the subchondral bone plate. Moreover, the MRI features of this lesion also are profoundly different from those of AVN studies.[25]

Avascular necrosis (also called atraumatic, ischemic, or idiopathic osteonecrosis) is a degenerative bone condition characterized by the death of the bone secondary to an interruption of the subchondral blood supply,[38] usually affecting the epiphysis of long bones in patients under 45 years. It can be secondary to systemic diseases, radiation, chemotherapy, or substance consumption of alcohol, corticosteroids, and tobacco. These underlying systemic conditions and bone infarcts at other locations can narrow the differential diagnosis between SONK and AVN.[27,34] In most cases, a "double-line sign," an inner high-signal-intensity band (vascularized granulation tissue), and an outer low-signal-intensity band (sclerotic appositional new bone), are visible on T2-weighted.[25] Advanced disease may result in subchondral collapse, which threatens the viability of the joint involved. Lesions involving more than one-third of the condyle on midcoronal MR images or the middle and posterior one- a third of the condyle on midsagittal MR images are at higher risk of collapse.[39]

Bone marrow lesions in osteoarthritis

Subchondral BMLs are a common finding in patients with both early and advanced OA. These are often associated with meniscus damage, thinning, or focal cartilage defects and subchondral cyst-like lesions.[5] The most common histologic findings in bone marrow edema-like lesions in OA include bone necrosis, fibrosis, hemorrhage, and trabecular abnormalities, while edema is infrequent. These findings might be seen as well in SIFK. However, the bone marrow edema-like pattern is typically localized in OA and extensive in SIFK. The articular cartilage may be preserved in early SIFK, while significant cartilage loss typically accompanies eburnation in osteoarthritis. Once SIFK progresses to collapse and articular surface destruction, distinguishing it from primary osteoarthritis at imaging may be impossible.[25] The evolution of BML in the setting of OA is exceptionally variable. Subchondral lesions may regress or resolve entirely within 30 months follow-up,[40] but some studies showed the persistence of BML in the majority of patients.[41,42] The clinical correlation of BMLs in the setting of OA is still under debate; moderate evidence supports that the severity and enlargement of BML are predictors of pain, the progression of cartilage damage, and subchondral bone attrition.[32,43,44]

A new topographic classification of BMLs named, the six-letter system, concerning their anatomical location in the distal femur or proximal tibia based on the coronal T2 MRI images of 520 patients was described recently by Compagnoni et al.[45]

Bone marrow lesions and cartilage

The subchondral bone plays a vital role in natural cartilage healing. Certain diseases of the cartilage are diseases of the osteochondral unit rather than the cartilage disease alone. Imhoff et al. showed the presence of arteriovenous complexes penetrating the subchondral bone plate and reaching into the calcified cartilage, so consequently, it possesses a blood supply layer up to the tidemark.[46] The study by Lane et al. demonstrated higher vascular perforations at higher stress areas, indicating that the subchondral bone responds to high loads by increasing the blood supply.[47] However, overloading the degenerated joint will impede the flow of nutrients from the subchondral bone to the cartilage and disturb natural healing. Although the mechanisms are still debated, pain may result from impaired venous drainage due to repetitive microtrauma.[48,49] A recent study by MacKay et al. demonstrated that subchondral bone texture is associated with radiographic knee osteoarthritis progression.[50] Besides, several studies correlate outcomes with known subchondral BMLs before cartilage restoration procedures. Severe subchondral bone marrow edema was associated with poor knee function in patients with chondral lesions. It was a reliable prognostic factor in the first year after autologous chondrocyte implantation.[51] Additionally, the persistence of edema-like signs in the subchondral bone is a predictor of poor clinical outcome after microfracture surgery.[52]

Biology of bmac and subchondral bone

Before aspirated bone marrow concentrate, commonly referred to as bone marrow aspirate concentrate (BMAC), becomes the concentrated MSC-containing biologic often used as a treatment method for various bone BMLs of the knee, unprocessed bone marrow aspirate (BMA) is obtained. Bone marrow aspirate mainly comprise hematopoietic tissue and fat cells and contain three major cell types: myelopoietic cells, erythropoietic cells, and lymphocytes.[53] Supporting cells also include fibroblasts, macrophages, adipocytes, osteoblasts, osteoclasts, endothelial cells, and hematopoietic cells.[53] Only 0.001% of nucleated cells in BMA are MSCs, a key factor in articular cartilage and subchondral bone repair, which has led to the concept of concentrating BMA via density-gradient centrifugation to produce BMAC.[53] BMAC contains increased amounts of MSCs, platelets containing growth factors, and hematopoietic cells.[53] Each of these more concentrated components contribute to the healing and repairing capabilities of BMAC, enabling it to be a useful treatment method for subchondral bone and cartilage pathologies. However, a recent study by Everts et al. concluded that the CFU/f counts were not significantly increased compared to the counts of the first 10 ml of BMA.[54] This study supported the results by Hernigou et al., who showed that large volume aspirates tend to be infiltrated by significant amounts of peripheral blood, which contains fewer MSCs, leading to lower CFU-f counts.[55]

Subchondral bone comprises a superficial plate and deep spongy bone, which together support and maintain overlying cartilage.[56] The subchondral bone can be further divided into the subchondral bone plate and the subchondral trabecular bone.[57] The subchondral bone plate lies immediately deep to the calcified articular cartilage, separated by a “cement line”.[58] Supporting trabeculae arise from the subchondral bone plate, and in combination with the deeper bone structure, comprises the subchondral trabecular bone.[57] The subchondral bone plate contains channels with arterial and venous vessels and nerves, directly linking the subchondral trabecular bone

Fig. 3. Osteo-core-plasty surgical instruments.

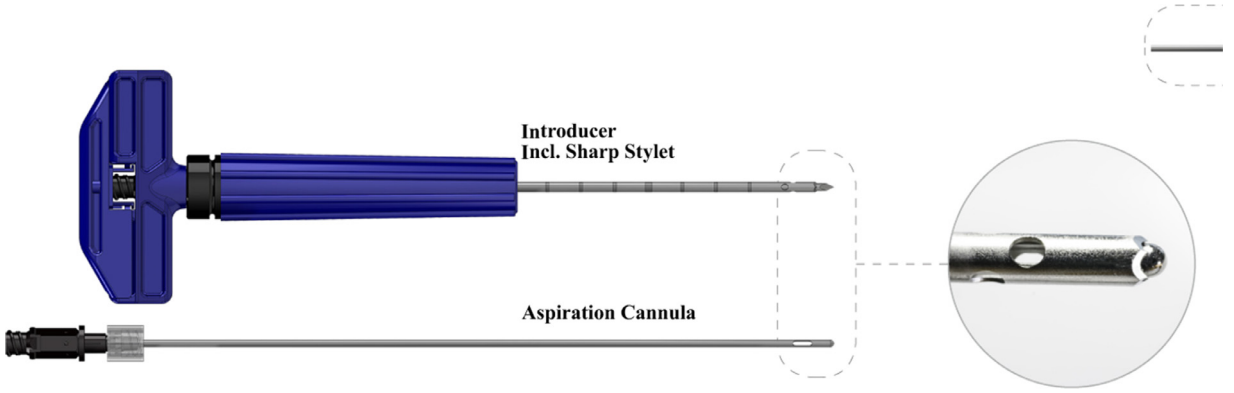

Fig. 4. Osteo-core-plasty surgical instruments. closed aspiration cannula tip to prevent aspiration of excess blood from the entry channel.

and the articular cartilage for communication via biochemical signals.[56,57] The subchondral trabecular bone is more metabolically active and porous than the subchondral plate and has higher contents of blood vessels, sensory nerves, and bone marrow.[57] Its makeup is directly related to its functions of shock absorption and joint support, as well as having a role in cartilage nutrient supply and metabolism.[57] Overall, subchondral bone has various bone density patterns and is dynamic and adaptable as it responds to mechanical stress on the joint via bone modeling and remodeling.[57] It plays an important interactive role with the overlying articular cartilage, forming the OCU, to support and maintain the environment of the joint.

Biomechanics of subchondral bone

Biomechanical dysfunction does not solely cause subchondral bone abnormalities or knee OA.[59] OA is the result of competing multi-factorial etiologies: mechanical, systemic and joint homeostasis, and physiological inputs.[60] Subchondral bone anatomy consists of two layers. The first is the subchondral bone plate, that is adjacent to and separated by the cement line from the calcified zone of the articular cartilage. The second is the subarticular spongiosa that is above the trabecular bone. Both layers often become diseased as OA progresses.[1]

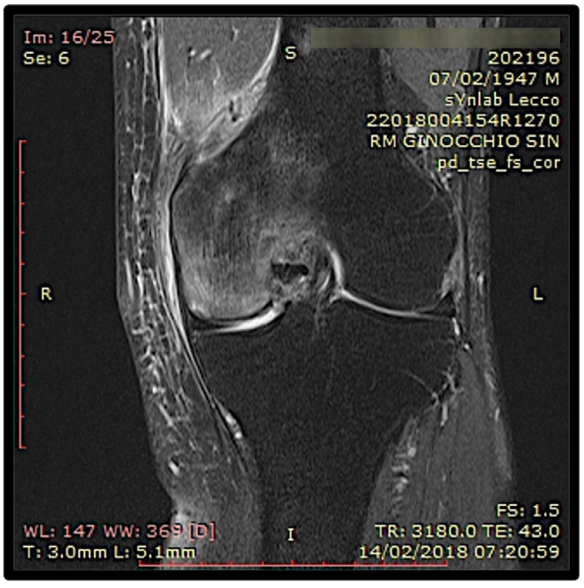

Fig. 5. A case example of Bone Marrow Lesion (BML) in the medial femoral condyle of the Knee treated with Osteo core plasty. Pre-treatment, coronal view of knee MRI.

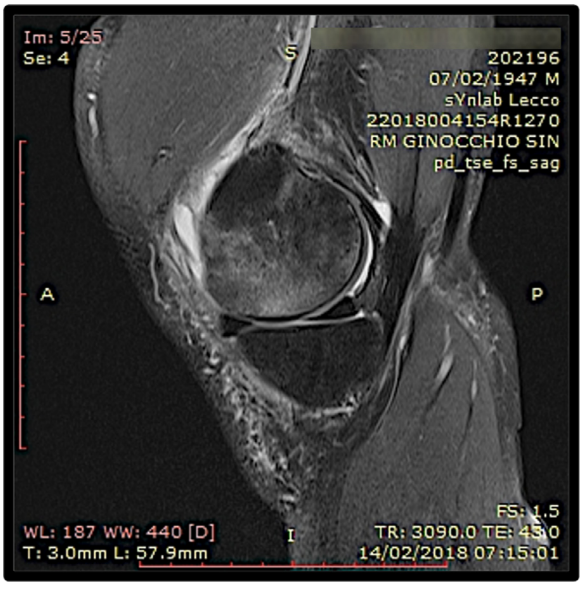

Fig. 6. A case example of Bone Marrow Lesion (BML) in the medial femoral condyle of the Knee treated with Osteo core plasty. Pre-treatment, sagittal view of knee MRI.

Abnormality of subchondral bone due to mechanical dysfunction can occur after traumatic insult, such as in the case of ligament tear. Damage of the subchondral bone can also result from adjacent tissue dysfunction or disease stemming from meniscal or cartilage deficiency. Finally, compartment overload due to varus or valgus malalignment can contribute to subchondral bone disease transformation along with the production of BMLs.[61]

BMLs result from microdamage to the bone and demonstrate localized fibrosis, fat necrosis and a response in bone remodeling that results in microfractures of the trabecular bone.[62] Diseased subchondral bone and subsequent development of bone marrow lesions (BML) are poorly understood. BMLs can occur with and without coronal mechanical plane malalignment of the knee. Although BMLs can arise when the meniscus is intact, most often the condition results from articular cartilage overload/disruption following meniscal root tear and/or extrusion.[63]

Fig. 7. A case example of Bone Marrow Lesion (BML) in the medial femoral condyle of the Knee treated with Osteo core plasty. Two months post-treatment, coronal view of knee MRI.

Treatment options

Treating subchondral bone marrow lesions requires consideration of both biologic as well as structural contributions to the overall clinical picture. Biological aspects of treatment include marrow stimulation techniques such as marrow stimulation, nano-fracturing, and core decompression.[64] This treatment strategy can also include additive therapies such as autologous Platelet Rich Plasma (PRP) injections,[65] adipose treatments, [66] and bone marrow aspirate/concentrate injections.[67] Structural aspects of treatment include consideration of sub chondroplasty and/or intraosseous bioplasty (IOBP) as well as realignment osteotomies. [68]

Osteo-core-plasty an emerging minimally invasive one-stage treatment for subchondral bone marrow lesions

Osteo-core-plasty is a novel, minimally invasive procedure for treating BMLs. During osteo-core plasty, bone marrow and small dowels of autologous bone are injected the affected area to fill the intertrabecular space, thereby inducing improved bone remodeling.

High-quality bone marrow is a readily available source of mesenchymal stromal/signaling cells (MSCs) and growth factors, including platelet-derived growth factor (PDGF), transforming growth factor-beta (TGF-β), and bone morphogenetic proteins (BMP-2, BMP-7), which have anabolic and anti-immunomodulatory effects.[69] Although high-quality bone marrow is one of the most attractive sources of MSCs, the amount and processing of BMA required are poorly understood. Bone autograft augmentation can deliver additional supportive and biologically active tissue to the subchondral lesion.

Studies have shown that bone marrow samples containing a relatively high CFU-fs/mL and CD34+/mL can be attained without the need for centrifugation.[70,71] The level of CFU-fs/mL was significantly higher in the Osteo-Core-Plasty compared to BMACs in side-by-side comparison from the same patients using the contralateral iliac crest. [71] Osteo-core-plasty had over twice as many fibroblast-like colony forming units (CFU-f) and only half as many nucleated cells compared to centrifugation techniques. Moreover, the Osteo-core-plasty showed the same numbers of CD34+and CD117+cells compared to centrifugation techniques. [71]

The technique

The procedure is initiated by aspiration of the bone marrow from the ipsilateral iliac crest using a sharp trocar with a hollow aspiration sleeve. The introducer needle with a sharp stylet is placed in the cancellous bone between the cortices. When 1 mL of bone marrow is aspirated to ensure proper positioning of the needle tip, a sharp stylet is replaced with a blunt one. From a single

Fig. 8. A case example BML in the Knee treated with Osteo core plasty. Twelve months post-treatment, coronal view of knee MRI.

stick, Marrow Cellution is capable of collecting up to 10 ml of high-quality bone marrow aspirate (BMA) (Marrow Cellution, Aspire Medical Innovation, Germany) equivalent or superior to other systems that require additional manipulation steps outside of the sterile field, such as centrifugation (BMAC) or chemical separation in a laboratory. Additionally, a sharp trocar is used to harvest some bone dowels (Fig. 3,4).[11]

The patient under regional or spinal anesthesia is placed in the supine position as for standard knee arthroscopy. Before BMA injection, any concomitant abnormalities such as chondral lesions, meniscal tears and ligament lesions should be addressed and treated. Limb alignment plays a crucial role in cartilage lesion treatment. Therefore, any abnormalities should be treated as well. A 30˚ 4.0 mm arthroscope (Smith & Nephew, USA) is used to perform a comprehensive arthroscopic examination of the knee. Antero-posterior (AP) and lateral fluoroscopic images cross-referenced with the MRI study are used to place the guide pin precisely in the bone marrow edema. A cannula is then placed over the guide pin, which is subsequently removed. It is left for a few minutes in the bone to perform core decompression.

Furthermore, bone dowels are inserted into the cannula and pushed through into the subchondral lesion by a blunt trocar. Then, the BMA is inserted through the cannula into the treated area. A final arthroscopic look is performed to confirm the lack of intra-articular leakage.

There are several benefits of Osteo-Core-Plasty. It allows the clinician to retain the product entirely on the sterile area rather than necessitating the product to leave the sterile area for centrifugation and re-enter the sterile area for administration to the patient, decreases procedural expenses and maintain all the cells and growth factors obtained during aspiration. Users of this technique reported that another advantage is the ability to advance into and retreat from the marrow area in a precise and controlled manner (Fig 5,6,7,8).

Conclusions

Future research of BMLs will be mandatory to address the different pathologies better and determining appropriate treatment strategies. Subchondral bone augmentation by osteo-core-plasty is a viable option in treating BMLs of the knee by reducing pain over the affected area, returning to activity early and improved MRI imaging showing increased hypo intensity over the subchondral bone

lesion. There is still a need for high-quality RCTs studies and systematic reviews in the future to enhance further treatment strategy in preventing or treating BMLs of the knee.

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Author contributions

All authors have made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

1. Madry H, van Dijk CN, Mueller-Gerbl M. The basic science of the subchondral bone. *Knee Surg Sports Traumatol Arthrosc*. 2010;18:419–433 Apr. doi:10.1007/s00167-010-1054-z.
2. Roemer FW, Frobell R, Hunter DJ, et al. MRI-detected subchondral bone marrow signal alterations of the knee joint: terminology, imaging appearance, relevance and radiological differential diagnosis. *Osteoarthritis Cartilage*. 2009;17:1115–1131. doi:10.1016/j.joca.2009.03.012.
3. Yates PJ, Calder JD, Stranks GJ, Conn KS, Peppercorn D, Thomas NP. Early MRI diagnosis and non-surgical management of spontaneous osteonecrosis of the knee. *Knee*. 2007;14:112–116 Mar. doi:10.1016/j.knee.2006.10.012.
4. Mont MA, Marker DR, Zywiel MG, Carrino JA. Osteonecrosis of the knee and related conditions. *J Am Acad Orthop Surg*. 2011;19:482–494 Aug. doi:10.5435/00124635-201108000-00004.
5. Marcacci M, Andriolo L, Kon E, Shabshin N, Filardo G. Aetiology and pathogenesis of bone marrow lesions and osteonecrosis of the knee. *EFORT Open Rev*. 2016;1:219–224 May. doi:10.1302/2058-5241.1.000044.
6. Bisson LJ, Phillips P, Matthews J, et al. Association between bone marrow lesions, chondral lesions, and pain in patients without radiographic evidence of degenerative joint disease who underwent arthroscopic partial meniscectomy. *Orthop J Sports Med*. 2019;7 Mar. doi:10.1177/2325967119830381.
7. Gobbi A, Karnatzikos G, Scotti C, Mahajan V, Mazzucco L, Grigolo B. One-step cartilage repair with bone marrow aspirate concentrated cells and collagen matrix in full-thickness knee cartilage lesions: results at 2-year follow-up. *Cartilage*. 2011;2:286–299 Jul. doi:10.1177/1947603510392023.
8. Gobbi A, Karnatzikos G, Mahajan V, Malchira S. Platelet-rich plasma treatment in symptomatic patients with knee osteoarthritis: preliminary results in a group of active patients. *Sports Health*. 2012;4:162–172 Mar. doi:10.1177/1941738111431801.
9. Gobbi A, Dallo I, Kumar V. Editorial commentary: biological cartilage repair technique-an "effective, accessible, and safe" surgical solution for an old difficult biological problem. *Arthroscopy*. 2020;36:859–861 Mar. doi:10.1016/j.arthro.2019.12.020.
10. Gobbi A, Whyte GP. Long-term clinical outcomes of one-stage cartilage repair in the knee with hyaluronic acid-based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate. *Am J Sports Med*. 2019;47:1621–1628 Jun. doi:10.1177/0363546519845362.
11. Szwedowski D, Dallo I, Irlandini E, Gobbi A. Osteo-core plasty: a minimally invasive approach for subchondral bone marrow lesions of the knee. *Arthrosc Tech*. 2020;9:e1773–e1777 Nov. doi:10.1016/j.eats.2020.07.023.
12. Lecouvet FE, van de Berg BC, Maldague BE, et al. Early irreversible osteonecrosis versus transient lesions of the femoral condyles: prognostic value of subchondral bone and marrow changes on MR imaging. *AJR Am J Roentgenol*. 1998;170:71–77 Jan. doi:10.2214/ajr.170.1.9423603.
13. Viskontas DG, Giuffre BM, Duggal N, Graham D, Parker D, Coolican M. Bone bruises associated with ACL rupture: correlation with injury mechanism. *Am J Sports Med*. 2008;36:927–933 May. doi:10.1177/0363546508314791.
14. Matiotti SB, Soder RB, Becker RG, Santos FS, Baldisserotto M. MRI of the knees in asymptomatic adolescent soccer players: a case-control study. *J Magn Reson Imaging*. 2017;45:59–65 Jan. doi:10.1002/jmri.25329.
15. Pappas GP, Vogelsong MA, Staroswiecki E, Gold GE, Safran MR. Magnetic resonance imaging of asymptomatic knees in collegiate basketball players: the effect of one season of play. *Clin J Sport Med*. 2016;26:483–489 Nov. doi:10.1097/jsm.0000000000000283.
16. Major NM, Helms CA. MR imaging of the knee: findings in asymptomatic collegiate basketball players. *AJR Am J Roentgenol*. 2002;179:641–644 Sep. doi:10.2214/ajr.179.3.1790641.
17. Sanders TG, Medynski MA, Feller JF, Lawhorn KW. Bone contusion patterns of the knee at MR imaging: footprint of the mechanism of injury. *Radiographics*. 2000;20 OctSpec No:S135-51. doi:10.1148/radiographics.20.suppl_1.g00oc19s135.
18. Berger N, Andreisek G, Karer AT, et al. Association between traumatic bone marrow abnormalities of the knee, the trauma mechanism and associated soft-tissue knee injuries. *Eur Radiol*. 2017;27:393–403 Jan. doi:10.1007/s00330-016-4339-x.
19. Koga H, Nakamae A, Shima Y, et al. Mechanisms for noncontact anterior cruciate ligament injuries: knee joint kinematics in 10 injury situations from female team handball and basketball. *Am J Sports Med*. 2010;38:2218–2225 Nov. doi:10.1177/0363546510373570.
20. Bretlau T, Tuxøe J, Larsen L, Jørgensen U, Thomsen HS, Lausten GS. Bone bruise in the acutely injured knee. *Knee Surg Sports Traumatol Arthrosc*. 2002;10:96–101 Mar. doi:10.1007/s00167-001-0272-9.
21. Costa-Paz M, Muscolo DL, Ayerza M, Makino A, Aponte-Tinao L. Magnetic resonance imaging follow-up study of bone bruises associated with anterior cruciate ligament ruptures. *Arthroscopy*. 2001;17:445–449 May. doi:10.1053/jars.2001.23581.
22. Vellet AD, Marks PH, Fowler PJ, Munro TG. Occult posttraumatic osteochondral lesions of the knee: prevalence, classification, and short-term sequelae evaluated with MR imaging. *Radiology*. 1991;178:271–276 Jan. doi:10.1148/radiology.178.1.1984319.
23. Johnson DL, Bealle DP, Brand Jr JC, Nyland J, Caborn DN. The effect of a geographic lateral bone bruise on knee inflammation after acute anterior cruciate ligament rupture. *Am J Sports Med*. 2000;28:152–155 Mar-Apr. doi:10.1177/03635465000280020301.
24. Filardo G, Kon E, Tentoni F, et al. Anterior cruciate ligament injury: post-traumatic bone marrow oedema correlates with long-term prognosis. *Int Orthop*. 2016;40:183–190 Jan. doi:10.1007/s00264-015-2672-3.
25. Gorbachova T, Melenevsky Y, Cohen M, Cerniglia BW. Osteochondral lesions of the knee: differentiating the most common entities at MRI. *Radiographics*. 2018;38:1478–1495 Sep-Oct. doi:10.1148/rg.2018180044.
26. Huizinga JL, Shah N, Smith SE, et al. Prevalence of undiagnosed subchondral insufficiency fractures of the knee in middle age adults with knee pain and suspected meniscal tear. *Osteoarthr Cartil Open*. 2020;2 Dec. doi:10.1016/j.ocarto.2020.100089.
27. Kon E, Ronga M, Filardo G, et al. Bone marrow lesions and subchondral bone pathology of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2016;24:1797–1814 Jun. doi:10.1007/s00167-016-4113-2.

28. Vidoni A, Shah R, Mak D, et al. Metaphyseal burst sign: a secondary sign on MRI of subchondral insufficiency fracture of the knee. *J Med Imaging Radiat Oncol*. 2018;62:764–768 Dec. doi:10.1111/1754-9485.12781.
29. Pareek A, Parkes CW, Bernard C, et al. Spontaneous osteonecrosis/subchondral insufficiency fractures of the knee: high rates of conversion to surgical treatment and arthroplasty. *J Bone Joint Surg Am*. 2020;102:821–829 May 6. doi:10.2106/jbjs.19.00381.
30. Sayyid S, Younan Y, Sharma G, et al. Subchondral insufficiency fracture of the knee: grading, risk factors, and outcome. *Skeletal Radiol*. 2019;48:1961–1974 Dec. doi:10.1007/s00256-019-03245-6.
31. Yao L, Stanczak J, Boutin RD. Presumptive subarticular stress reactions of the knee: MRI detection and association with meniscal tear patterns. *Skeletal Radiol*. 2004;33:260–264 May. doi:10.1007/s00256-004-0751-4.
32. Roemer FW, Neogi T, Nevitt MC, et al. Subchondral bone marrow lesions are highly associated with, and predict subchondral bone attrition longitudinally: the MOST study. *Osteoarthritis Cartilage*. 2010;18:47–53 Jan. doi:10.1016/j.joca.2009.08.018.
33. Ahlbäck S, Bauer GCH, Bohne WH. Spontaneous Osteonecrosis of the Knee. *Arthritis & Rheumatism*. 1968;11:705–733. doi:10.1002/art.1780110602.
34. Karim AR, Cherian JJ, Jauregui JJ, Pierce T, Mont MA. Osteonecrosis of the knee: review. *Ann Transl Med*. 2015;3:6 Jan. doi:10.3978/j.issn.2305-5839.2014.11.13.
35. Yamamoto T, Bullough PG. Spontaneous osteonecrosis of the knee: the result of subchondral insufficiency fracture. *J Bone Joint Surg Am*. 2000;82:858–866 Jun. doi:10.2106/00004623-200006000-00013.
36. Hussain ZB, Chahla J, Mandelbaum BR, Gomoll AH, LaPrade RF. The role of meniscal tears in spontaneous osteonecrosis of the knee: a systematic review of suspected etiology and a call to revisit nomenclature. *Am J Sports Med*. 2019;47:501–507 Feb. doi:10.1177/0363546517743734.
37. Fujita S, Arai Y, Honjo K, Nakagawa S, Kubo T. A case of spontaneous osteonecrosis of the knee with early and simultaneous involvement of the medial femoral condyle and medial tibial plateau. *Case Rep Orthop*. 2016;2016. doi:10.1155/2016/2574975.
38. Shah KN, Racine J, Jones LC, Aaron RK. Pathophysiology and risk factors for osteonecrosis. *Curr Rev Musculoskelet Med*. 2015;8:201–209 Sep. doi:10.1007/s12178-015-9277-8.
39. Sakai T, Sugano N, Nishii T, Haraguchi K, Yoshikawa H, Ohzono K. Osteonecrosis of the patella in patients with nontraumatic osteonecrosis of the femoral head: MRI findings in 60 patients. *Acta Orthop Scand*. 2000;71:447–451 2000/01/01. doi:10.1080/000164700317381108.
40. Roemer FW, Guermazi A, Javaid MK, et al. Change in MRI-detected subchondral bone marrow lesions is associated with cartilage loss: the MOST Study. A longitudinal multicentre study of knee osteoarthritis. *Ann Rheum Dis*. 2009;68:1461–1465 Sep. doi:10.1136/ard.2008.096834.
41. Hunter DJ, Zhang Y, Niu J, et al. Increase in bone marrow lesions associated with cartilage loss: a longitudinal magnetic resonance imaging study of knee osteoarthritis. *Arthritis Rheum*. 2006;54:1529–1535 May. doi:10.1002/art.21789.
42. Kornaat PR, Kloppenburg M, Sharma R, et al. Bone marrow edema-like lesions change in volume in the majority of patients with osteoarthritis; associations with clinical features. *Eur Radiol*. 2007;17:3073–3078 Dec. doi:10.1007/s00330-007-0711-1.
43. Felson DT, Niu J, Guermazi A, et al. Correlation of the development of knee pain with enlarging bone marrow lesions on magnetic resonance imaging. *Arthritis Rheum*. 2007;56:2986–2992 Sep. doi:10.1002/art.22851.
44. Yusuf E, Kortekaas MC, Watt I, Huizinga TW, Kloppenburg M. Do knee abnormalities visualised on MRI explain knee pain in knee osteoarthritis? A systematic review. *Ann Rheum Dis*. 2011;70:60–67 Jan. doi:10.1136/ard.2010.131904.
45. Compagnoni R, Lesman J, Ferrua P, et al. Validation of a new topographic classification of bone marrow lesions in the knee: the six-letter system. *Knee Surg Sports Traumatol Arthrosc*. 2021;29:333–341 Feb. doi:10.1007/s00167-020-05957-y.
46. Imhof H, Breitenseher M, Kainberger F, Rand T, Trattnig S. Importance of subchondral bone to articular cartilage in health and disease. *Top Magnet Reson Imag*. 1999;10:180–192.
47. LB L, A V, PG B. The vascularity and remodelling of subchondrial bone and calcified cartilage in adult human femoral and humeral heads. An age- and stress-related phenomenon. *The Journal of Bone and Joint Surgery British volume*. 1977;59-B:272–278. doi:10.1302/0301-620x.59b3.893504.
48. Arnoldi CC, Djurhuus JC, Heerfordt J, Karle A. Intraosseous phlebography, intraosseous pressure measurements and 99mTC-polyphosphate scintigraphy in patients with various painful conditions in the hip and knee. *Acta Orthop Scand*. 1980;51:19–28 Feb. doi:10.3109/17453678008990764.
49. Saltzman BM, Riboh JC. Subchondral bone and the osteochondral unit: basic science and clinical implications in sports medicine. *Sports Health*. 2018;10:412–418 Sep/Oct. doi:10.1177/1941738118782453.
50. MacKay JW, Kapoor G, Driban JB, et al. Association of subchondral bone texture on magnetic resonance imaging with radiographic knee osteoarthritis progression: data from the osteoarthritis initiative bone ancillary study. *Eur Radiol*. 2018;28:4687–4695 Nov. doi:10.1007/s00330-018-5444-9.
51. Niemeyer P, Salzmann G, Steinwachs M, et al. Presence of subchondral bone marrow edema at the time of treatment represents a negative prognostic factor for early outcome after autologous chondrocyte implantation. *Arch Orthop Trauma Surg*. 2010;130:977–983 2010/08/01. doi:10.1007/s00402-010-1049-8.
52. Blackman AJ, Smith MV, Flanigan DC, Matava MJ, Wright RW, Brophy RH. Correlation between magnetic resonance imaging and clinical outcomes after cartilage repair surgery in the knee: a systematic review and meta-analysis. *Am J Sports Med*. 2013;41:1426–1434 Jun. doi:10.1177/0363546513485931.
53. Madry H, Gao L, Eichler H, Orth P, Cucchiarini M. Bone marrow aspirate concentrate-enhanced marrow stimulation of chondral defects. *Stem Cells Int*. 2017;2017. doi:10.1155/2017/1609685.
54. Everts PA, Ferrell J, Mahoney C, et al. A comparative quantification in cellularity of bone marrow aspirated with two new harvesting devices, and the non-equivalent difference between a centrifugated bone marrow concentrate and a bone marrow aspirate as biological injectates, using a bi-lateral patient model. *J Stem Cell Res Ther*. 2020;10:1–10.
55. Hernigou P, Homma Y, Flouzat Lachaniette CH, et al. Benefits of small volume and small syringe for bone marrow aspirations of mesenchymal stem cells. *Int Orthop*. 2013;37:2279–2287 Nov. doi:10.1007/s00264-013-2017-z.
56. Seow D, Yasui Y, Hutchinson ID, Hurley ET, Shimozono Y, Kennedy JG. The subchondral bone is affected by bone marrow stimulation: a systematic review of preclinical animal studies. *Cartilage*. 2019;10:70–81. doi:10.1177/1947603517711220.
57. Li G, Yin J, Gao J, et al. Subchondral bone in osteoarthritis: insight into risk factors and microstructural changes. *Arthritis Res. Ther.*. 2013;15:223. doi:10.1186/ar4405.
58. Madry H, Van Dijk CN, Mueller-Gerbl M. The basic science of the subchondral bone. *Knee Surg, Sport Traumatol, Arthroscop*. 2010;18:419–433. doi:10.1007/s00167-010-1054-z.
59. van Tunen JAC, Dell'Isola A, Juhl C, et al. Association of malalignment, muscular dysfunction, proprioception, laxity and abnormal joint loading with tibiofemoral knee osteoarthritis - a systematic review and meta-analysis. *BMC Musculoskelet Disord*. 2018;19:273 Jul 28. doi:10.1186/s12891-018-2202-8.
60. Chen D, Shen J, Zhao W, et al. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. *Bone Res*. 2017;5:16044. doi:10.1038/boneres.2016.44.
61. Primorac D, Molnar V, Rod E, et al. Knee osteoarthritis: a review of pathogenesis and state-of-the-art non-operative therapeutic considerations. *Genes (Basel)*. 2020;11 Jul 26. doi:10.3390/genes11080854.
62. Driban JB, Tassinari A, Lo GH, et al. Bone marrow lesions are associated with altered trabecular morphometry. *Osteoarthritis Cartilage*. 2012;20:1519–1526 Dec. doi:10.1016/j.joca.2012.08.013.
63. Heijink A, Gomoll AH, Madry H, et al. Biomechanical considerations in the pathogenesis of osteoarthritis of the knee. *Knee Surg Sports Traumatol Arthrosc*. 2012;20:423–435 Mar. doi:10.1007/s00167-011-1818-0.
64. Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. *Knee Surg Sports Traumatol Arthrosc*. 2014;22:1986–1996 Sep. doi:10.1007/s00167-013-2676-8.
65. Sánchez M, Delgado D, Pompei O, et al. Treating severe knee osteoarthritis with combination of intra-osseous and intra-articular infiltrations of platelet-rich plasma: an observational study. *Cartilage*. 2019;10:245–253 Apr. doi:10.1177/1947603518756462.
66. Gobbi A, Dallo I, Rogers C, et al. Two-year clinical outcomes of autologous microfragmented adipose tissue in elderly patients with knee osteoarthritis: a multi-centric, international study. *Int Orthop*. 2021; doi:10.1007/s00264-021-04947-0

67. Hernigou P, Bouthors C, Bastard C, Flouzat Lachaniette CH, Rouard H, Dubory A. Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis: what better postpone knee arthroplasty at fifteen years? A randomized study. *Int Orthop*. 2021;45:391–399 Feb. doi:10.1007/s00264-020-04687-7.
68. Cohen SB, Sharkey PF. Subchondroplasty for treating bone marrow lesions. *J Knee Surg*. 2016;29:555–563 Oct. doi:10.1055/s-0035-1568988.
69. Chen WCW, Péault B, Huard J. Regenerative translation of human blood-vessel-derived MSC precursors. *Stem Cells Int*. 2015;2015 2015/07/26. doi:10.1155/2015/375187.
70. Everts V, van der Zee E, Creemers L, Beertsen W. Phagocytosis and intracellular digestion of collagen, its role in turnover and remodelling. *Histochem J*. 1996;28:229–245 Apr.
71. Scarpone M, Kuebler D, Chambers A, et al. Isolation of clinically relevant concentrations of bone marrow mesenchymal stem cells without centrifugation. *J Transl Med*. 2019;17:10 Jan 5. doi:10.1186/s12967-018-1750-x.