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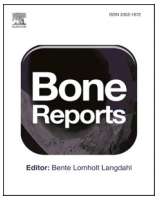

Mesenchymal stem cells for subchondral bone marrow lesions: From bench to bedside

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ABSTRACT

Subchondral bone marrow lesions (BMLs) are areas of disease within subchondral bone that appear as T1 hypointense and T2 hyperintense ill-defined areas of bone marrow on magnetic resonance imaging. The most common bone marrow lesions include subchondral lesions related to osteoarthritis, osteochondral defects, and avascular necrosis. Emerging therapies include autologous biologic therapeutics, in particular mesenchymal stem cells (MSCs), to maintain and improve cartilage health; MSCs have become a potential treatment option for BMLs given the unmet need for disease modification. Active areas in the preclinical research of bone marrow lesions include the paracrine function of MSCs in pathways of angiogenesis and inflammation, and the use of bioactive scaffolds to optimize the environment for implanted MSCs by facilitating chondrogenesis and higher bone volumes. A review of the clinical data demonstrates improvements in pain and functional outcomes when patients with knee osteoarthritis were treated with MSCs, suggesting that BM-MSCs can be a safe and effective treatment for patients with painful knee osteoarthritis with or without bone marrow lesions. Preliminary data examining MSCs in osteochondral defects suggest they can be beneficial as a subchondral injection alone, or as a surgical augmentation. In patients with hip avascular necrosis, those with earlier stage disease have improved outcomes when core decompression is augmented with MSCs, whereas patients in later stages post-collapse have equivalent outcomes with or without MSC treatment. While the evidence for the use of MSCs in conditions with associated bone marrow lesions seems promising, there remains a need for continued investigation into this treatment as a viable treatment option.

1. Introduction

Bone marrow lesions (BML) are areas of disease within subchondral bone that are typically visualized with magnetic resonance imaging (MRI) (Munsch et al., 2021). The first description in the literature was by Wilson and colleagues in 1988 (Wilson et al., Jun 1988); when imaging patients with severe hip and knee pain, he used the term "bone marrow edema" to describe ill-defined areas of bone marrow in the affected joint with decreased T1 signal intensity and increased T2 signal intensity. This term was revised by Zanetti and colleagues in 2000 (Zanetti et al., 2000), who recommended "ill-defined signal intensity abnormality" or "edema-like MR imaging abnormality" as new terms, given that histopathology studies had also shown fibrosis, necrosis, and trabeculae abnormalities in addition to edema (Plenk et al., Jan 1997). These changes are thought to result from culminating effects of microdamage and altered bone remodeling (Driban et al., 2012). It is thought that the T2 hyperintense MRI signal changes of BML may represent the increased vascularization and increased bony remodeling within the region (Shabestari et al., 2016). More recently, the term "bone marrow lesion" has become standard usage to describe these focal MRI signal changes in the subchondral bone, especially in the osteoarthritis (OA) imaging research community (Hunter et al., 2006; Roemer et al., Sep 2009; Li et al., 2013).

Bone marrow lesions have complex pathological mechanisms. The initial classifications were based on three etiologies: ischemic, mechanical, and reactive (Hofmann et al., 2004); however, this has evolved to broader classifications such as traumatic versus atraumatic, reversible versus irreversible, cystic versus non-cystic, transient versus chronic

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(Roemer et al., 2009; Hunter et al., 2008). The most common bone marrow lesions include subchondral lesions related to osteoarthritis, osteochondral defects, and avascular necrosis (AVN)/primary osteonecrosis. These subtypes can be further categorized by their unique clinical and imaging characteristics (Table 1). Other less common BML subtypes include post-surgical, subchondral bone erosion, transient osteoporosis, osteochondritis dissecans, red marrow, tumor and malignant infiltration (Munsch et al., 2021; Roemer et al., 2009; Kon et al., 2016; Gobbi et al., 2021).

Subchondral bone is complex and has a rich arteriovenous network that permeates the entire layer up to the calcified cartilage (Imhof et al., Jun 1999). When the subchondral bone is stressed with higher loads, it responds by increasing the blood supply (Lane et al., Aug 1977). While subchondral bone pain mechanisms are still being elucidated, one proposed etiology of pain in bone marrow lesions is that repetitive microtrauma may impair venous drainage, causing increased intraosseous pressure (Arnoldi et al., 1980). Given that bone and bone marrow have rich concentrations of nociceptive pain fibers, this increased pressure may give rise to increase in hyperalgesia. This mechanism has been demonstrated to reduce pain by mechanically reducing intraosseous pressure through bone fenestrations in patients (Dey et al., 1989). Another mechanism that contributes to an increase in nociceptive pain is the replacement of normal fatty bone marrow with fibrovascular tissue, driving an increase in nerve growth factor expression and unmyelinated sensory nerves growth into the non-calcified articular cartilage (Walsh et al., 2010; Saltzman and Riboh, 2018).

Currently, there are no disease-modifying treatments for subchondral bone marrow lesions. Current standard of care treatments have included oral non-steroidal anti-inflammatory drugs, joint offloading with protected weight-bearing, pharmacologic treatment with prostacyclin and bisphosphonates, and surgical treatments such as core decompression, bone grafting with osteochondral restoration, and end-stage joint replacements (Munsch et al., 2021; Kon et al., 2016). More recently, emerging therapies have included autologous biologic therapeutics, in particular mesenchymal stem cells (MSCs) to maintain and improve cartilage health, and these have become a potential treatment option for BMLs given the unmet need for disease modification.

There are two major types of mesenchymal stem cells: pluripotent and adult. Pluripotent stem cells can undergo self-renewal and develop into mesenchymal, hematopoietic, or neural stem cells (Wobus and Boheler, 2005). There are two types of pluripotent stem cells: embryonic stem cells (derived from the inner cell mass of pre-implanted embryos) and induced pluripotent stem cells (cell reprogramming of adult somatic cells) (Romito and Cobellis, 2016). Adult mesenchymal stem cells are also self-renewing but are multipotent, and can develop only into the various cell types of the mesodermal lineage (i.e. bone, cartilage, muscle, fat, tendons/ligaments) (Caplan, 1994). MSCs can be isolated from different tissues, including adipose, bone marrow, synovium, and umbilical cord blood (Caplan, 2015). MSCs affect the healing response via activation of cell proliferation and differentiation, as well as decreased cell apoptosis and inflammation (Caplan and Dennis, 2006).

MSCs have been an area of therapeutic interest since their initial description by Friedenstein and colleagues in 1968 as multipotent progenitor cells with variable proliferative, differentiation, and immunoregulatory potential (Friedenstein et al., 1968). Emerging technologies in tissue engineering and regenerative medicine are highlighting the potential of MSCs as an effective treatment of damaged tissues. As such, MSCs have risen to the forefront of treatment for difficult musculoskeletal conditions such as BMLs. The scope of this review will focus on the application of MSCs obtained from adult bone marrow (BM-MSC), as well as adipose tissue (AD-MSC); clinically, these cells are gaining favor due to their availability for point-of-care use, ease of extraction, and favorable properties for isolation, expansion, and differentiation into chondrogenic and osteogenic lineages (Arinzeh, 2005). Given the need for more precise definitions to help standardize stem cell research, the International Society for Cellular Therapy (ISCT) published their position paper in 2006 establishing minimal criteria for defining multipotent mesenchymal stromal cells. At that time the following criteria were established: plastic adherence in standard culture conditions, expression of CD105, CD73, negativity for CD45, CD34, CD14, CD11b, CD19, HLA-DR, and trilineage differentiation potential in osteoblasts, adipocytes, and chondroblasts in vitro (Dominici et al., 2006). Since the publication of these criteria, there has been an increased focus in both pre-clinical and clinical research regarding the use of MSCs to treat and augment procedures relating to bone pathology, including BMLs found in osteoarthritis, osteochondral lesions, and avascular necrosis.

The first clinical application of MSCs in orthopedics was described in a case report by Hernigou and colleagues in 1997; a bone marrow allograft was used to treat osteonecrosis of the humeral head secondary to sickle cell disease (Hernigou et al., Nov 1997-a). After three months, the patient demonstrated reconstruction of the humeral head with normalization in the marrow signal, which remained stable during their four-year follow up. Since then, the safety of injecting MSCs for orthopedic conditions has been examined (Yubo et al., 2017; Hernigou et al., 2013; Centeno et al., 2016), as well as the role of MSCs in articular cartilage and subchondral bone repair (Madry et al., 2017; Orth et al., 2013), which we will discuss in more detail below.

The scope of this narrative review is to examine the applications of mesenchymal stem cells as potential disease-modifying therapies that result in reduced pain and improved function in bone marrow lesions. We will highlight in brief the pre-clinical works of MSCs as they directly apply to subchondral bone, osteochondral defects and avascular necrosis. We will further discuss more in depth the clinical evidence for MSCs in the treatment of BMLs related to three clinical disease states: osteoarthritis, osteochondral lesions, and avascular necrosis.

2. Pre-clinical evidence for the direct and regulatory effects of MSCs in bone healing

Early in vitro models by Kadiyala and Jaiswal demonstrated osteogenic differentiation of MSCs in vitro by manipulating culture conditions through the inclusion of dexamethasone, L-ascorbic acid-2-phosphate,

Table 1
Clinical characteristics of three common bone marrow lesions.

Diagnosis	Location	Clinical history	Typical appearance on MRI	Associated imaging findings	Prognosis
Subchondral osteoarthritis-associated BML	Subchondral anywhere in the joint, but commonly weight-bearing surfaces	Non-traumatic, degenerative, in patients >40 years old with cartilage lesions	Diffuse BML directly adjacent to cartilage lesion; will enhance after contrast (Fig. 1)	Other signs of OA (joint space narrowing, subchondral cysts, subchondral sclerosis, osteophytes)	Lesions can fluctuate in size
Osteochondral defect	Localized defect of articular cartilage and subchondral bone	May occur acutely or as a result of chronic conditions (osteochrondritis dissecans, collapse of subchondral bone, etc.)	Osteochondral lesion with surrounding BML (Fig. 2)	Effusion with possible osteochondral fragmentation or associated soft tissue injuries	Depends on stage of disease
Avascular necrosis/ primary osteonecrosis	Epiphyseal and metaphyseal	Non-traumatic, usually ages 40–50, may have risk factors (i.e. steroid use, alcohol abuse, underlying systemic disease, etc.)	Subchondral lesion of centrally preserved fatty marrow +/− peripheral rim sign (Fig. 3)	Peripheral rim will enhance after contrast administration. +/− focal flattening of subchondral bone and underlying cartilage	Depends on size of lesion and if there is articular collapse

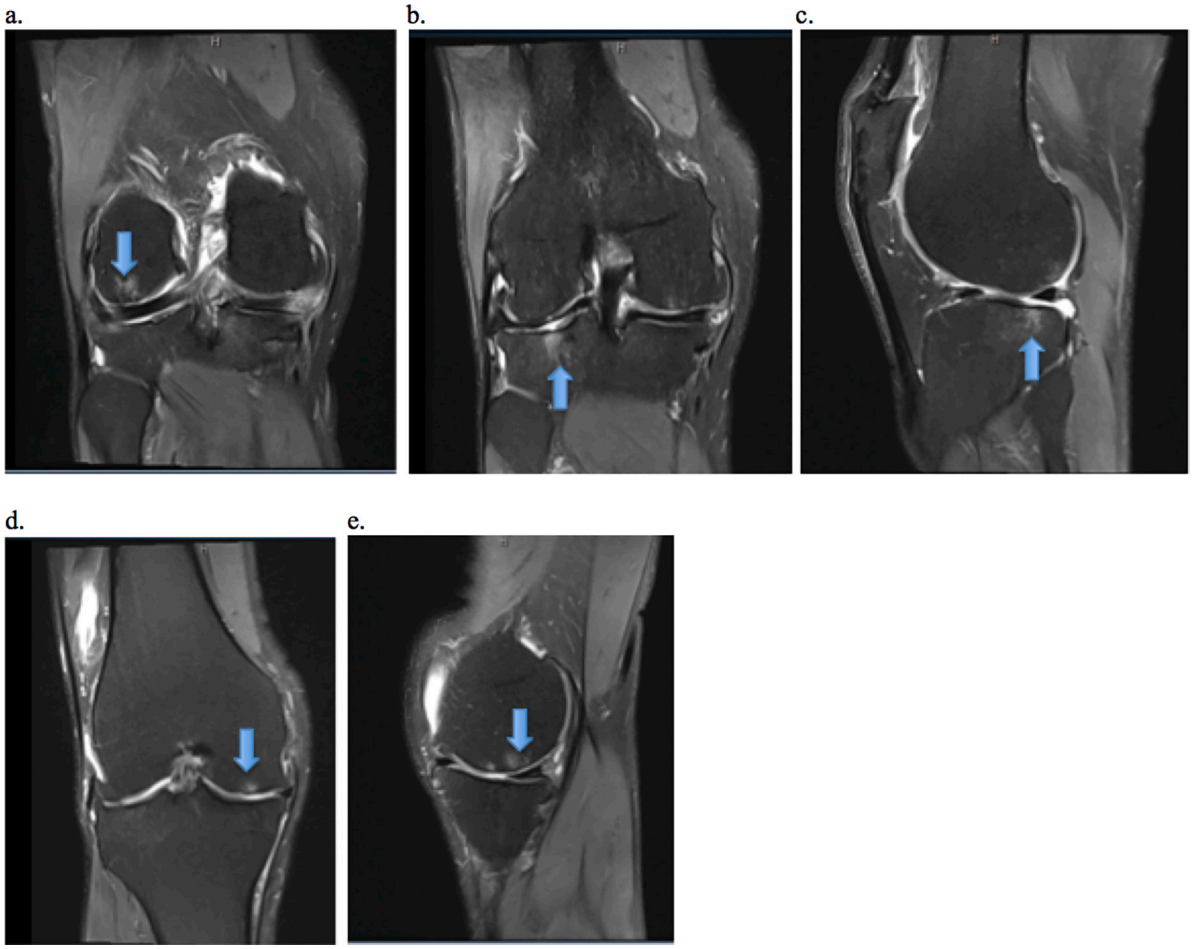

Fig. 1. Typical MRI appearance of subchondral osteoarthritis-associated BML in the knee: (a-c) Coronal and sagittal PD FS images showing diffuse cartilage thinning of the lateral compartment with focal full-thickness chondral defects along the weightbearing femoral condyle and tibial plateau with underlying reactive signal change in the subchondral bone (arrows); (d-e) Coronal and sagittal PD FS images showing diffuse cartilage thinning of the medial compartment with scattered focal full-thickness chondral defects along the weightbearing femoral condyle with underlying reactive signal change in the subchondral bone (arrows).

and Beta-glycerophosphate. By doing so, they found consistent differentiation though morphologic analysis, mineralization of the extracellular matrix, and expression of osteogenic markers such as alkaline phosphatase and osteocalcin (Jaiswal et al., 1997; Kadiyala et al., 1997a). Subsequent in vivo fracture models demonstrated osteogenic differentiation with effective bone and cartilage formation, as well as evidence of neovascularization in both rat and larger animal canine models when loading BM-MSCs on implanted scaffolds (Kadiyala et al., 1997a; Kadiyala et al., 1997b).

Following these initial models, a more nuanced understanding has developed of the complex pathways leading to osteogenic differentiation of MSCs and subsequent bone repair (Shibli et al., 2022). Important signaling pathways include BMP, TGF-β, Ca^{2+}, FGF, IGF, PDGF/VEGF, and Notch (Hayrapetyan et al., 2015). BMP/TGF-β signaling contributes to many cellular processes involving osteogenesis, and disruption of this signaling is implicated in the development of osteoarthritis. While Ca^{2+} signaling and the wnt pathways are vital for osteoblast differentiation, FGF and IGF also play an important role. Cytokines/growth factors such as TGF-β, FGF, IGF, and PDGF are involved in osteoblast activity and bone formation, whereas Notch signaling prevents osteoclast precursors from differentiating into mature osteoclasts. Currently in the United States, the FDA restricts use of cells exceeding minimal manipulation leading to alteration of relevant characteristics of the tissue relating to the utility for reconstruction, repair or replacement, or processing that alters relevant biologic characteristics, pre-clinical work continues to expand our understanding of the mechanisms at play leading to the potential therapeutic effects of MSCs (Manchikanti et al., 2020; Food and Drug Administration and Department of Health and Human Services, 2020).

Additionally, there is increasing interest in the paracrine function of MSCs (Doorn et al., 2012). MSCs have been found to regulate osteogenesis and osteoclastogenesis via various cytokines and growth factors (Fernández Vallone et al., 2013). PDGF, IGF, TGF-β, IL-17, RANKL and others act as migration factors when they are released at injured tissue and help to attract MSC movement toward the damaged microenvironment (Yagi et al., 2010). VCAM-1, MMP-2, and β-1/α-4 integrins help circulating MSCs with migration as well as adherence to the vascular endothelium. MSCs themselves also secrete various growth factors and cytokines such as IL-6, IL-11, LIF, and M-CSF that influence the differentiation of hematopoietic stem cells (Kim et al., 2005). These effects have been best demonstrated by a study by Zhang and colleagues in which femoral defects were induced in a mouse model with subsequent intramuscular injection of AD-MSCs transduced with bFGF adjacent to the fracture site. In comparison to controls, improved bone healing was observed in the bFGF group; however, only a small fraction of AD-MSCs remained in the healing callus at 21 days, suggesting a mechanism of bone healing driven by paracrine function rather than direct cell replacement (Zhang et al., 2017).

3. Pre-clinical evidence for MSCs in treatment of bone marrow lesions

3.1. Subchondral (cortical and trabecular) bone

Treatment of subchondral bone in weight-bearing joints is challenging given limited physiologic remodeling at sites of persistent joint loading, thereby leading to increased stress and impaired healing. As such, BMLs can be significant sources of pain, dysfunction, and progressive damage leading to joint collapse and potential need for joint arthroplasty in the end-stages of disease. As further mechanisms of BML are elucidated, the interactions between subchondral cortical and trabecular bone, and the cartilage interface are increasingly investigated as therapeutic targets. Additionally, there is interest in intervening at the early stages to prevent disease progression (Goldring and Goldring, 2016) through interventions such as subchondroplasty (SCP) and MSC treatments (Zhu et al., 2020).

In its original development, SCP is a surgical technique utilizing bioactive materials such as calcium phosphate as bone substitute materials (BSMs). BSMs can be injected into the subchondral bone to provide a scaffold for local bone remodeling and stabilization of the local bone environment. To improve the efficacy of this procedure, recent studies have investigated the use of biologics in augmenting SCP in post-traumatic subchondral bone marrow lesions. In a canine model, Oliver and colleagues compared SCP alone vs SCP with PRP and BMAC. At six months they found an improved comfortable range of motion in the PRP and BMAC-treated canines compared to controls. At one year post-treatment, the percentage of total pressure index was higher in treated groups, with improvements in pain range of motion seen in the PRP and BMAC groups compared to control. Interestingly, no statistically significant differences in arthroscopic or histological pathology were noted further highlighting the discordance between functional and structural endpoints (Oliver et al., 04 2020).

Yu and colleagues explored the use of injectable hydrogel along with AD-MSCs genetically modified to overexpress TGF-β1 in a surgically-induced rat osteoarthritis model. The hydrogel with properties similar to native extracellular matrix was associated with a favorable micro-environment for cell proliferation when injected intraarticularly into the rat knees. Furthermore, paracrine effects from TGF-β1 were observed to decrease expression of pro-inflammatory TNF-α leading to reductions in cartilage degeneration, joint inflammation, and subchondral bone loss (Yu et al., 2021).

3.2. Osteochondral defects

Osteochondral defects involve disruption of both the chondral surface and underlying subchondral bone. To address the challenges of osteochondral defect repair, there has been much attention to the role of surgically implanted scaffolds in optimizing the environment for implanted MSCs. This is an active area of research spanning from pre-conditioning, genetic modification, and increasing interest in various bioactive scaffolds to enhance cell survival, engraftment, and osteogenic potential of MSCs (García-Sánchez et al., 2019). Advancements in 3D bioprinting technologies have led to the creation of a BM-MSC-laden 3D–printed multilayer bioactive scaffolds for osteochondral defect repair. In comparison to 2D scaffolds, 3D scaffolds demonstrate higher metabolic activity of MSCs with an associated decrease in bone resorption (Spreda et al., 2021). BM-MSCs in such scaffolds in vitro create a favorable environment resulting in greater formation of cartilage-specific extracellular matrix, while in vivo studies in rat models found improved chondrogenesis and function in treatment of osteochondral defects at the femoral trochlea by promoting collagen II and suppressing IL-1β (Liu et al., 12 2021). Recent in vitro models of bone remodeling and regeneration have recognized the natural homeostasis occurring in bone remodeling between osteoblasts and osteoclasts. This has led to investigations of the role co-cultured scaffolds combining both osteoblasts and osteoclasts to more closely replicate the dynamic remodeling process that occurs in vivo (Borciani et al., 05 2020).

Xu and colleagues utilized an ultra-purified alginate gel containing BM-MSCs (UPAL-BMAC) in the treatment of osteochondral defects in a rabbit model. Defects treated with UPAL-BMAC demonstrated favorable histological qualities as seen in hyaline cartilage with well-structured collagen formation and increased bone volume, as well as improved mechanical function compared to control groups (Xu et al., 2021). In a rabbit model with surgically induced osteochondral defects of the knee, a hyaluronic acid (HA)-based scaffold was applied to the defect area with microfractures. The experimental group also received adipose-derived stromal vascular fraction (SVF) injected intraarticularly at the knee. Near complete filling of the defect area with hyaline cartilage was observed in the experimental group at 8 weeks (Şahin et al., 2021).

Although there is encouraging data, the utilization of MSCs in osteochondral defects is an ongoing area of investigation and biochemical changes do not always correlate with improved functional outcomes. In a sheep model of large condylar osteochondral defects, Tamaddon and colleagues implanted concentrated BM-MSCs with a collagen/hydroxyapatite scaffold. At six months, there were no differences between groups in bone regrowth, mineral density, or functional weightbearing despite an upregulation in type-I and type-II collagens in the BM-MSC group (Tamaddon et al., Oct 2021).

Given the ease of administration, there is interest in the utility of injection-based therapies for osteochondral defects compared to traditional surgical approaches. Zhang and colleagues investigated the efficacy of human MSC exosomes for the repair of osteochondral defects in a micropig model (Zhang et al., 2022). Bilateral osteochondral defects were surgically induced at the medial femoral condyle. MSC exosomes and HA or HA alone were injected intraarticularly after surgery at 8 and 15 days. Exosomes + HA treated defects demonstrated improved MRI scores compared to HA-treated defects at 15 days, 2 and 4 months. Additionally, defects treated with exosome + HA had improved histologic and biomechanical properties at 4 months with micro-CT evidence of higher bone volume and increased trabecular thickness in subchondral bone.

3.3. Avascular necrosis/primary osteonecrosis

The underlying pathology of avascular necrosis is complex; however, it has been shown that increased apoptosis of osteocytes, lipid accumulation in osteoblasts and osteocytes lead to deficient bone repair, thus negatively affecting the osteoblastic differentiation of native mesenchymal progenitor cells (Weinstein et al., Aug 2000; Yin et al., 2006). This disruption in the resorptive component of bone repair leads to structural instability and subchondral fracture (Shah et al., Sep 2015). This alteration in the bone microenvironment is attributed to vascular disruption with resulting ischemia leading to the severely hypoxic nature of osteonecrotic bone (Ciapetti et al., 2016). Implantation of MSCs to necrotic bone in AVN has been observed to increase the number of osteoblasts, capillary formation, as well as improve expression of VEGF and BMP-2 (Song et al., 2015). Further supporting the role of angiogenesis, Müeller and colleagues cultured human MSCs in vitro. When cultured in low-oxygen tensions, decreased proliferation and osteogenic differentiation was noted; however, significant secretion of VEGF was seen in the presence of interferon-gamma (Müller et al., 2008).

Other notable cellular changes in AVN include increased adipogenesis of MSCs (Gillet et al., 2017). In this environment, protective mechanisms against lipotoxicity such as stearyl-coenzyme A desaturase 1 and carnitine palmitoyl transferase are dysregulated, leading to a pro-inflammatory environment. Looking particularly at the Wnt pathway, Huang and colleagues found higher MSC expression of GSK3β in stem cells in osteonecrosis of the femoral head, with resulting downregulation of the Wnt signaling pathway, including Runx2 and β-catenin, leading to reduced osteogenic differentiation (Huang et al., 2018).

These characteristics have made MSCs an intriguing therapeutic

option for treatment of AVN, both on their own, and as a modality to augment procedures such as core decompression. In a canine model of osteonecrosis, Yan and colleagues transplanted autologous MSCs after decompression of the femoral head and tracked them utilizing green fluorescent protein (GFP). GFP-positive cells were found in the necrotic area up to 12 weeks after transplantation and demonstrated proliferation from 15 % at week 2 to 38 % at week 12. Furthermore, a statistically significant improvement in trabecular bone volume was noted at 8 and 12 weeks compared to saline controls (Yan et al., 2009). In a rabbit model utilizing allogeneic peripheral blood derived MSCs, cells were transplanted locally into osteonecrotic areas of the femoral head with an observed increase in bone density and trabeculation (Fu et al., 2016). Ciapetti and colleagues conducted an in vitro analysis of BM-MSCs from patients with AVN of the femoral head under hypoxic conditions (Ciapetti et al., 2016). They found enhanced proliferation and colony forming ability in hypoxia exposed MSCs. Additionally, increased expression of bone-related genes such as ALP, Type-I collagen, and osteocalcin was seen under hypoxic conditions, suggesting that MSCs can proliferate and differentiate in the hypoxic environment of AVN with appropriate pre-conditioning.

Following core-decompression in a canine model of osteonecrosis of the femoral head, Hang and colleagues implanted transgenic VEGF(165) BM-MSCs. A significant increase in newly generated capillaries were noted after treatment with VEGF(165) cells compared to normal BM-MSCs and core decompression alone. Additionally, improved trabeculation and organization of bony tissue was seen, reinforcing the important relationship between vascularization and osteogenesis in treatment of osteonecrosis (Hang et al., 2012). FGF-2 transfected BM-MSCs in a rabbit model of ONFH in vivo demonstrated >80 % repair at six weeks, and complete repair at 12-weeks following implantation. Compared to control groups, greater new bone formation and vascular density were observed (Zhang et al., 2018). In vitro studies of rabbit BM-MSCs found enhanced activity and inhibition of apoptosis in co-cultured osteoblasts. When co-cultured, cells demonstrated greater concentrations of VEGF and BMP-2. Furthermore, in vivo treatment of a rabbit osteonecrosis of the femoral head with BM-MSCs demonstrated improved osteoblast concentrations and vascularization, as well as increased expression of VEGF and BMP-2 resulting in improved capillary formation (Song et al., 2015).

An alternative delivery strategy was investigated in a rabbit model of osteonecrosis of the femoral head. Wen and colleagues utilized a fibrin glue with hepatocyte growth factor (HGF) transduced BM-MSCs. In vitro fibrin glue did not alter the molecular activity of MSCs. In vivo the femoral heads of rabbits with MSCs implanted with fibrin glue were found to have greater MSC concentrations at 8 weeks and prolonged gradual release of HGF with improved proliferation and osteogenesis (Wen et al., 2014).

Additionally, a potential role for intra-osseous injections was explored by Lebouvier and colleagues. In a pig model, BM-MSCs were injected directly into the pig femoral head and detected by quantitative real-time polymerase chain reaction, cytometry, or combination of histologic analysis and in situ hybridization. At 30 min and 24 h, the grafted cells were detected in isolation at the injection site. Initial bone healing was observed as early as two weeks, with complete healing at nine weeks with MRI, and histological analysis similar to that of normal femoral head morphology (Lebouvier et al., 2015).

4. Clinical evidence for MSCs in the treatment of bone marrow lesions

4.1. Osteoarthritis

The role of MSCs in osteoarthritis (OA) has expanded over the previous 10 years with emerging clinical evidence regarding its efficacy and safety. Treatment options vary from intra-articular (IA) injections to intra-osseous (IO) subchondral injections directly addressing the bone marrow or chondral lesion. Most of the evidence to date lies within prospective case series and clinical trials for intra-articular injections that involve three primary types of MSC interventions: bone marrow aspirate concentrate (BMAC), microfragmented adipose tissue (MFAT), and stromal vascular fraction (SVF). Intra-articular treatments are readily integrated in outpatient care, performed under local anesthesia with precision-guided ultrasound utility and minimal patient discomfort. These IA injections allow placement of autologous MSCs that allow for the modulation of a wide range of trophic factors that can inhibit inflammatory pathways, apoptosis, and oxidative stress. These trophic factors also play a part in mobilizing MSCs from the synovium to promote cell proliferation (Hernigou et al., 2021; Zhang et al., 2019). We will further delineate the various tissue specific autologous MSC's in clinical trials.

4.1.1. Bone marrow aspirate concentrate (BMAC)

Several randomized clinical trials have investigated the use of IA-BMAC (Table 2). Centeno and colleagues randomized 48 patients with Kellgren-Lawrence (KL) grades 2 or 3 knee osteoarthritis to receive either BMAC or an exercise therapy protocol. At three months, pain and function significantly improved within the BMAC group compared to the exercise therapy group, and all patients within the exercise group crossed over to receive BMAC. The clinical improvement continued two years after the initial treatment (Centeno et al., 2018). Another study investigated 111 patients with KL 2–4 knee osteoarthritis randomized to BMAC, hyaluronic acid (HA), or leukocyte-rich platelet rich plasma (LR-PRP). Within the first 21 days, BMAC had the highest improvement in pain and function measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), Knee Injury and Osteoarthritis Outcome Score (KOOS), and International Knee Documentation Committee (IKDC). Although all groups improved over 12 months, the highest statistically significant improvement was seen in the BMAC group, with no difference found between hyaluronic acid and LR-PRP (Dulic et al., 2021). The efficacy of BMAC over hyaluronic acid is further supported in a single blinded randomized pilot trial studying 32 patients with knee OA. Significant improvement in the KOOS for the BMAC group peaked at 12 months versus 6 months in the HA group; however, there was no significant difference between the two groups at 12 months (Ruane et al., 2021). These trials encompassed a total of 176 patients treated with BMAC and the results suggest that BMAC is an effective treatment option for knee OA with or without bone marrow lesions.

It should be noted that despite the clinical success of these above studies, three randomized clinical trials demonstrated no significant difference between BMAC and other treatment modalities in patients with bilateral knee OA. Shapiro and colleagues randomized 25 patients to receive a single injection of BMAC in one knee and a single injection of saline in the other. Both groups had a similar decrease in pain without a significant difference seen between the two (Shapiro et al., Oct 2019). Another trial investigated IA PRP versus BMAC in 86 patients and demonstrated no difference in WOMAC or IKDC between either treatment group at all time points up to 12 months (Anz et al., 2020). Boffa and colleagues compared BMAC to HA in 56 patients and claimed no significant clinical superiority between groups, finding similar clinical scores, failures, adverse events, and minimal clinically important difference (Boffa et al., 2021).

While the safety profile of autologous BMAC is apparent in the above studies, there is lack in standardization of BMAC therapy resulting in conflicting outcomes between studies. For example, in Boffa's study, extracted bone marrow from the proximal tibial metaphysis may have led to decreased cell count and reduced efficacy of treatment. It has been established that the optimum location to isolate stem cells is from the iliac crest, as there exists a higher number of MSCs in this location compared to the tibia and femur (Davies et al., 2017). Anz and Boffa used a larger 30 mL syringe for aspiration; aspirations obtained from smaller 10 mL syringes have greater concentration of MSCs and

Table 2
Clinical randomized trials examining intra-articular BMAC in knee OA.

Author	Primary intervention	Comparator	Study Design	Harvest site	N	Age	Follow-up (mos)	Adverse events	Conclusion
Centeno et al. 2018	BMAC + platelet products	Exercise therapy	Unblinded RCT	PSIS	26/22	54/57	24	1 (persistent popliteal fossa fluid)	BMAC + platelet products cohort had significantly improved pain and function compared to exercise therapy cohort in moderate-severe OA
Shapiro et al. 2019	BMAC	Saline in contralateral knee	Blinded RCT	PSIS	25	60	12	None	Both groups had a significant improvement in pain and quality of life, with no difference between cohorts in patients with bilateral knee OA
Anz et al. 2020	BMAC	Leukocyte-rich PRP	Unblinded RCT	PSIS	45/41	54.1/55.8	12	None	Both groups had a significant improvement in pain and function, with no difference between cohorts in patients with mild-moderate knee OA
Boffa et al. 2021	BMAC	Hyaluronic acid in contralateral knee	Double-blinded RCT	Tibia	56	57.8	24	None	Compared to HA, BMAC showed a significantly higher improvement in pain and function at longer timepoints and in knees with mild OA.
Dulic et al. 2021	BMAC	PRP or hyaluronic acid	RCT	Tibia	111/34/30	56.9/59.4/58.8	12	None	All groups significantly improved in pain and function after 21 days and long-term, but BMAC group was significantly more improved compared to HA/PRP at all time points in moderate-severe knee OA.
Ruane et al. 2021	BMAC then PRP	Hyaluronic acid (Gel-One)	Single-blinded RCT	Posterior iliac crest	17/15	58.1/58.6	12	None	Both groups had a significant improvement in function with no difference between cohorts. The BMAC cohort had significantly decreased long-term pain compared to HA in knee OA.

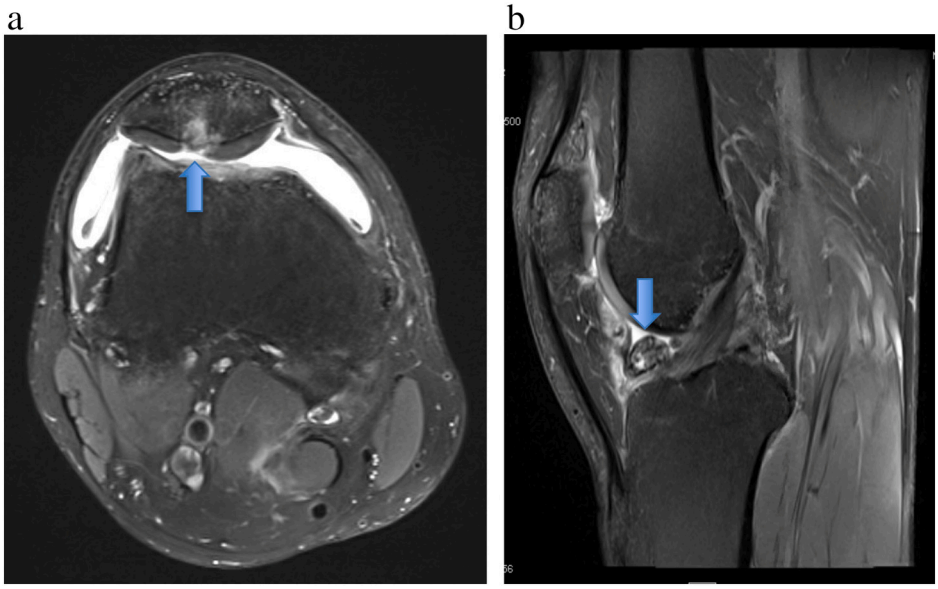

Fig. 2. Typical MRI appearance of an osteochondral defect in the knee: (a) Axial PD FS image showing osteochondral injury of the patella with 6.5 mm full-thickness chondral defect (arrow) and underlying marrow edema; (b) Sagittal PD FS image redemonstrating the chondral defect with associated intra-articular loose body (arrow).

progenitor cells than when taken from larger syringes (Hernigou et al., Nov 2013-b). Both studies also extracted cells from a single site. There is debate within the literature as to if extraction from multiple sites provides a higher number of MSCs with Oliver and colleagues reporting similar outcomes (Oliver et al., 2017), but Peters and Watts noting that multiple insertions (up to four) result in a higher volume and concentration of BMAC components (Peters and Watts, 2016). Finally, and most importantly, cell count and molecular characterization should always be reported and analyzed for all patients. Although the optimal cell count, composition, and dosage are not yet known, a larger cell count (>4 × 10^8 nucleated cells) has been shown to have a greater clinical effect than a low count (Centeno et al., 2015). Boffa and colleagues did not mention cell count; Anz and colleagues only analyzed the cellular components of four patients, which is below the minimal reporting of biologics studies (Murray et al., 2017). Shapiro and colleagues did analyze cell counts on each patient, but the study was designed for establishing safety; therefore, only 25 patients (50 knees) were investigated, which would not be enough to establish therapeutic efficacy. Within those 25 patients who received BMAC, there was a high variability of MSCs, which may alter the efficacy of the treatment.

Despite these study flaws, trials that suggest no significant improvement between treatments are important to consider given that the average cost of bone marrow in the US is $3000 versus the average cost of PRP is $714, and hyaluronic acid is covered by most insurance

companies (Anz et al., 2020; Piuzzi et al., Sep 2019). Cost alone warrants further trials to further determine the efficacy of MSCs and proper patient selection.

4.1.2. Microfragmented adipose tissue (MFAT)

There are few high quality investigations examining the efficacy of MFAT, however no double blind randomized placebo control trials. In an observational prospective study of 110 patients with knee osteoarthritis, there was a statistically and clinically significant improvement in Visual Analog Scale (VAS) and Oxford Knee Score (OKS) 12 months after treatment (Heidari et al., 2020). In a case series of 220 patients, there was a statistically significant improvement in the quality of life at 24 months in patients who were deemed suitable for knee replacement (Heidari et al., 2021).

A similar time of efficacy was observed in a multi-centric international open label study of 75 elderly patients (120 knees) with KL2–4 OA. At 24 months, 88.3 % of patients had functional and quality of life improvement measured by the KOOS at all time points (Gobbi et al., May 2021). Efficacy was further supported in the largest cohort to date which showed clinical and functional response at 24 months in a total of 456 patients (Borg et al., 2021). Interestingly, the study demonstrated that 90 % of women responded to the treatment versus only 60 % of men, while 64 % of women had a >20-point drop in VAS compared to only 40 % of men. The discrepancy in outcomes based on gender opens the question as to who the ideal candidate is for each procedure and what factors influence outcomes. This question paired with the difficult decision in discerning the optimal MSC treatment remains a primary challenge.

Only one retrospective comparative study looked at outcomes for BMAC versus MFAT in knee osteoarthritis. In this retrospective review of prospectively collected data, Mautner and colleagues concluded no difference in pain and function between groups, both providing improvement at 1.9 and 1.08 years, respectively (Mautner et al., Nov 2019). Overall, treatment results with MFAT have a high percentage of success totaling over 900 knees treated in the literature up to now, supporting its potential for further use. The lack of comparison and randomized clinical trials highlight a further need for research within this area before making treatment recommendations and guidelines.

4.1.3. Stromal vascular fraction (SVF)

SVF is an alternative treatment measure that involves the enzymatic digestion and culture expansion of adipose derived tissue. This method is not currently approved within the United States as it is considered by the FDA to be more than minimally manipulated tissue. Trials can be conducted with proper approval using an investigational new drug protocol, and the use is still implemented internationally. Still, there are few randomized clinical trials to date that support its use.

In a small, prospective double-blinded randomized-controlled trial examining the effect of high-dose SVF, low-dose SVF, or placebo intra-articular knee injections for 39 patients with painful knee OA, both SVF groups had significantly improved WOMAC scores at one year compared to placebo (Garza et al., 2020). In a small randomized trial of 16 patients with bilateral knee osteoarthritis, Hong and colleagues compared arthroscopic debridement with either SVF or hyaluronic acid. At 12 months, the SVF-treated knees showed significant improvement in VAS, WOMAC, and range of motion compared to the HA-treated group. The SVF group also demonstrated improvement of the articular cartilage as judged by the Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) scoring system (Hong et al., 2019). In one of the only trials comparing different biologics, 89 patients with knee osteoarthritis were treated with either intra-articular PRP, BMAC, or adipose-derived MSC (SVF) (Estrada et al., 2020). Those with stage I OA received PRP, stage II received BMAC, and stage III received SVF. All groups demonstrated similar statistically significant improvement in knee function up to one year. It is important to acknowledge the limitations of this study as each group treated a different degree of pathology with different biologics.

Beyond these clinical trials, there exists a paucity of literature on SVF. Several case series demonstrate positive outcomes (Gibbs et al., 2015; Koh et al., Apr 2013; Nguyen et al., Jan 2017; Pintat et al., Dec 2017), but the effects are difficult to discern given the heterogeneity of treatments, and inclusion of other confounding factors such as single or multiple injections of PRP, hyaluronic acid or other surgical treatments. In addition, not all of these series have included quantification of cell count, growth factors, cytokines, and molecular analysis of treatments. These details are necessary in further evaluating efficacy to determine optimal dosage, effect, and cellular contents.

4.2. Osteochondral defects

4.2.1. Percutaneous treatments

Few studies have investigated the use of subchondral injections for osteochondral lesions. One unblinded trial examining patients with both primary and secondary OA investigated a single subchondral injection of BMAC in one knee and compared to the contralateral knee that received a total knee arthroplasty rather than any injection treatments (Hernigou et al., Nov 2018-c). At 12 years follow up, 3 % of knees that received cell therapy progressed to surgery vs 20 % in the TKA group that required subsequent surgical intervention or revision. Clinical and functional outcomes improved similarly in both groups. Those that received the cellular based treatment demonstrated an increased percentage of cartilage volume measured with MRI compared to baseline, and a regression of the bone marrow lesion over 5 years.

Another trial investigating an elder population with bilateral knee OA treated one knee with a subchondral injection of BMAC and the other knee with a single intra-articular injection of BMAC (Hernigou et al., Feb 2021). At 15 years, the yearly arthroplasty incidence was significantly lower in the subchondral cell therapy group compared to the intra-articular group. In another pilot study, patients with knee OA received both an IA and two subchondral injections of BMAC into the femoral condyle and tibial plateau; this resulted in clinical improvement at 3, 6, and 12 months as measured by the IKDC, KOOS, and VAS with objective MRI evidence of reduction in bone marrow edema (Kon et al., Dec 2021). The conclusions warrant larger multicenter placebo-controlled trials.

Only one study concluded equivocal outcomes of subchondral BMAC for knee osteoarthritis; in a non-randomized prospective study, patients underwent either an IA knee injection with BMAC and PRP or an intra-osseous and IA injection with BMAC and PRP for the treatment of advanced knee osteoarthritis (Centeno et al., May 2021). Although both treatment groups improved, there was no difference between the two at 24 months. Notable limitations of the study were the small sample size, inability to control for multiple injections, having multiple providers perform the procedure, and variable sizes of the bone marrow lesion.

There have been surgical techniques described in the treatment of pediatric osteochondritis dessicans lesions, utilizing retrograde drilling/decompression and intraosseous injection of BMAC, but no clinical trials or comparative studies (Andelman et al., 2020).

4.2.2. Surgical treatments – scaffold base

Multiple surgical options exist for the treatment of osteochondral bone marrow lesions. These include marrow stimulation techniques, fixation procedures, transplantation grafts and cell-based procedures, which require a two-step procedure, such as autologous chondrocyte implantation (ACI). Marrow stimulation procedures such as microfracture have the most historical data, in addition to fixation techniques where the OCD is preserved or fixated with pins or screws. Autograft and allograft osteochondral grafts have gained the most clinical traction over recent years (Fig. 4). The implementation of MSC-based treatment into surgical practice has challenged these traditional methods. More research has developed using MSCs combined with a bioscaffold for management of BMLs with successful results. Seeding a bio-scaffold with

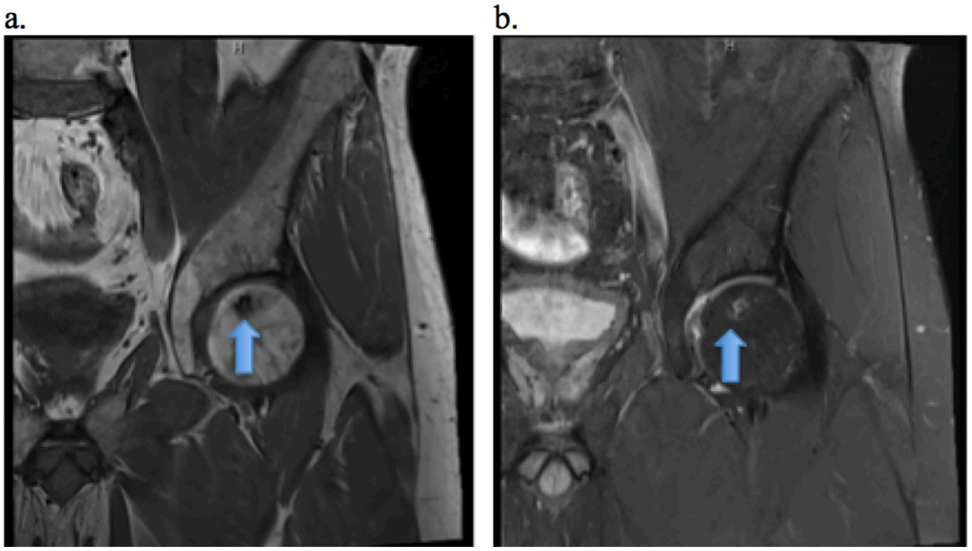

Fig. 3. Typical MRI appearance of avascular necrosis in the hip: (a) T1 coronal image showing a focal area of T1 hypointensity (arrow) within the superior aspect of the femoral head measuring 8 × 8 mm with <25 % involvement of the femoral head and the overlying chondral surface is intact without fragmentation or collapse; (b) T2 coronal image redemonstrating the focal area as T2 hyperintense signal (arrow).

MSCs and progenitor cells must be compatible with the local tissue and provide an environment that would promote cellular differentiation. Several scaffolds exist that have been studied in the literature to accomplish this including fibrin, collagen fibers (either hydrogel or sponge), and hyaluronic acid.

Gigante and colleagues published the first clinical study using BMAC with a scaffold for treatment of cartilage lesions of the knee (Gigante et al., 2010). In this small study of five patients with mean lesion size of 3.7 cm^2, the affected knee underwent arthroscopic microfracture with implant of a type 1 collagen scaffold seeded with bone marrow

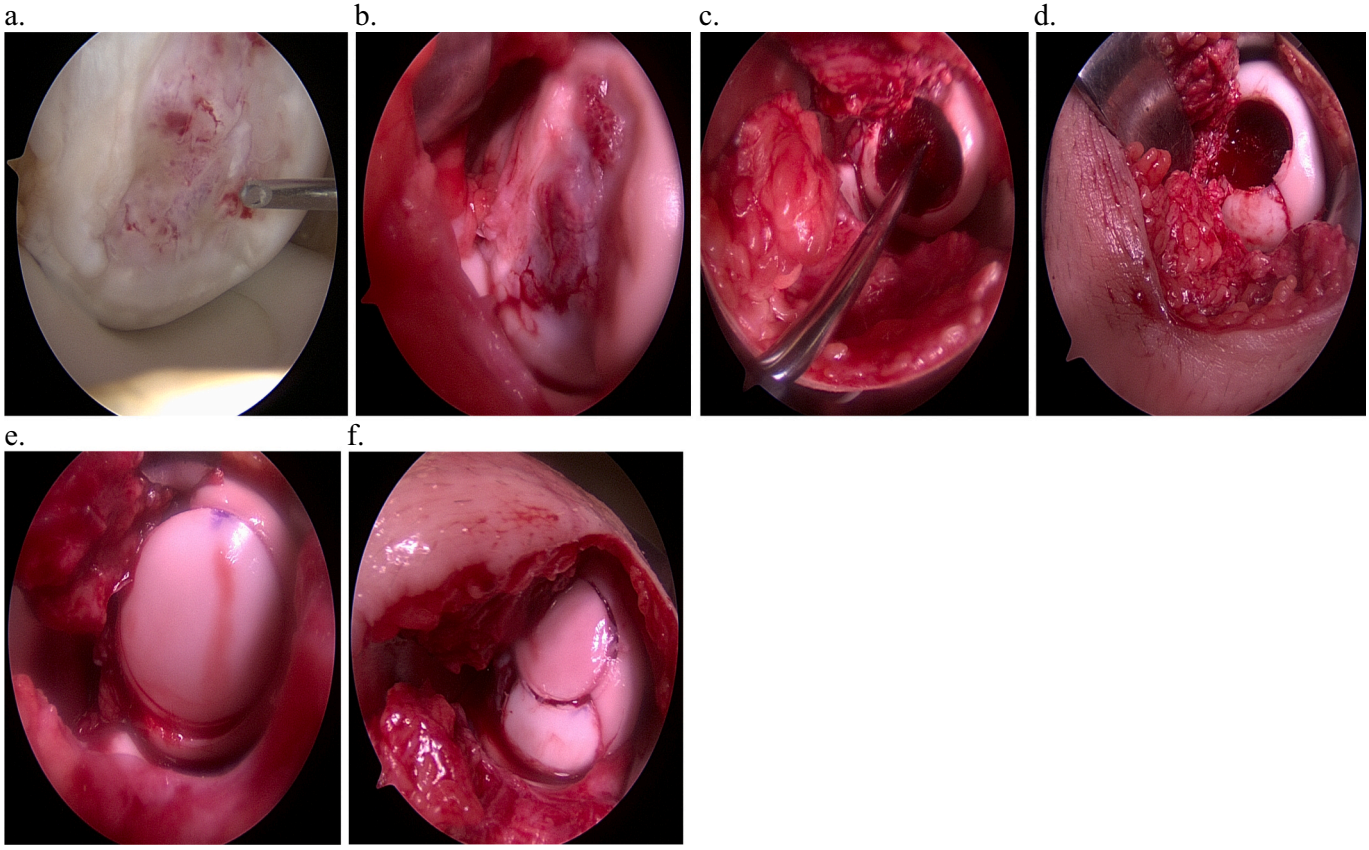

Fig. 4. Example of an osteochondral allograft transplantation, a technique that has gained traction in the United States as a standard of care, prior to any implementation of MSCs; (a-b) arthroscopic views of the femoral condyle showing an osteochondral defect measuring 34 × 20 mm; (c-d) arthroscopic image through the lateral viewing portal showing a cored-out site of the defect to prepare for recipient site where 2 plugs were necessary to fill in the defect; (e-f) final result after impaction of the donor graft.

concentrate. At 12 month follow up, clinical and histological data suggested that the procedure achieved a nearly normal arthroscopic appearance and satisfactory repair of damaged tissue.

Primary findings in a systematic review of 23 studies (13 human clinical) investigating BMAC in the treatment of focal chondral lesions of the knee found that chondral defect filling could be achieved with fibrocartilage or hyaline-like cartilage material (Cavinatto et al., 2019). The studies achieved good to excellent clinical results for both short- and long-term outcomes without any adverse events, but it should be noted that most of the research was low level evidence with several limitations. The systematic review included two prospective cohorts that compared different treatment options, ACI and microfracture. Gobbi and Whyte investigated 50 patients with grade IV chondral lesions of the knee treated either with HA-BMAC or microfracture. At two years follow up, 100 % of knees in the HA-BMAC were classified as normal or near normal on the IKDC, significantly greater than those in the microfracture group (Gobbi and Whyte, 2016). Of interest, age >45, increased size of lesion (>4 cm^2), and treatment of multiple lesions did not affect outcomes in the HA-BMAC group, but poorer outcomes were observed in the microfracture group. Another small study comparing HA-BMAC to matrix-induced chondrocyte implantation (MACI) for patellofemoral chondral defects found significant improvements in pain and function in both groups at 2 years, without a significant difference between the two treatments (Gobbi et al., 2015). The findings in this study are important given the higher cost and potential complications of a two-step MACI procedure.

These effects of MSC applications have been mirrored in osteochondral lesions of the talus (OLT), although limited quality studies exist. A systematic review of only four studies examining BMAC for OLT showed varying degrees of beneficial outcomes for the treatment of moderately sized defects (Chahla et al., 2016). Three of the four studies supported good cartilage defect filling as demonstrated by MRI, and most patients were able to return to athletic activity. BMAC in these studies was not used alone, but in conjunction with synthetic scaffolds, OAT, or bone marrow stimulation (BMS). More recently, Vannini and colleagues reported on 56 patients that underwent a one-step procedure of BMAC-seeded in situ on a scaffold for OLT, where there was statistically significant improvement in pain and function at 10 years post treatment (Vannini et al., 2021); however, 33 % of subjects were considered failures to treatment.

Overall, surgical management with scaffolds and MSCs have shown successful results both clinically and radiographically in osteochondral lesions of the knee and talus. It should be considered as a viable treatment option with other procedures such as autograft and allograft OATs procedures, MACI, and microfracture, but further higher-level clinical trials are necessary to standardize its applications and indication of use.

4.2.3. Surgical treatments – subchondroplasty

Subchondroplasty is an alternative option for BMLs that has increased in its use over the previous decade. Subchondroplasty involves the injection of calcium phosphate into the trabeculae of cancellous bone within the subchondral region of the joint, which fills in the trabecular space of a bone marrow lesion providing a scaffold for osseous remodeling. A recent systematic review identified 17 studies with 756 patients that have investigated subchondroplasty as a treatment for BML (Nairn et al., Nov 2021). Of the 17 studies, 13 involved the knee versus 4 of the ankle. All but one of the studies were level IV evidence. The results demonstrated significant clinical and functional success measured by the VAS, IKDC, and KOOS with median time for follow up at 12 months, with low rates of conversion to knee arthroplasty. There were seven complications (incidence 0.009 %), some of which were serious including avascular necrosis, osteomyelitis, and deep vein thrombosis. Only one clinical study to date has augmented subchondroplasty with MSCs; 11 patients with symptomatic osteochondral defect of the talus (average defect size 1.3 cm × 1.4 cm) underwent subchondroplasty with BMAC in a retrospective review, and experienced statistically significant decreased pain with weight-bearing and increased function (Chan et al., 2018).

The literature for subchondroplasty continues to evolve, but long-term outcomes are needed to continue to evaluate its success and whether MSCs can provide a superior outcome. However, it remains an alternative treatment to potentially delay total knee arthroplasty.

4.3. Avascular necrosis/primary osteonecrosis

The standard of care for AVN in the femoral head is total hip arthroplasty (THA). Although hip arthroplasty has a high success rate in the general population, survival of the prosthesis can be of concern in AVN, given that the condition can affect younger and middle-aged individuals. It therefore becomes critical to recognize AVN in its early stages to halt progression to THA. With early recognition, procedures such as core decompression can be a successful treatment (Jindal et al., 2021). Core decompression (CD) works by providing a channel within the femoral head and neck for neovascularization to occur. Success rates have been described as up to 84 % for stage I, 63 % for stage II, and 29 % for stage III AVN (Castro and Barrack, 2000). Recently, MSCs have been added to core decompression to improve those success rates. In AVN, it is hypothesized that the femoral head is devoid of progenitor cells and by adding MSCs in the necrotic area, the healing potential is enhanced (Pawar et al., Jan 2022).

This combination technique was first researched in 2002 in a prospective study examining functional outcomes and progression to THA over 10 years in patients with hip AVN (Hernigou and Beaujean, 2002). Of patients with stages I and II AVN, only 6 % progressed to THA, compared to patients with stages III and IV, where 57 % required THA. Those with higher progenitor cell counts were found to have better outcomes. Similar long-term positive results were reported in a retrospective study investigating 10-year data on 44 patients with hip AVN who underwent core decompression with BMAC (Tomaru et al., 2019); they found that across all patients, 34 % required conversion to THA, but for patients with stages I and II, the number decreased to 14 %.

The low success rates in patients with stages III and IV AVN in these studies are consistent across the literature and post-collapse AVN remains difficult to treat. A retrospective review on 100 patients with hip AVN found that among collapsed cases of AVN, there was no difference in clinical failure rate for core decompression versus core decompression with BMAC (Kang et al., 2018). Another small study investigated CD with saline compared to CD with BMAC in patients with stage III AVN, and found no difference between THA requirements, clinical tests, or radiological evolution, and 65 % of these patients progressed to THA at 24-months follow up (Hauzeur et al., 2018). A systematic review and meta-analysis evaluating CD plus BMAC in the treatment of post collapse AVN of the hip found that 40 % of stage III cases worsened to stage IV after treatment, and approximately 30–40 % of stages III and IV hips eventually required THA over five years.

The consensus remains that the results for MSCs for stage III and IV AVN are inconclusive. Nonetheless, there has been some success with additional treatments combined with CD and BMAC; one study augmented core decompression with BMAC and PRP (Houdek et al., 2021). At 7 years follow up, the overall survivorship free of femoral head collapse leading to THA was 84 % and survivorship free from THA for all causes was 67 %; these rates increased to 96 % and 72 % for stages I and II.

It is unclear at this time if other methods of MSC extraction would provide different outcomes, and BMAC remains the predominant choice for MSC extraction in this patient population. Only one study used adipose-derived MSCs enzymatically digested to produce SVF cells in 17 patients, and 82 % did not require THA at 2 years (Yoon et al., 2021). This small study is in line with BMAC outcomes, but further studies are needed to confirm its success and determine the ideal cell count and patient selection for each group.

4.4. Clinical safety of MSCs

The overall safety of MSC treatments has been well established. A retrospective analysis examined a cohort of 1873 adult patients treated with autologous bone marrow-derived concentrated progenitor cells for various orthopedic conditions (Hernigou et al., 2013). They found that none of the patients developed cancer at the site of injection, and the rate of cancer diagnosed at other sites was less than the incidence in the general population over an average follow up of 12.5 years. Similar findings were demonstrated in a multi-center analysis of 2372 adult patients who underwent percutaneous autologous stem cell therapy for various orthopedic conditions examined overall safety and risk of neoplasm over a period of 2.2 years (Centeno et al., 2016). The study reported a total of 325 adverse events; most events were post-procedure pain (3.9 %) or pain secondary to progressive joint disease (3.8 %). Only seven cases reported neoplasm within that time, which was a lower rate than in the general population. Recently, a Delphi study examining the utility of BMAC applications practices to treat musculoskeletal diseases demonstrated consensus among experts in BMAC's safety profile (Centeno et al., 2021).

In a systematic review of minimally manipulated MSCs in the treatment of knee osteoarthritis, SVF resulted in zero serious adverse events (utilized in 13 articles) (Di Matteo et al., 2019). In an alternative review of 8 studies of knee OA, they described no complications reported with BMAC treatment (Keeling et al., 2021). Furthermore, no adverse events were reported in trials that utilized cellular therapy for intra-osseous injections (Hernigou et al., 2021; Hernigou et al., Nov 2018-c; Centeno et al., May 2021), and only few with core decompression similar to typical post-surgical complications (Hernigou and Beaujean, 2002).

5. Conclusion

The literature examining the use of MSCs in bone marrow lesions has dramatically increased over the past several decades; however, there are still translational gaps in its clinical applications. While the mechanism of MSC's application in BML is complex, there is robust data to support the strong paracrine function of MSCs in pathways of angiogenesis and inflammation (Doorn et al., 2012; Bouland et al., 2021). Another active area of research includes the use of bioactive scaffolds to optimize the environment for implanted MSCs by facilitating chondrogenesis and higher bone volumes, especially in osteochondral defects (García-Sánchez et al., 2019; Cavinatto et al., 2019); future preclinical and clinical studies should examine a head-to-head comparison of the various scaffolds including fibrin, collagen fibers, and hyaluronic acid.

We understand the patient population studied in the literature reflects the most commonly affected joints related to each pathology; however, one limitation we experienced is that the majority of clinical literature published on subchondral-associated BMLs in osteoarthritis and BMLs related to osteochondral defects focused mainly on the knee, with relatively few studies on the ankle and other joints. In contrast, the literature on avascular necrosis almost exclusively concentrates on the hip joint. Future research of treatment of bone marrow lesions should include patient populations with other affected joints.

In knee osteoarthritis, most of the evidence for MSCs thus far lies in case series and small, randomized trials. Overall, there were improvements in pain and functional outcomes when patients were treated with MSCs, and the results suggest that BM-MSCs can be a safe and effective treatment for patients with painful knee osteoarthritis with or without bone marrow lesions. In patients with hip avascular necrosis, those with earlier stage disease have improved outcomes (longer time to THA) when core decompression was augmented with BM-MSCs, whereas patients in later stages post-collapse have equivalent outcomes with or without MSC treatment. Given that an osteochondral defect is a morphologic finding and is found in several clinical conditions (both acute and chronic), there is a wide variety of treatment strategies that range from conservative to surgical (Gorbachova et al., 2018; Badekas et al., 2013; Howell et al., 2021). Preliminary data in smaller cohort studies examining MSCs in osteochondral defects suggest they can be beneficial as a subchondral injection alone, or as a surgical augmentation with a bioscaffold or subchondroplasty and should be considered as a viable treatment option with other procedures such as OAT, MACI, and microfracture; additional clinical trials with robust designs are necessary to support its use in the future.

In order to improve the quality of future clinical trials, studies need to standardize methodology in harvesting MSC's, for example restricting BMAC collection to the iliac crest and using smaller syringes for aspiration to optimize yield and ensure quality (Davies et al., 2017; Hernigou et al., Nov 2013-b). We also recommend that studies report the cell count and molecular characterization to help researchers identify the optimal cell count for these procedures that would correlate with patient outcomes (Centeno et al., 2015).

While the evidence for the use of MSCs in conditions with associated bone marrow lesions seems promising, there remains a need for continued investigation into this treatment as a viable treatment option. There is a need for well-powered, randomized-controlled trials examining MSCs as a treatment for bone marrow lesions, both as a non-surgical therapy and in augmentation of surgical procedures.

Declaration of competing interest

Kenneth Mautner, MD is a speaker/consultant for Lipogems.

Data availability

No data was used for the research described in the article.

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