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Subchondral Bone and the Osteochondral Unit: Basic Science and Clinical Implications in Sports Medicine

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Context: Articular cartilage injuries and early osteoarthritis are among the most common conditions seen by sports medicine physicians. Nonetheless, treatment options for articular degeneration are limited once the osteoarthritic cascade has started. Intense research is focused on the use of biologics, cartilage regeneration, and transplantation to help maintain and improve cartilage health. An underappreciated component of joint health is the subchondral bone.

Evidence Acquisition: A comprehensive, nonsystematic review of the published literature was completed via a PubMed/MEDLINE search of the keywords "subchondral" AND "bone" from database inception through December 1, 2016.

Study Design: Clinical review.

Level of Evidence: Level 4.

Methods: Articles collected via the database search were assessed for the association of bone marrow lesions and osteoarthritis, cartilage regeneration, and ligamentous and meniscal injury; the clinical disorder known as painful bone marrow edema syndrome; and the subchondral bone as a target for medical and surgical intervention.

Results: A complex interplay exists between the articular cartilage of the knee and its underlying subchondral bone. The role of subchondral bone in the knee is intimately related to the outcomes from cartilage restoration procedures, ligamentous injury, meniscal pathology, and osteoarthritis. However, subchondral bone is often neglected when it should be viewed as a critical element of the osteochondral unit and a key player in joint health.

Conclusion: Continued explorations into the intricacies of subchondral bone marrow abnormalities and implications for the advent of procedures such as subchondroplasty will inform further research efforts on how interventions aimed at the subchondral bone may provide durable options for knee joint preservation.

Keywords: bone; edema; marrow; osteochondral; subchondral

Articular cartilage injuries and early osteoarthritis (OA) are among the most common conditions seen by sports medicine physicians.[18] Nonetheless, treatment options for articular degeneration are limited once the osteoarthritic cascade has started. Intense research is focused on the use of biologics,[24] cartilage regeneration, and transplantation[40] to help maintain and improve cartilage health. An underappreciated component of joint health is subchondral bone, which should be viewed as a critical element of the osteochondral unit and a key player in joint health.[5] In this review, we summarize the current body of knowledge on the role of subchondral bone in joint health followed by potential clinical implications in sports medicine and considerations for future research directions.

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The following authors declared potential conflicts of interest: Bryan M. Saltzman, MD, receives royalties from Nova Science Publishers, and Jonathan C. Riboh, MD, is a paid consultant for Ceterix.

DOI: 10.1177/1941738118782453

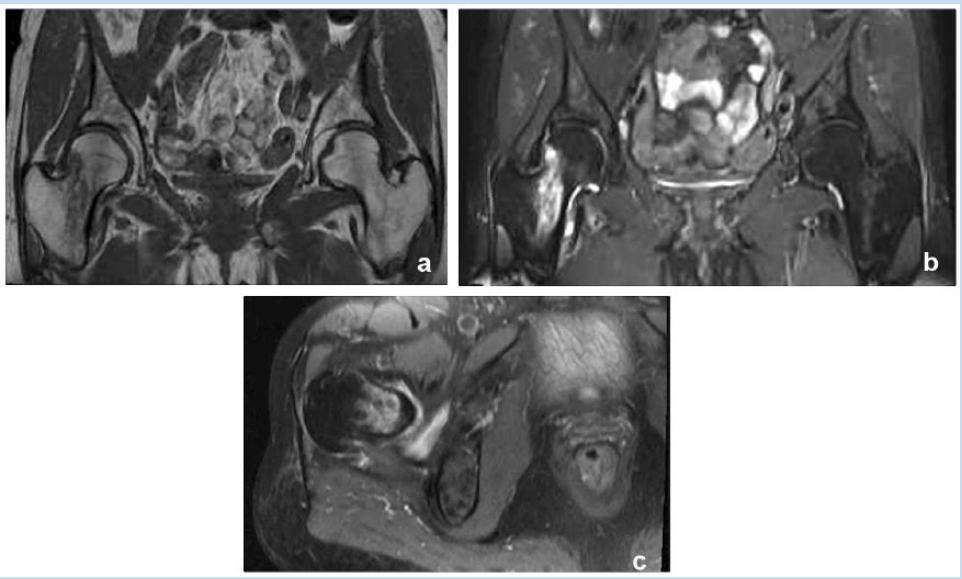

Figure 1. Bony changes from a stress fracture in the right femoral neck of a 62-year-old woman. (a) T1-weighted coronal magnetic resonance imaging (MRI). (b) T2-weighted coronal MRI. (c) T2-weighted axial MRI.

CLINICAL EVALUATION OF SUBCHONDRAL BONE HEALTH

Differential Diagnosis: Traumatic Versus Nontraumatic

Signal abnormalities with bone marrow lesions (BMLs) are relatively nonspecific; many pathologic conditions appear similarly on magnetic resonance imaging (MRI). The patient's history and recollection of the presence or absence of traumatic injury can be helpful in evaluating the meaning of these BMLs. The clinician should expect to see BMLs after acute trauma. The lesions frequently are poorly defined, exhibiting heterogeneous patterns of subchondral signal changes.[43] A true osteochondral injury will also show concurrent cartilage pathology. Repetitive microtrauma after increased physical activity, however, leads to insufficiency fractures, fatigue fractures, or stress fractures (Figure 1). T1-weighted imaging shows irregular, discontinuous, low-intensity strands surrounded by the more diffuse BMLs.

Nontraumatic BMLs include several additional pathologic disorders. Progression of avascular necrosis demonstrates a localized BML around the infarct after osteochondral collapse. Spontaneous osteonecrosis of the knee is a result of insufficiency fracture about the knee and presents with nonspecific focal subchondral BML patterns about the pathologic region.[32] Reactive inflammatory polyarthritis and tumors may have ill-defined subchondral BMLs as well and should be included in the differential (Figure 2). Bone marrow edema syndrome is characterized by large, reversible, diffuse BMLs.[30]

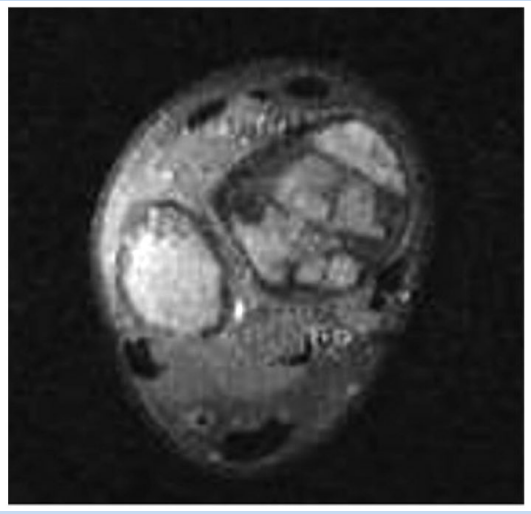

Figure 2. Multicentric sarcoma: T2-weighted axial magnetic resonance imaging of the distal tibia-fibula demonstrating sarcoma-related bone marrow lesions.

BONE MARROW LESIONS IN OSTEOARTHRITIS

Clinical Symptoms

There are studies that suggest no association exists between BMLs and patient pain.[29,38] Other studies, however, suggest just the opposite.[14,35,51] A strong association has been shown

between BMLs on MRI and both patient pain[14] and the progression of clinical manifestations from OA.[15] Pain may be a result of either ingrowth of both fibrovascular tissue and sensory nerves into the region of BMLs[35,51] or impaired venous drainage,[1] although the mechanisms are still debated. While subchondral bone marrow edema on MRI does not explain fully the presence or absence of knee pain, evidence does demonstrate that in the setting of full-thickness articular cartilage defects, women with bone marrow edema and subchondral cortical bony defects have significantly greater likelihood of painful OA.[45] A recent systematic review of 22 studies suggests that there is moderate evidence associating knee pain with BMLs.[53]

Clinical Outcomes

BMLs are associated both with radiologic progression of joint destruction and OA in the knee[7,13,15,42,52] and with MRI-verified chondral loss,[22] evidence of the pivotal role of subchondral bone lesions in OA. Elevated subchondral bone uptake on MRI and SPECT/CT (single photon emission computed tomography/CT) imaging suggests that remodeling processes are associated with the grade of the overlying cartilage lesion.[34] In patients with no history of significant knee pain or trauma, BMLs have been associated with changes in knee cartilage over a 2-year period, with the progression of chondral defects seen to increase in proportion with the size of the lesion.[52] Higher grades of articular cartilage defects seen during arthroscopy are associated with a higher prevalence and greater depth or cross-sectional area, or both, of subchondral bone marrow edema.[28]

BMLs in patients with early OA changes and varus malalignment may be more common in the medial compartment, suggesting overload of the subchondral bone due to malalignment.[15] Kroner and colleagues[31] evaluated the influence of high tibial osteotomy on subchondral bone marrow edema in patients with varus deformity and medial knee OA. After lateral closing-wedge osteotomy, subchondral marrow edema was reduced, which correlated with clinical improvement, suggesting an association between pain in knee OA with presence of BMLs in the setting of malalignment.[31]

A direct relationship between Kellgren-Lawrence OA grade and subchondral bone marrow edema was seen in 81% of patients with grade IV knee OA.[33] MRI evidence of cartilage degradation has also been associated proportionally with increasing bone marrow edema lesion signal intensity.[54] In a study by Kijowski et al,[28] the overall prevalence of subchondral bone marrow edema in patients with surgically confirmed chondral degeneration in the knee was found to be 60%. They also reported bone marrow edema in 87.4% of patients with cartilage defects of grade 2B or greater.[28] The location of subchondral bone marrow edema, however, did not predict the location of the patient's knee pain, suggesting factors other than just subchondral bone marrow edema contribute to knee pain in patients with degenerative joint disease of the knee. Conversely, OA progression is unlikely when bone marrow edema is absent on MRI.[37]

The rapid and predictable need for total knee arthroplasty (TKA) is often seen once a BML has developed in a patient with OA of the knee[31,46] due to progressive bony deformities and collapse.[42] The severity of BMLs at baseline is indicative of reduced baseline tibial cartilage volume, increased loss of tibial cartilage over a 2-year period, and increased risk for a TKA in the coming 4 years after the baseline MRI was performed.[46] Over a 3-year period, patients with bone marrow edema and OA were nearly 9 times more likely to need TKA compared with those with knee OA but no subchondral bone edema. Furthermore, those with a global edema pattern were 13.04 times more likely to require TKA.[44]

BONE MARROW LESIONS AND CARTILAGE REGENERATION

Preoperative and Postoperative BMLs

As the gold standard for evaluation of the morphologic status of cartilage defects, MRI is widely used to evaluate the size of cartilage defects to analyze the maturation process of repair tissues.[16] Recent studies on cartilage treatment suggest that changes in the extent, frequency, and timing of presentation of subchondral bone changes affect the outcome of cartilage procedures.[4,12,36,41,48]

Impact of Preoperative BMLs on Outcomes After Cartilage Treatment

Several studies correlate outcomes with known subchondral BMLs prior to cartilage restoration procedures. In 56 patients undergoing matrix-induced autologous chondrocyte implantation (ACI), preoperative MRI (obtained within 3 months of surgery) showed 35 (62%) patients with some form of subchondral bone edema at the site of chondral abnormality.[12] After 5 years of follow-up, there was no association between the degree of preoperative subchondral bone marrow edema and patient-reported knee pain, symptoms, or graft repair viability.

Niemeyer et al[36] reported on 67 patients treated with ACI for chondral defects of the knee. Edema was graded as absent (grade 1, n = 18), mild (grade 2, n = 17), moderate (grade 3, n = 19), or severe (grade 4, n = 13). Patients were reevaluated at 6 and 12 months after ACI. Patients with severe edema had significantly worse International Knee Documentation Committee (IKDC) and Lysholm scores than all other patients. At 6- and 12-month follow-up, patients with no subchondral edema before surgery had the best clinical function scores, while those with the most severe edema demonstrated clinically inferior results.[36] Severe subchondral bone marrow edema was associated with poor knee function in patients with cartilage defects. Patients with severe edema prior to surgery were a reliable prognostic factor in the first year after ACI.

Impact of Postoperative BMLs on Outcomes After Cartilage Treatment

The persistence of edema-like signals in the subchondral bone is a predictor of poor clinical outcome,[41] which correlates with clinical results and outcome scores after microfracture surgery.[4]

An evaluation of 41 patients treated with ACI for femoral condyle cartilage lesions demonstrated that bone marrow changes beneath the graft were common (n = 23; 56%).[48] MRI findings of signal intensity change in underlying bone marrow could not predict ACI graft histologic features.[48]

An evaluation of 38 chondral defects in 30 patients after matrix-based ACI showed subchondral bone marrow edema in 79% of chondral defects postoperatively, with the initial appearance occurring the first year. Despite this high incidence of subchondral bone edema after surgery, its presence (at any time) did not correlate with patient clinical outcomes (via IKDC) over the 3-year postoperative period.

In a review of 10 years of follow-up imaging of subchondral bone edema in knees after matrix-assisted autologous chondrocyte transplantation, edema was found to be present in about half of scans during the initial 2 years of cartilage maturation.[16] Over the next 2 years (years 3-4 after surgery), this decreased to approximately 30%. At mid- to long-term follow-up (>42 months), 60% showed subchondral bone edema.[16] There was no correlation between bone marrow edema and clinical outcomes after matrix-assisted autologous chondrocyte transplantation.

TRAUMATIC BONE BRUISES IN THE ATHLETE'S KNEE

Using BML Pattern to Determine Ligamentous Injury

Bone bruising at the sulcus terminalis of the lateral femoral condyle and the posterior region of the lateral tibial plateau are often pathognomonic for an anterior cruciate ligament (ACL) rupture because of the translation and impact of the femur on the tibia at the time of injury (Figure 3).[2,3,21,23,25,43] Bone bruises often disappear by 2 to 3 months after injury.[19,49] The injury mechanism (contact vs noncontact) can be predicted by the severity and location of bone bruising.[50] Viskontas et al[50] reported that the noncontact mechanism of injury appears to cause more frequent, deeper, and intense bone bruising in both medial and lateral compartments. In addition, bone bruising occurred more commonly in the lateral compartment than the medial compartment after both contact and noncontact mechanisms of injury.

Bone bruising of the anterior tibia suggests a hyperextension event, which may be an ACL tear. An acute lateral patellar dislocation similarly provides an identifiable bone bruise pattern, located at the inferomedial patella and lateral aspect of the lateral femoral condyle (Figure 4).[10] The lateral femoral condyle or patella may additionally demonstrate an osteochondral fracture or defect related to the dislocation/relocation event. Subcortical, linear, discrete regions of diminished signal intensity on T1-weighted MRI with a sharp zone of transition to the adjacent bone marrow fat are suggestive of an occult fracture; when depression of the chondral surface is present concurrently, this indicates an impaction fracture.[10] A bone bruise over the anterior tibia secondary to a direct blow on a flexed knee should raise suspicion for a posterior cruciate ligament tear (dashboard mechanism). Finally, a valgus overload producing matching bone bruises to the lateral tibial plateau and lateral femoral condyle may represent a medial collateral ligament tear.[10]

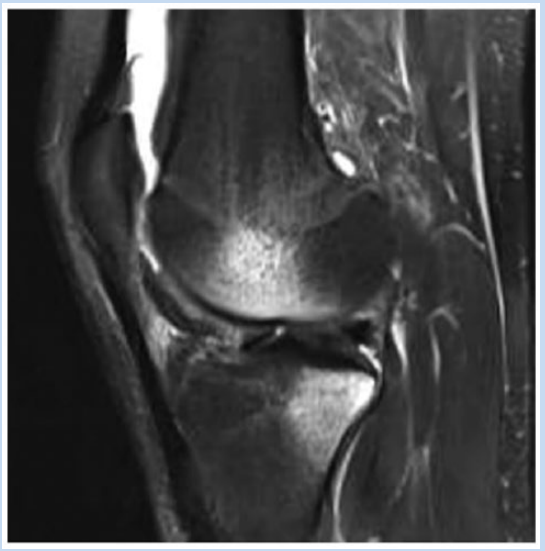

Figure 3. Anterior cruciate ligament rupture. T2-weighted sagittal magnetic resonance image demonstrating the bony edema pattern on the lateral femoral condyle and lateral tibial plateau characteristic of an acute anterior cruciate ligament injury.

Correlation With Chondral Damage

Subchondral bone bruising at the time of acute ligamentous injury can lead to loss of articular cartilage and the development of focal OA.[17] Thinning of the articular cartilage has been observed more than 2 years after injury to the subchondral bone.[27] Other theories suggest that subchondral bone injuries heal with callus formation (similar to that seen after a fracture) that is stiffer than normal subchondral bone.[8] The resulting decreased compliance may require the articular cartilage to absorb more compressive mechanical forces, which may lead to greater degenerative changes.[8]

Ten patients with BMLs on MRI after acute ACL rupture showed large type II lesions contiguous to the subchondral bone, which revealed abnormal subchondral bone homeostasis (ie, chondrocyte degeneration, proteoglycan loss, and chondrocyte necrosis).[27]

A prospective observational study of 42 knees (28 reconstructed, 14 nonoperative) with acute, isolated ACL injury showed that all suffered concomitant chondral injury.[39] Initial bone marrow edema pattern was associated with chondral degeneration from time of injury to 3 years after injury.

Correlation With Clinical Outcomes

Johnson et al[26] evaluated 20 patients with isolated ACL rupture and evidence of subchondral bone marrow edema of the lateral femoral condyle in the 4 weeks after injury. An additional 20

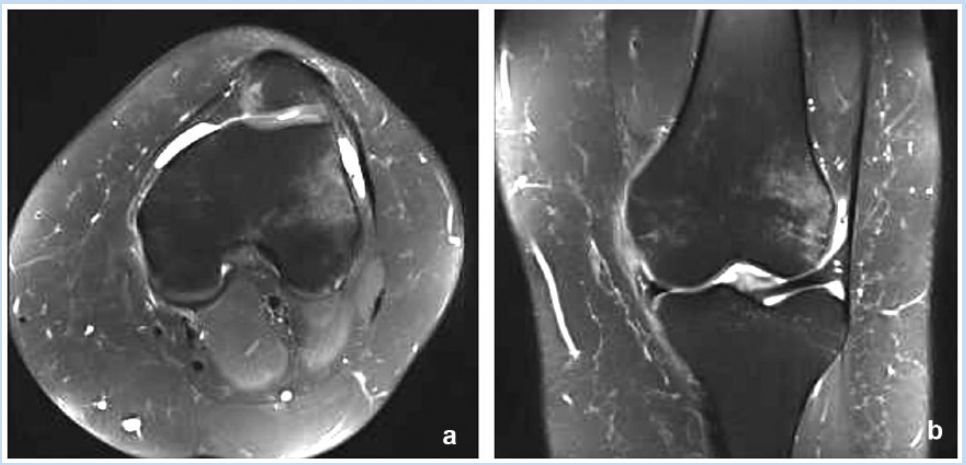

Figure 4. Acute lateral patellar dislocation. Magnetic resonance images (MRIs) demonstrating the bony edema pattern on the inferomedial patella and lateral aspect of the lateral femoral condyle. (a) T2-weighted axial MRI. (b) T2-weighted coronal MRI.

patients without evidence of subchondral bone marrow edema were also evaluated. Patients with bone bruises prior to ACL reconstruction had increased size and duration of effusion, greater number of days to unassisted ambulation, poor range of motion, and higher pain scores than patients without subchondral bruising.[26]

In a cohort of 21 patients whose initial MRI scans showed ACL ruptures with associated bone bruises, 71% of patients had resolution of bone bruising within 2 years of follow-up.[8] The long-term clinical implications of these findings remain uncertain.

In their 12-year follow-up study of 44 patients who had undergone ACL reconstruction, Hanypsiak et al[20] reported resolution of subchondral bone bruising after ACL injury from all patients. No associations were observed between the presence of subchondral bone bruising at the time of initial injury and patient-oriented outcomes (IKDC) after reconstruction.

A total of 525 patients in the Multicenter Orthopaedic Outcomes Network (MOON) study were evaluated to determine which factors were associated with preoperative knee pain and symptoms.[11] Subchondral bone bruising was present in 419 (80%) patients but not associated with preoperative pain or symptoms.

BONE MARROW LESIONS AND MENISCAL PATHOLOGY

A linear T2 hyperintensity on MRI within the subchondral bone occurred in 71% of patients with radial or root meniscal tears. In contrast, only 5% of patients with horizontal tears in the meniscus displayed subchondral bone bruising.[47]

SUBCHONDRAL BONE AS A THERAPEUTIC TARGET

Surgical Intervention

Subchondroplasty is a minimally invasive surgical procedure where calcium phosphate bone substitute is injected under fluoroscopic guidance to treat symptomatic subchondral BMLs identified from T2-weighted MRI scans. The goal is a joint-preserving intervention to delay the need for joint replacement.[7]

At a median follow-up of 12 months for 22 patients treated with subchondroplasty for grade III to IV chondral lesions predominantly on the tibia (15/22), Knee injury and Osteoarthritis Outcome Score (KOOS) scores had significantly improved from a mean of 39.5 to 71.3.[7] Tegner-Lysholm scores were also significantly improved from 48 to 77.5. Unfortunately, 10 patients were "failures" (7 poor, 3 fair results), and there was no control group raising further questions.[7]

In a retrospective review of 50 patients with knee OA who underwent subchondroplasty for symptomatic BMLs, improvement in pain, as measured on a visual analog scale, was 4.7 points, with 88% experiencing improvement and 72% reporting improvements in pain-free walking distance at follow-up (mean, 14.6 months). While 48% underwent additional interventions, including 18 injections (36%) and 4 conversions to TKA (8%), mean patient satisfaction was a 7.8 out of 10, and 78% of patients said they would undergo the procedure again.[9]

In a consecutive case series of 66 patients with subchondroplasty for symptomatic BMLs in a weightbearing region of the femoral condyle or tibial plateau, there were significant improvements in IKDC subjective knee evaluation and visual analog scale pain measurement scores at 2 years postoperatively; 70% of patients did not pursue arthroplasty at the 2-year follow-up assessment.[6]

CONCLUSION

A complex interplay exists between the articular cartilage of the knee and its underlying subchondral bone. The role of the subchondral bone is intimately related to the outcomes from cartilage restoration procedures, meniscal pathology, and OA. While subchondroplasty may be a promising technique going

forward in the treatment of BMLs, evidence to date is limited to small case series without comparative cohorts, and thus, conclusive evidence of its comparative efficacy is yet to be demonstrated.

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