Subchondral Bone Marrow Lesions Associated With Knee Osteoarthritis

Peter F. Sharkey, MD, Steven B. Cohen, MD, Charles F. Leinberry, MD, and Javad Parvizi, MD

Abstract

Knee osteoarthritis (OA) is a prevalent condition typically measured by the level of joint space thinning. However, it has been shown that the degree of joint space narrowing correlates poorly with the incidence and magnitude of knee pain. A review of recent and past literature suggests that chronic bone marrow edema (BME) or bone marrow lesions may be linked to pain, the progression of cartilage damage, and the acceleration of joint degeneration. The literature further provides strong support that chronic BME may be an additional target for treatment.

This case study has shown that a treatment to repair BME by restoring support and relieving abnormal stresses with accepted internal fixation and bone stimulating surgical techniques is effective in relieving knee OA pain. The literature review and case study herein are provided as a basis for the treatment of chronic BME as an important addition to the current knee OA treatment paradigm.

Knee osteoarthritis (OA), generally defined by the narrowing of the joint space,[1] is a prevalent condition that is often associated with debilitating pain. It is estimated that 1 in 2 Americans will have painful knee OA in their lifetime leading to considerable socioeconomic impact.[2] End–stage knee OA is the leading indication for total knee arthroplasty (TKA), with more than 600,000 TKAs performed in 2008 in the United States.[2]

Knee pain reduces an individual's quality of life and has been shown to be a significant contributor to lost work days, physician visits,[3] and a large percentage of medical treatments and medical costs.[4] It has been shown that the degree of joint space narrowing correlates poorly with the incidence and magnitude of knee pain.[5-7] Although commonly performed, injections of viscosupplements and arthroscopic debridement or lavage have been associated with inconsistent results,[8,9] and the American Academy of Orthopedic Surgeons has indicated that the evidence to support their use is inconclusive.[10]

Treatment options focused on regenerating or replacing lost cartilage related to OA have been explored, however, these techniques have resulted in inconsistent pain relief and are limited to younger patients (<40 years).[11] Surgical interventions, including arthroscopic partial meniscectomy and loose body removal, are only recommended in osteoarthritic patients with mechanical symptoms.[10] For patients with severe pain associated with osteoarthritis, surgical interventions such as high tibial osteotomy, TKA, or partial knee arthroplasty, are often recommended. These procedures are considered end–stage surgical interventions and may be associated with significant complications, morbidity, and occasionally mortality.[12]

While TKA provides predictable pain relief, patients often report that the replaced knee lacks a "natural

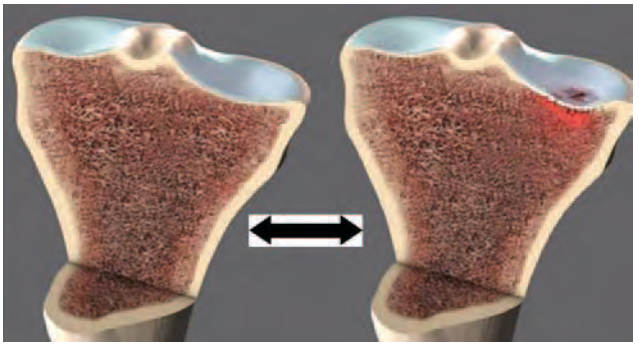

Figure 1. Schematic conception of physiologic and pathologic bone remodeling.

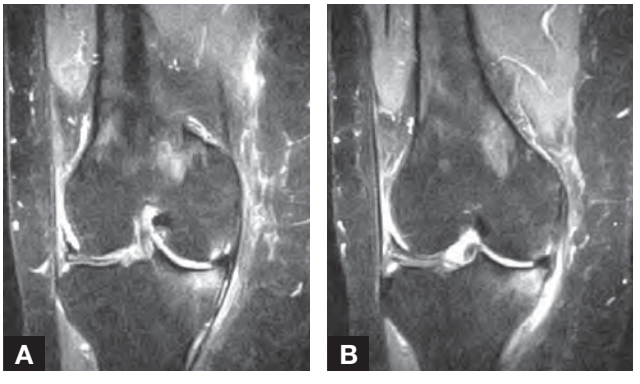

Figure 2. Two consecutive slices, (A) and (B), of a T2 fat suppressed MRI.

Dr. Sharkey is Professor, Department of Orthopaedic Surgery, Thomas Jefferson University Hospital, Riddle Memorial Hospital, Media, Pennsylvania.
Dr. Cohen is Director, Sports Medicine Research and Associate Professor; Dr. Leinberry is Associate Professor; and Dr. Parvizi is Director of Clinical Research and Professor, Department of Orthopaedic Surgery, Thomas Jefferson University Hospital, Philadelphia, Pennsylvania.

Address correspondence to: Peter F. Sharkey, MD, Rothman Institute Orthopaedics, Thomas Jefferson University Hospital, Riddle Memorial Hospital, 1110 W. Baltimore Pike, Suite 302, Media, PA 19063 (tel, 610-480-6559; fax, 215-503-5651; e-mail, kerrianne.valichka@rothmaninstitute.com).

Am J Orthop. 2012;41(9):413-417.

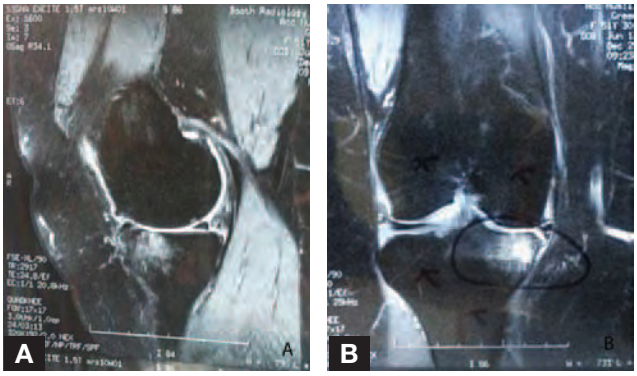

Figure 3. Case study preoperative MRI: (A) sagittal T2 image and (B) coronal T2 image.

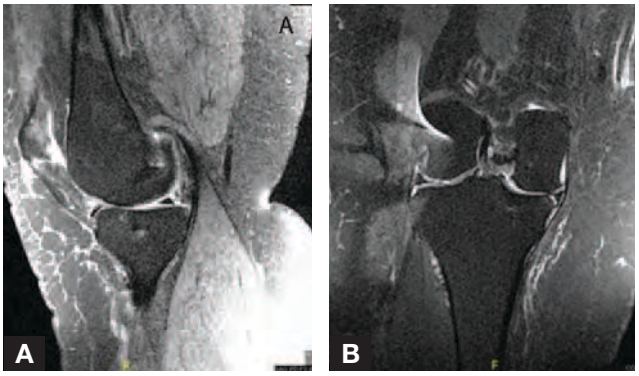

Figure 4. Case study postoperative MRI: (A) sagittal T2 image and (B) coronal T2 image.

feel," and has functional limitations.[13] A minimally invasive intervention that delivers reliable pain relief of OA while preserving the native joint has been elusive.

In a healthy joint, daily activities of repetitive loading cause acute subchondral damage which is balanced by consistent repair (Figure 1). When damage persistently exceeds repair or bone is unable to heal with periods of rest or unloading, a chronic bone marrow edema lesion (BME/BML) develops (Figure 2). Since Felson's seminal article in 2001,[14] the correlation between BME and symptomatic OA pain has been well documented.[15] Felson and colleagues[14] showed that patients with painful knee OA were 2.5 times as likely to have BME, compared with asymptomatic subjects. A longitudinal analysis further showed that an increase in the volume of BME correlated with increased pain.[16] A more recent study demonstrated that the amount of denuded subchondral bone and the BML volume were strongly correlated with the severity of reported pain.[17]

Knee OA related BMLs should not be confused with edema found in osteonecrosis or avascular necrosis (AVN) of the knee, spontaneous osteonecrosis, or contusion of the knee. Lafforgue[18] states that AVN is triggered by "intraluminal obliteration of blood vessels by microscopic fat emboli, sickle cells, nitrogen bubbles (caisson disease), or focal clotting due to procoagulant abnormalities although the final mechanism is always critical ischemia." AVN can lead to subchondral plate fracture and collapse of the necrotic segment of the epiphysis. AVN is generally surgically treated by TKA, as the bone is necrotic and beyond physiological repair. Many types of bone pathology lead to BME-like signals, including bone contusions, fractures, cysts, overuse injuries, transient osteoporosis, and bone destroying tumors.

The objective of this investigation was to provide a literature review of BME associated with knee OA, as well as present a clinical case utilizing a novel, minimally invasive treatment technique to alleviate the pain associated with BME. The procedure, trademarked Subchondroplasty, was first described in 2007 as a possible treatment to alleviate symptomatic pain in knee OA patients with MRI identified BME.[19] The principles of Subchondroplasty are based on familiar and accepted internal fixation and bone stimulating techniques for treating non–healing bone injuries (fractures). The primary hypothesis was that the clinical outcomes of Subchondroplasty would reduce knee pain and improve the patient's quality of life.

The patient provided written and informed consent for print and electronic publication of this case report.

Case Report

A 51-year-old female employed full-time as a hairdresser presented for evaluation in May 2008. She reported severe pain in her right knee, which had worsened over 8 months. She had difficulty walking and had a significant limp. Her pain was noted as greatly impacting her ability to perform daily activities, including work. Extensive nonoperative care (ie, corticosteroid injection, viscosupplementation, nonsteroidal anti-inflammatory drugs) did not provide meaningful relief and her activity-related pain was described as causing a significant deterioration in quality of life. No prior surgeries were performed on the painful knee.

Physical examination was consistent with knee OA. The patient was overweight at approximately 1.65 m and 100 kg. All ligaments were stable, with good range of motion (0° to 130°), however, with painful extension and flexion. She had marked tenderness over the proximal tibial plateau on the medial side. Hip range of motion was good and painless. In addition, she had good pedal pulses, sensation, and motor strength in the right lower extremity. Radiographs and MRI were reviewed and consistent with degenerative arthritis of the knee, with a significant BME or stress fracture of the medial tibial plateau (Figure 3).

Treatment options, including partial or TKA, were discussed, and only after detailed informed consent, augmentation of the tibial plateau was chosen as the surgical procedure. Potential risks and benefits of the surgery were discussed in detail. The patient understood that the procedure would not obviate future TKA, but expressed a desire to delay TKA and lose weight.

On May 12, 2008, the patient was treated as an outpa-

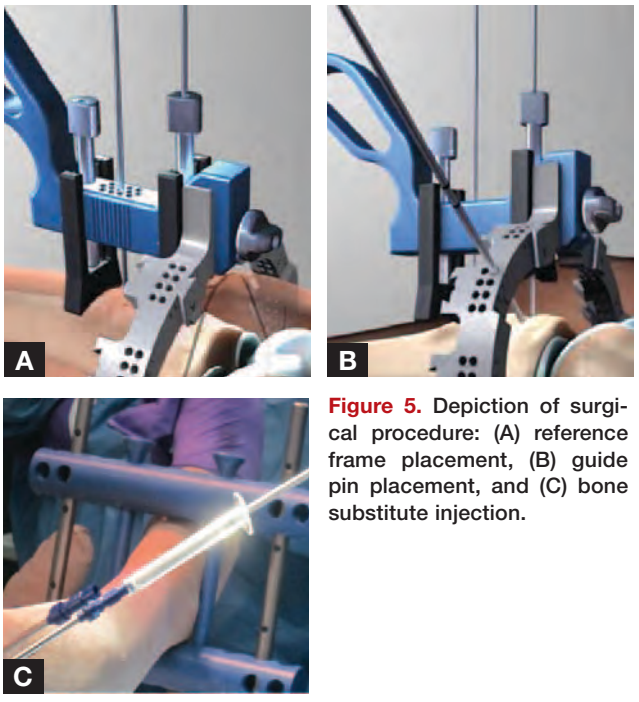

Figure 5. Depiction of surgical procedure: (A) reference frame placement, (B) guide pin placement, and (C) bone substitute injection.

tient without complications. Standard portal arthroscopy was performed with all compartments well visualized. There were mild degenerative changes of the patellofemoral compartment, minimal degenerative changes of the lateral compartment, and severe degenerative arthritis of the medial compartment, with complete eburnation of the medial tibial plateau. There was no significant meniscal pathology, but there was some synovitis and a synovectomy was performed arthroscopically.

With the aid of arthroscopy and fluoroscopy, a pin was inserted into the tibial plateau in the region consistent with the MRI identified BML/stress fracture. A cannulated needle was placed over the pin to create a portal into the bone. A polymerizable calcium phosphate bone substitute was injected into the area, and proper placement was confirmed with arthroscopy and fluoroscopy. The knee was thoroughly irrigated and the arthroscopy portals were closed with nylon sutures.

Postoperatively, the patient was advised to be 50% weight bearing as needed for 2 weeks and physical therapy was instituted immediately. Early pain relief was achieved and the patient returned to work after 1 week. At the most recent follow-up, 31 months after Subchondroplasty, the patient reported an active lifestyle, described her knee pain as 1/10 on a VAS, and reported no additional treatment for her knee OA. Radiographs demonstrated minimal progression of joint space narrowing and an MRI revealed resolution of the subchondral BME (Figure 4).

Proposed Surgical Technique

Preoperative evaluation should be performed to identify the presence, size, and location of BME on a T2-fat suppressed MRI in patients with painful knee OA.

Surgical approaches and treatment strategies would vary depending on the location and size of the defect. Small peripheral defects may require a single approach, while larger defects may require multiple approaches. A reference frame, which triangulates MRI findings to anatomy, can be utilized to create accurate access through percutaneous incisions. The reference frame should be securely fixed to the femur or tibia as needed allowing guided insertion through the bone directly into the BML, without disturbing the overlying joint (Figure 5). Once appropriate guide wire placement is confirmed using fluoroscopy, a cannulated device can be placed over the guide wires as a means of injecting a bone substitute into the edematous region.

The bone substitute theoretically restores the structural integrity of healthy, cancellous bone, and induces healing of the damaged bone. A resorbable, osteoconductive bone graft substitute has been shown to promote healing and increase strength of cancellous bone.[20] In addition, a bone substitute will not likely compromise the surgical opportunity or performance of a future osteotomy or TKA, if required.

Discussion

As early as 1743, William Hunter[21] recognized the minimal potential for lost or damaged cartilage to regenerate. This lack of ability is due to the inherent biology of cartilage, which has minimal blood supply and is nourished only by the synovial fluid. It has been previously shown that immature marrow cells below the articular cartilage can be stimulated and may facilitate healing of articular defects.[22] However, access to these cells is blocked by a calcified cartilage layer and the subchondral bone plate. Penetrating this layer has been shown to occasionally result in bleeding, clot formation, vascular in growth, and fibrocartilage development. However, production of this fibrocartilage is unpredictable and because it lacks the normal properties of articular cartilage, results of this type of surgical intervention are inconsistent and good outcomes often lack longevity.[11] Due to these findings, it has been suggested that cartilage restoration techniques be utilized only for younger patients (<40 years) with full-thickness lesions limited in size to less than 2 cm.[11] These criteria exclude the vast majority of patients with arthritic related knee pain and almost all patients who are candidates for TKA.[23]

Previously, investigators described the knee as an organ system designed to accept, transfer, and dissipate loads within a confined set of boundaries.[24] This has been termed the *envelope of function,* within which there is no persistent damage or chronic pain. However, when these loads cannot be appropriately dissipated due to other issues such as anatomical, physiological, or pathological factors, damage can exceed repair.[24] In a typical healthy joint, loading creates a constant equilibrium between damage and repair. BME has been described in military recruits with bone stress injuries of the talus.[25]

It was proposed that vascular pressures experienced during strenuous exercise exceeded peak arterial pressure. In our case report, bone tissue temporarily suffered from ischaemia caused by reduced blood flow, which was followed by remodeling post-injury. BME has also been noted in long distance runners following the completion of a marathon.[26] These types of BME are usually acute and often heal with rest. Persistent or chronic BME may occur in the arthritic knee due to recurrent challenges outside Dye's envelope of function.

Physiologically, subchondral damage initially stimulates the bone to respond with increased repair.[27] A small focal region of very hard, sclerotic bone usually forms in response.[28] This region of hard or sclerotic bone is postulated to be at the core of BME lesions and can be readily visualized on T1 weighted MRI by a signal void. While temporarily solving the issue of increased damage, the hard sclerotic bone creates a new problem. Forces are transmitted through and concentrated at the periphery of the hard bone where an interface exists with weaker surrounding cancellous bone. Due to significant force generation, the equilibrium between repair and damage at this junction is shifted with accelerated bone injury with the creation of vascular hemorrhage, fibrin, and fibroplasia.[29] BME occurs at this junction between the hardened sclerotic bone and the weaker juxtaposed cancellous bone. BME represents a chronic stress injury (ie, non-healing fracture) of this interface. If reparative mechanisms can compensate, the sclerotic lesion expands and no BME develops. However, if damage overwhelms repair, then the interface breaks down and a non–healing stress fracture occurs with chronic BME, which becomes apparent on T2-weighted MR images. This MRI-demonstrated BME reflects significant injury and chronic inflammation at the interface between the hard sclerotic bone and weaker adjacent cancellous bone. Individuals with altered mechanical alignment or impaired bone healing potential are predisposed to BME. Likewise, pathological loss of cartilage leads to increased subchondral bone damage. In this sense, chronic BME associated with knee OA can be further classified as a type of insufficiency fracture.

A growing understanding of the pathophysiology of knee OA has led some investigators to suggest that the pain from OA may predominantly emanate from subchondral BME and remodeling either in conjunction with, or possibly preceding, articular cartilage degeneration.[30,31] The resulting pain may be perceived via the glutamate transporters and receptors.[32] Glutamate is a cell-stimulating agent, which regulates the expression of osteoclasts in response to mechanical stimulation. Activation of these receptors leads to remodeling and the receptors have been reported to exist in proportion to the extent of arthritic damage in the subchondral bone and have been shown to play a role in chronic pain.[33] When a soft, edematous area experiences focal loads, the cartilage above this defect is not able to spread the forces laterally, and instead, the force is transmitted vertically. These changes create shear stress on the cartilage at the edge between the edematous bone and healthy bone, leading to cartilage attrition (Figure 6).[34] The relationship between chronic BME and progressive cartilage damage has a strong theoretical basis. Subchondral bone supports articular cartilage, and the cartilage in turn distributes loading to the bone. Articular cartilage is a relatively spongy tissue and therefore dependent on its subchondral base for its continued integrity. Chronic BME represents damage and inflammation of the subchondral bone, which may render the junction between sclerotic and cancellous bone weaker. With this loss of articular cartilage support, cartilage attrition may accelerate.[35]

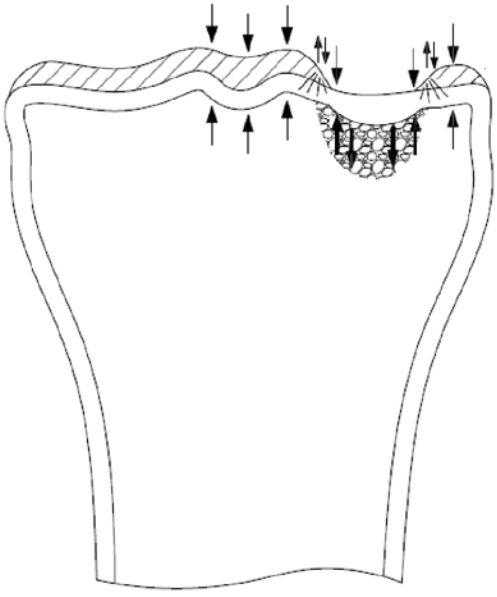

Figure 6. Depiction of shearing of cartilage margin related to BML.

Zanetti and colleagues[36] preformed a study to evaluate the histology of BME. The study evaluated patients scheduled for a total knee replacement and who had a preoperative MRI. When the knee replacement was performed, the patient's proximal tibia was resected as part of the routine procedure and evaluated microscopically. They found that areas where BME was identified histologically corresponded to a number of abnormalities, including bone marrow necrosis, bone marrow fibrosis, and trabeculae abnormalities.[36] In addition, they noted that the appearance of these microscopic discovered abnormalities were consistent with the histologic appearance of a stress fracture.

There is a strong scientific basis for treatment of chronic BME as a means for relieving knee OA pain. The goal of this procedure, deemed Subchondroplasty, is to repair and strengthen the interface between weaker cancellous bone and hardened sclerotic bone. This restored support may positively alter the progression of OA related cartilage changes. The previous case report with 31-month follow-up provides support to this theory. A larger series and long-term follow-up of patients will help to deter-

mine the length of sustained benefit and also define patient selection.

The potential of Subchondroplasty is based on the procedure's ability to access the subchondral space and insert a device that not only provides immediate bone stability, but also can serve as a delivery system for biologically active agents. As the pathophysiology of knee OA is better understood, Subchondroplasty will become more refined and delivery of cytokines and other cell signaling agents that create some combination of osteogenesis, chondrogenesis, and angiogenesis may further enhance the results of Subchondroplasty. Subchondroplasty may be a safe, effective, joint preserving treatment for BME, and could play an important role in the treatment spectrum for patients with knee OA.

Authors' Disclosure Statement

Drs. Sharkey, Leinberry, and Cohen wish to note that they are consultants for and receive royalties from Knee Creations, LLC.

References

1. Mazzuca SA, Brandt KD. Is knee radiography useful for studying the efficacy of a disease-modifying osteoarthritis drug in humans? *Rheum Dis Clin North Am.* 2003;29(4):819-830.
2. Murphy L, Schwartz TA, Helmick CG, et al. Lifetime risk of symptomatic knee osteoarthritis. *Arthritis Rheum.* 2008;59(9):1207-1213.
3. United States Department of Health and Human Services. National Center for Health Statistics, National Health Interview Survey, 2005. http://www.cdc.gov/nchs/nhis/nhis_2005_data_release.htm. Published June 23, 2006. Accessed May 28, 2010.
4. US Department of Health and Human Resources. Health, United States, 2009 With Special Feature on Medical Technology. Table 54. http://www.cdc.gov/nchs/data/hus/hus09.pdf. Published in 2010. Accessed May 28, 2010.
5. Hadler NM. Knee pain is the malady – not osteoarthritis. *Ann Intern Med*. 1992;116(7):598-599.
6. Bedson J, Croft PR. The discordance between clinical and radiographic knee osteoarthritis: A systematic search and summary of the literature. *BMC Musculoskelet Disord.* 2008;9:116.
7. Bollet AJ. Edema of the Bone Marrow Can Cause Pain in Osteoarthritis and Other Diseases of Bone and Joints. *Ann Intern Med*. 2001;134(7):591-593.
8. Kirkley A, Birmingham TB, Litchfield RB, et al. A randomized trial of arthroscopic surgery for osteoarthritis of the knee. *N Engl J Med.* 2008;359(11):1097-1107.
9. Divine JG, Zazulak BT, Hewett TE. Viscosupplementation for knee osteoarthritis: a systematic review. *Clin Orthop Relat Res.* 2007;455: 113-122.
10. Richmond J, Hunter D, Irrgang J, et al. Treatment of Osteoarthritis of the Knee (Nonarthroplasty). *J Am Acad Orthop Surg.* 2009;17(9):591-600.
11. Mandelbaum BR, Browne JE, Fu F, et al. Articular Cartilage Lesions of the Knee. *Am J Sports Med*. 1998;26(6):853-861.
12. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. *N Engl J Med.* 2002;346(15):1128–1137.
13. Singh JA, O'Byrne M, Harmsen S, Lewallen D. Predictors of moderate–severe functional limitation after primary Total Knee Arthroplasty (TKA): 4701 TKAs at 2-years and 2935 TKAs at 5-years. *Osteoarthritis Cartilage.* 2010;18(4):515-521.
14. Felson DT, Chaisson CE, Hill CL et al. The Association of Bone Marrow Lesions with Pain in Knee Osteoarthritis. *Ann Intern Med.* 2001;134(7):541–549.
15. Koo KH, Ahn IO, Kim R, et al. Bone Marrow Edema and Associated Pain in Early Stage Osteonecrosis of the Femoral Head: Prospective Study with Serial MR Images. *Radiology.* 1999;213(3):715-722.
16. 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(9):2986-2992..
17. Moisoi K, Eckstein F, Chmiel JS, et al. Denuded Subchondral Bone and Knee Pain in Persons with Knee Osteoarthritis. *Arthritis Rheum*. 2009;60(12):3703-3710.
18. Lafforgue P. Pathophysiology and natural history of avascular necrosis of bone. *Joint Bone Spine.* 2006;73(5):500-507.
19. Sharkey PF, Leinberry CF, inventors; Knee Creations, LLC, assignee. Osteoarthritis treatment and device. US patent 8,062,364. November 22, 2011.
20. Bajammal SS, Zlowodzki M, Lelwica A, et al. The Use of Calcium Phosphate Bone Cement in Fracture Treatment. A meta-analysis of randomized trials. *J Bone Joint Surg Am.* 2008;90(6):1186-1196.
21. Hunter W. Of the Structure and Disease of Articulating Cartilages. 1743. *Clin Orthop Relat Res.* 1995;317:3-6.
22. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: Surgical Technique and Rehabilitation to Treat Chondral Defects. *Clin Orthop Relat Res.* 2001;391S:S362–S369.
23. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. *Arthroscopy.* 1997;13(4):456-460.
24. Dye SF. The Knee as a Biologic Transmission With an Envelope of Function. *Clin Orthop Relat Res.* 1996;325:10-18.
25. Sormaala MJ, Niva MH, Kiuru MJ, Mattila VM, Pihlajamäki HK. Bone stress injuries of the talus in military recruits. *Bone*. 2006;39(1):199–204.
26. Krampla WW, Newrkla SP, Kroener AH, Hruby WF. Changes on magnetic resonance tomography in the knee joints of marathon runners: a 10-year longitudinal study. *Skeletal Radiol.* 2008;37(7):619–626.
27. Plenk H Jr, Hofmann S, Eschberger J, et al. Histomorphology and bone morphometry of the bone marrow edema syndrome of the hip. *Clin Orthop Relat Res.* 1997;334:73–84.
28. Hunter DJ, Gerstenfeld L, Bishop G, et al. Bone marrow lesions from osteoarthritis knees are characterized by sclerotic bone that is less well mineralized. *Arthritis Res Ther.* 2009;11(1):R11.
29. Norrdin RW, Kawcak CE, Capwell BA, McIlwraith CW. Subchondral bone failure in an equine model of overload arthrosis. *Bone.* 1998;22(2):133-139.
30. Lajeunesse D, Massicotte F, Pelletier J-P, Martel-Pelletier J. Subchondral bone sclerosis in osteoarthritis: not just an innocent bystander. Mod Rheumatoly. 2003;13:7–14.
31. Felson DT, Neogi T. Osteoarthritis: Is It a Disease of Cartilage or Bone? *Arthritis Rheum.*2004;50(2):341-344.
32. Wilson C. Expression of glutamate receptors and transporters in human subchondral bone in osteoarthritis. Abstract presented at: Knee Society 2009 Meeting; October 2009; Boston, MA.
33. Bleakman D, Alt A, Nisenbaum ES. Glutamate receptors and pain. *Semin Cell Dev Biol.* 2006;17(5):592–604.
34. Radin EL, Rose RM. Role of Subchondral Bone in the Initiation and Progression of Cartilage Damage. *Clin Orthop Relat Res*. 1986;213:34-40.
35. 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(1):47–53.
36. Zanetti M, Bruder E, Romero J, Hodler J. Bone marrow edema pattern in osteoarthritic knees: correlation between MR imaging and histologic findings. *Radiology.* 2000;215(3):835-840.