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CARTILAGE REPAIR TECHNIQUES IN THE KNEE (A DHAWAN, SECTION EDITOR)

Knee cartilage defect: marrow stimulating techniques

M. Zain Mirza[1] · **Richard D. Swenson**[1] · **Scott A. Lynch**[1]

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Abstract Painful chondral defects of the knee are very difficult problems. The incidence of these lesions in the general population is not known since there is likely a high rate of asymptomatic lesions. The rate of lesions found during arthroscopic exam is highly variable, with reports ranging from 11 to 72 % Aroen (Aroen Am J Sports Med 32: 211-5, 2004); Curl(Arthroscopy13: 456-60, 1997); Figueroa(Arthroscopy 23(3):312-5, 2007;); Hjelle(Arthroscopy 18: 730-4, 2002). Examples of current attempts at cartilage restoration include marrow stimulating techniques, ostochondral autografts, osteochondral allografts, and autologous chondrocyte transplantation. Current research in marrow stimulating techniques has been focused on enhancing and guiding the biology of microfracture and other traditional techniques. Modern advances in stem cell biology and biotechnology have provided many avenues for exploration. The purpose of this work is to review current techniques in marrow stimulating techniques as it relates to chondral damage of the knee.

Keywords Bone marrow stimulation · Marrow stimulating techniques · Microfracture · Platelet-rich plasma · Scaffolding · Osteochondral lesion

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✉ Scott A. Lynch
slynch@hmc.psu.edu

M. Zain Mirza
mmirza@hmc.psu.edu

Richard D. Swenson
rswenson@hmc.psu.edu

[1] Penn State Hershey Bone and Joint Institute, 30 Hope Drive, Building B, Suite 2400, Hershey, PA 17033-0850, USA

Introduction

Chondral defects of the knee can be causes of knee pain. However, its incidence in the general population is not known since there is likely a high rate of asymptomatic lesions. Rates of lesions among patients undergoing routine arthroscopy are highly variable, with reports ranging from 11 to 72 % [1–4].Though not specifically reported in the literature, there does seem to be an increasing incidence of chondral restoration surgeries being performed. The goal of chondral restoration is to produce a normal, biomechanically functioning articular surface that has normal load sharing properties. In theory, this would alleviate pain and be chondroprotective to prevent or delay the onset of osteoarthritis. Examples of current attempts at cartilage restoration include marrow stimulating techniques, osteochondral autografts, osteochondral allografts, and autologous chondrocyte transplantation.

Marrow stimulating techniques were first described by Kenneth Pridie in 1959 [5]. In his technique, he drilled the bony base of chondral defects inducing bleeding with the goal of stimulating healing from the bone marrow. Later techniques involved using a burr to remove several millimeters of bone from the chondral lesion [6]. Unfortunately, early drilling and abrasion produced marginal results [7, 8]. Steadman described microfracture as a technique to improve cartilage defects. His group reported good clinical results even after 10 years [9, 10]. However, others have called into question the results of microfracture noting that MRI and second look arthroscopy reveal incomplete defect filling or bony ingrowth into the defect resulting in deterioration of initial results after 18–36 months [11, 12].

Current research in marrow stimulating techniques has been focused on enhancing and guiding the biology of microfracture and other traditional techniques. Modern

advances in stem cell biology and biotechnology have provided many avenues for exploration. The purpose of this work is to review current techniques in marrow stimulating techniques as it relates to chondral damage of the knee.

Basic science and biology

Articular cartilage is a hyaline cartilage structure that provides strength and decreases friction at the bearing surface of the knee joint. Its collagen building blocks are mainly of the type II variety. The articular cartilage interface can be divided into four zones: superficial, middle, deep, and tidemark. The superficial zone consists of a thin layer of collagen with minimal proteoglycans. These fibers are oriented parallel to the joint surface and contain a high water concentration. This structure provides the decreased friction properties characteristic to the joint surface. Chondrocytes in this layer are flat or disc-shaped and progenitor cells have been observed [13]. The middle layer contains a thick layer of collagen in an oblique orientation. This layer has increased proteoglycan and decreased water concentration when compared to the superficial layer. Chondrocytes are round, and progenitor cells are absent. The deep layer contains collagen fibers that are oriented perpendicular to the bone with a continued increasing proteoglycan concentration. The deep layer resists compression as the collagen attaches to the calcified layer at the base of the cartilage-bone interface known as the tidemark. The tidemark separates true articular cartilage from chondral remnants left over from appositional growth and creates a barrier to nutrient diffusion.

Articular cartilage is avascular. This limits its regeneration and healing potential. Efforts to stimulate cartilage defect healing and regeneration by marrow stimulating techniques have hinged around creating bleeding at the defect site. The initial blood clot that forms in the cartilage defect contains mesenchymal cells. Days after clot formation, these mesenchymal cells begin to proliferate. Several weeks later, cell differentiation produces cells similar in histological appearance to cartilage progenitor cells. The presence of such cells is short lived. By 3–4 years, fibrocartilage predominates. This fibrocartilage lacks the durability of the surrounding articular cartilage and tends to degenerate with time.

Current research has focused on increasing the number of mesenchymal cells in the clot, improving chemical signals within the clot, and enhancing clot stabilization. These methods have included microfracture, abrasion, scaffolding placement, platelet-rich plasma augmentation, and other various techniques to improve the body's ability to heal.

Marrow stimulating techniques and outcomes

Techniques

In 1959, Pridie was the first to advance the concept of accessing bone marrow space by drilling holes in the subchondral bone to elute bone marrow stem cells [5].His concept involved drilling holes of about 2–2.5 mm in width to access bone marrow but produced inconsistent results and long recovery times. Based upon the same principle of marrow stimulation, Johnson introduced abrasion chondroplasty in the 1980s which involved removal of 1–3 mm of bone with a burr. Results were also inconsistent and the trauma to subchondral bone resulted in worse post-operative function in as much as 33 % of the patients when compared to their pre-operative function [14].

Steadman introduced the technique of microfracture in the 1990s [10]. Microfracture involves debridement of loose and unstable cartilage back to a stable rim. It is important to remove the calcified cartilage layer and to create a well contained lesion with vertical articular cartilage walls at the rim. Following meticulous preparation of the lesion, perforation of the subchondral bone is performed with angled awls. The roughly 2 mm diameter holes are made about 3–4 mm apart. It is important to make sure the holes extravasate blood. This results in the chondral defect being filled by a blood clot. This clot includes multipotent stem cells from the bone marrow. These cells are able to differentiate into fibrochondrocytes which stimulate fibrocartilage repair [12].

Outcomes

Steadman and colleagues have reported symptomatic improvement in 80 % of patients at an 11-year follow-up [11]. Steadman's study included younger patients with defects that are less than 4 cm^2. Others have shown deterioration after initial improvement, especially in patients who are older than 40 [11, 12]. The best results seem to occur in young patients with small lesions (<2–3 cm^2) that are less than 1 year old [15]. Treatment failure is common beyond the 5 year post-operative period [16].

Solheim et al. evaluated 110 patients in a 10–14-year follow-up study and found that poor long-term outcome was more frequent in patients with arthroscopic signs of mild degenerative changes in the cartilage surrounding the treated defect. Their study showed significant improvement of Lyshom score and mean pain score from baseline to midterm follow-up. There were almost no changes when comparing midterm to long-term follow-up, indicating that much of the clinical deterioration occurs during short to midterm follow-up. Normal knee function was generally not achieved, and about 39 % of patients needed additional surgeries during the observation period. Almost half of the patients had poor

long-term outcome as defined by a Lysholm score below 64, or subsequent knee arthroplasty surgery [17].

A similar study performed by Bae et al. showed that survival of the repair tissue after microfracture declined from 89 % at 5 years, to 68 % at 10 years, and 46 % at 12 years. Lesions <2 cm^2 had a better outcome [18•]. Gobi et al. found similar results in a mean 15-year follow-up study of defects that were an average of 4 cm^2 in athletes with mean age of 31. Lyshom score showed initial improvement from baseline but declined at 5 and 15 years, although still better than baseline score [19].

Quality of repair depends on patient age, surgical technique, size and location of the lesion, and post-operative rehabilitation [17]. Surgical technique can also play a role in outcomes, although limited studies exist. In a cadaver study, Kroell et. al reported variability of the microfracture technique among experienced surgeons. Surface shearing was associated with penetration depth >4 mm and angles >20 degree. Inter-hole infraction was found in holes less than 2.5 mm apart. [20] Of note, a previous study using rabbits showed that deeper subchondral perforation (whether with drilling or microfracturing) resulted in improved repair matrix with better cartilage defect fill and increased type II collagen and glycosaminoglycan [21]. A recent sheep study showed 1.0 mm subchondral drill holes had improved osteochondral repair, with better histological matrix staining, subchondral bone plate microstructure restoration, and bone mineral density when compared to 1.8 mm drill holes [22]. A recent clinical study of 52 National Football League athletes showed 4.4 times less likelihood of return to NFL for patients undergoing chondroplasty with microfracture when compared to chondroplasty alone. Only 10 of 21 athletes who underwent concomitant microfracture returned to play. For both groups, those who did return to play took a mean time of about 8 months [23]. Steadman has reported about 76 % return to play in a previous study [24]. A second Steadman study showed 95 % (19 of 20) return to competitive skiing in elite ski racers following microfracture, with a mean Lysholm score of 86, and excellent patient satisfaction at 2-year follow-up [25].

Histological and immunohistochemical analysis of the failed repair tissue shows fibrocartilaginous repair with an increased cell number to extracellular matrix ratio and incomplete subchondral bone restoration [26].

Animal studies have shown that subchondral drilling alters the microarchitecture of the subchondral bone. This makes the repair more fragile and causes formation of intralesional osteophytes and cysts [27].

One reason for incomplete filling of the defect following microfracture may be the limited number of stem cells found in the blood clot. The clot that is formed by bone marrow penetration that would fill several milliliters in volume contains less than 100 bone marrow mesenchymal stem cells. A similar sized area of articular cartilage normally contains approximately 10 million cells. This significantly limits the number of cells that can differentiate into chondrocytes that have the ability to form hyaline-like cartilage [28, 29]. Future goals are to improve the environment and the cell count for better tissue regeneration.

Direct comparison of microfracture to other chondral restoration techniques is limited. Knutsen and colleagues performed a prospectively randomized trial comparing microfracture to autologous chondrocyte implantation with results reported at 2-year and 5-year follow-up [30, 31]. Both methods provided satisfactory results in 77 % of the patients at 5-year follow-up, as measured by the International Cartilage Repair Society, Lysholm, Short Form-36, and Tegner scores. There were no statistically significant differences in any clinical outcomes or rate of radiographic changes between the two groups at either follow-up time. One-third of the patients in each group developed radiographic evidence of osteoarthritis at 5-year follow-up. Kon et al., at 5-year follow-up in a non-randomized comparison study of microfracture and second generation autologous chondrocyte implantation, did find better clinical improvement in the autologous chondrocyte implantation group, as measured by the International Knee Documentation Committee score [32]. Both groups did improve over the course of the study. Goyal et al. performed a systematic review that compared microfracture with autologous chondrocyte implantation and ostoechondral cylinder transfers [16]. Only 15 studies met the inclusion criteria for a Level I or II study. Microfracture was observed to have declining clinical results after 5 year follow-up, regardless of lesion size. Younger patients did better irregardless of lesion size. But no conclusions could be drawn as to whether the other cartilage restoration techniques performed any better than microfracture.

Microfracture with scaffolding/biomembrane

This technique aims to provide a stable environment for the cells to proliferate by protecting them with a scaffold or biomembrane to prevent loss of cells from the clot. The microfracture technique is the same, but there is an added step of using a scaffold or membrane to hold the clot. More voluminous and adherent clot produces a better repair [33]. Chung et al. showed better radiographic results in patients treated with microfracture and a cartilage extracellular matrix biomembrane versus microfracture alone at 2 years. However, there was no statistically clinical difference as measured by the Analog Score (VAS) and International Knee Documentation Committee (IKDC) score at the 2-year follow-up [34]. Similar radiographically promising results have been shown with the use of scaffolds at short-term follow-up [35].

Dai et al. studied decalcified cortical-cancellous bone matrix (DCCBM) with microfracture in a rabbit model. The authors found better matrix staining and biomechanical

properties that were closer to that of normal cartilage in a group treated with combined microfracture plus DCCBM, as compared to microfracture alone, or DCCBM alone [36]. Another technique utilized chitosan, a glucosamine polysaccharide derived from exoskeleton of crustaceans, which increases adhesion. BST-CarGel is a chitosan-based gel that has properties to help stabilize clot formation without interfering with the normal coagulation cascade [33, 37•]. Stanish et al. used BST-CarGel in a single-blinded study of two randomized groups—microfracture and microfracture with BST-CarGel. Mean lesion size was 2 $cm^{2.}$ Eighty patients, ages 18–55 were enrolled in the multicenter international study. Follow-up was done with a blinded magnetic resonance imaging analysis at 12 months. This analyses revealed greater lesion filling, and more hyaline cartilage-like T2 values in the group that was treated with the BST-CarGel. However, at 12 months, there was no significant clinical difference between the two groups as measured by Western Ontario and McMaster Universities Osteoarthritis Index [37•]. Another recently published study involved assessment of the same group of people at 5 years. Another blinded MRI was performed in the two patient populations. This showed similar results, with better quality and quantity of healing when compared to microfracture alone. It also showed much improved pain, stiffness and function in both groups when compared to baseline. However, as in the previous study, no clinical difference was observed between the groups [38•]. Similarly, many animal studies also show that better marrow stimulation and improved hyaline-like cartilage is achieved when a chitosan/blood implant is used along with the microfracture or drilling techniques [39–41].

Biologic enhancement of microfracture technique

Platelets are known to carry many growth factors including vascular endothelial growth factor, epidermal growth factor, platelet-derived growth factor, IGF-1, fibroblast growth factor, TFG-β1, and others. These factors promote anabolic pathways and inhibit catabolic pathways. The chemoattractants recruit fibrin and other proteins to form a biological scaffolding for the bone marrow derived stem cells to proliferate and differentiate [42]. Some studies have shown better results with the addition of platelet-rich plasma (PRP) to the conventional microfracture or drilling techniques. [29, 42] Specimens treated with PRP show improved staining for type II collagen and proteoglycans, when compared to untreated specimens [43].

Siclari et al. followed 52 patients (mean age 44 years) who underwent subchondral drilling and covering with a cell-free polyglycolic acid-hyaluronan implant that was immersed in autologous PRP. They obtained biopsies at 2 years. Results showed tissue rich in type II collage, proteoglycans and chondrocytes. They also showed good clinical outcomes when compared to baseline, although no control group was used [44]. The same patient population was followed for 5 years. These results showed continued improvement in Knee Injury and Osteoarthritis Outcome Scores, no clinical signs of implant loosening, and excellent defect filling as seen on MRI. No significant clinical differences were found in a sub-group analysis looking at defect size, location, or degenerative condition [45•]. This suggests that the addition of PRP has good clinical outcomes at midterm follow-up, although comparative studies are warranted.

The field of tissue regeneration and marrow stimulating techniques is constantly evolving. There are other new and novel techniques that have shown good short-term outcomes.

Microfracture combined with a collagen membrane immersed in bone marrow concentrate from the iliac crest showed improved short-term knee function and hyaline-like cartilage [46]. Animal studies also suggest better hyaline-like tissue formation on histological evaluation in goats that underwent drilling with bone marrow cells harvested from the iliac crest when compared to drilling alone [47].

A 9-month post-operative histological analysis revealed 85 % hyaline cartilage in patients that were treated with a chondral allograft consisting of native viable chondrocytes, chondrogenic growth factors and extracellular matrix proteins that was used in combination with marrow stimulation. This was compared to only 5 % hyaline cartilage in a group treated with marrow stimulation alone [48].

Another novel technique includes the use of pulse electromagnetic fields with microfracture. This showed better midterm clinical outcome when compared to microfracture alone [49].

Use of hyaluronic acid with microfracture has also showed some promise in marrow stimulation [29].

Rehab protocol

Post-operative rehabilitation following any of these techniques is a crucial step. The goal of rehab is to promote an ideal environment for mesenchymal cell differentiation. Rehab generally involves flat foot weight bearing for 6 weeks with progressive range of motion and physical therapy. This is followed by gradual increase towards full weight bearing [12, 17]. Exercises include stretching, straight-leg raise, and passive range of motion followed by closed-chain exercises. Return to sports is restricted for about 6 months [50•].

Steadman's rehab protocol for NFL players following microfracture included a continuous passive motion machine (CPM) [24]. Animal studies suggest that CPM increases nutrient delivery to healing tissue and increased metabolic activity. Additionally, CPM is thought to enhance pluripotent cell maturation into articular cartilage and the resulting regenerated animal tissue has been shown to have higher structural integrity with CPM [51]. While animal studies appear promising, the use of CPM in humans has been debated religiously with minimal high-level evidence. Recently, Karnes et al.

reviewed 28 studies evaluating CPM following microfracture and noted a lack of consistent reporting and protocol. [52] For those who used CPM, most adjusted the ROM from 0 to 30 degrees for 6–8 hours a day lasting 6 weeks in duration. Similarly, Vogt conducted a survey of European knee experts demonstrating the popularity of CPM [53]. His group found that CPM was used by 80 % of respondents, with the most common duration of therapy lasting longer than 3 weeks (61 %). 70 % of the 245 responding surgeons started PT on post-op day 1 with the most common duration of therapy lasting 6 weeks (55 %) and 60 % used NSAIDs postoperatively. Again, Vogt emphasized that these numbers were for current practices and not level 1 evidence.

Last year, Schmitt et al. provided a systematic review of the literature and found 5 studies from a single group advocating accelerated weight bearing following cartilage procedures [54]. In these studies, the accelerated groups had improved 6-minute walk test and straight leg raise test scores; however, no difference was observed with respect to persistent gait abnormalities, Once again, the authors caution that the reviewed articles may be skewed by small sample sizes and differences in populations and injuries compared between studies.

Limitations

Shortcomings of marrow stimulation techniques include the following: limited production of hyaline repair tissue, unpredictable repair cartilage volume, deterioration of results over time, and potential negative impacts on later cellular transplantation, if required [55].

Conclusions

In the USA, there is about a 5 % annual incidence of growth of articular cartilage repair procedures. Chondroplasty, which is more of a palliative care procedure, remains much more common than repair or restoration techniques because of the relative lack of predictable results with articular surface repair procedures [56]. Microfracture remains a current tool for attempts at articular cartilage repair for smaller isolated lesions, particularly in younger patients. In this setting, the technique shows reasonable short to midterm outcomes. Recent studies show some promise when combining microfracture with other adjuncts such as PRP or other progenitor cell stimulants, or scaffolding. However, further work needs to be done to prove their efficacy.

Compliance with Ethics Guideline

Conflict of Interest The authors have nothing to disclose.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors

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