

# Science and Animal Models of Marrow Stimulation for Cartilage Repair

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## Abstract

Microfracture of subchondral bone to enhance cartilage repair is a popular surgical technique used in human and animal patients. Clinical results with resolution or improvement in pain are promising and last on average for 2 to 3 years. Animal studies aimed at understanding microfracture indicate that the repair tissue continues to remodel toward chondrogenesis for at least a year, but longer term results are not available to gain insight into the mechanism of microfracture function or failure over time. Subchondral bone sclerosis and central lesional osteophyte formation following subchondral bone microfracture have been observed in animal models of microfracture, but studies do not provide any insight into the etiology of these pathologies. The continued maturation of microfracture repair tissue over time supports further investigation of microfracture or microfracture-augmented cartilage repair procedures with caution for the investigator and clinician to be observant for conditions that lead to subchondral bone sclerosis or central osteophyte formation, and what affect these bony reactions have on clinical outcome.

## Keywords

- ▶ microfracture
- ▶ microdrilling
- ▶ central osteophyte
- ▶ micropic

Microfracture perforation of the subchondral bone for cartilage repair was originally described by Steadman in 1994.<sup>1</sup> Microfracture involves penetration of the subchondral bone plate with an arthroscopic awl to allow bone marrow contents to fill the defect and form a “superclot.”<sup>2</sup> In humans,<sup>1,3,4</sup> and nonhuman primates,<sup>5</sup> microfracture results in increased tissue volume and improved patient comfort and function for an average of 2 to 3 years. There are other described methods of bone marrow stimulation such as drilling and abrasion, but less research and clinical data are available to critically evaluate the efficacy of these techniques.

## The Superclot

In theory, enhanced cartilage repair following microfracture is the result of the superclot thought to be laden with bone marrow-derived mesenchymal stem cells (MSCs) and growth

factors.<sup>6</sup> Although there have been several in vitro and in vivo animal studies aimed at understanding how microfracture repair tissue remodels over time, it has never been well documented that the superclot contains MSCs or growth factors. In a small study of 11 human patients with femoral condylar defects, superclot from microfracture was compared with bone marrow aspirate from the iliac crest and concentrated by centrifugation.<sup>7</sup> The two cellular populations were different with respect to cell surface markers. Neither cell type carried CD34 or CD45 marker expression suggesting that there were no hematopoietic cells in either bone marrow aspirate concentrate or microfracture superclot. This result might suggest that neither cell source is derived from the bone marrow, but it must be interpreted with great caution because both cell sources were cultured for at least two passages and the cells were treated with trypsin before flow cytometry analysis, both of which have been

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documented to alter cell surface protein expression on stem cells.<sup>8,9</sup> In a similar study where cells were derived from subchondral corticospongy bone, and cultured over time, the cells retained their multilineage potential to undergo trilineage differentiation into cartilage, adipose, and bone phenotypes.<sup>10</sup> Interestingly, MSC-based cartilage studies continue to focus predominantly on the ability of the cells to differentiate into and form neocartilage despite the growing evidence that MSCs function at least in part to modulate the local environment through a paracrine effect and recruitment of other progenitor cells and immunomodulation.<sup>11,12</sup>

Understanding the source and type of cells that populate microfracture defects is critically important given the number of studies where drugs, growth factors, devices, scaffolds, growth factors, technologies, gene therapy, and rehabilitation recommendations that have been and are being developed, investigated, and marketed predicated on the concept that they support chemotaxis, adherence, and or proliferation of bone marrow-derived MSCs.<sup>13–19</sup> These cited studies represent only a few of the many studies investigating the use of scaffolds, devices, drugs, etc., in vitro and in rabbit, canine, ovine, laprine, or equine animal models for augmentation of microfracture to enhance articular cartilage repair. This intense level of investigation into scaffold/device-augmented microfracture and their potential recruitment of MSCs lie in the thought that these technologies could improve the clinical results of microfracture alone and the relative ease and marketability of such technologies when compared with cultured or manipulated stem cell articular cartilage grafts.

If the cell population of the subchondral bone is truly different from that of bone marrow aspirated from a bone marrow space, then perhaps the results of in vitro studies done on bone marrow aspirate or metaphyseal-derived MSCs are not directly applicable to microfracture where the cell will likely derived from the subchondral bone plate in the area 2 to 4 mm underlying the calcified cartilage layer.<sup>13,15</sup> During the process of maturation, the cell population in a superclot might be composed of cells derived from the bone marrow, subchondral bone, surrounding host cartilage, synovium, synovial fluid, or a combination thereof. Studies are routinely performed in vitro and using bone marrow-derived MSCs to investigate a method to improve microfracture and the results can change clinical practice. For example, a recent study showed that chondrogenic differentiation of bone marrow-derived MSCs is impaired by rheumatoid arthritis synovial fluid as compared with synovial fluid from patients with osteoarthritis or normal patients.<sup>20</sup> Another study which suggested that age in males, but not in females, negatively affects their ability to undergo chondrogenic differentiation.<sup>21</sup> The potential clinical ramifications of this study, where clinicians might presume failure of microfracture in patients with rheumatoid arthritis or in older males, underscore the need for a more refined understanding of the basic biology of microfracture.

### Animal Model Studies

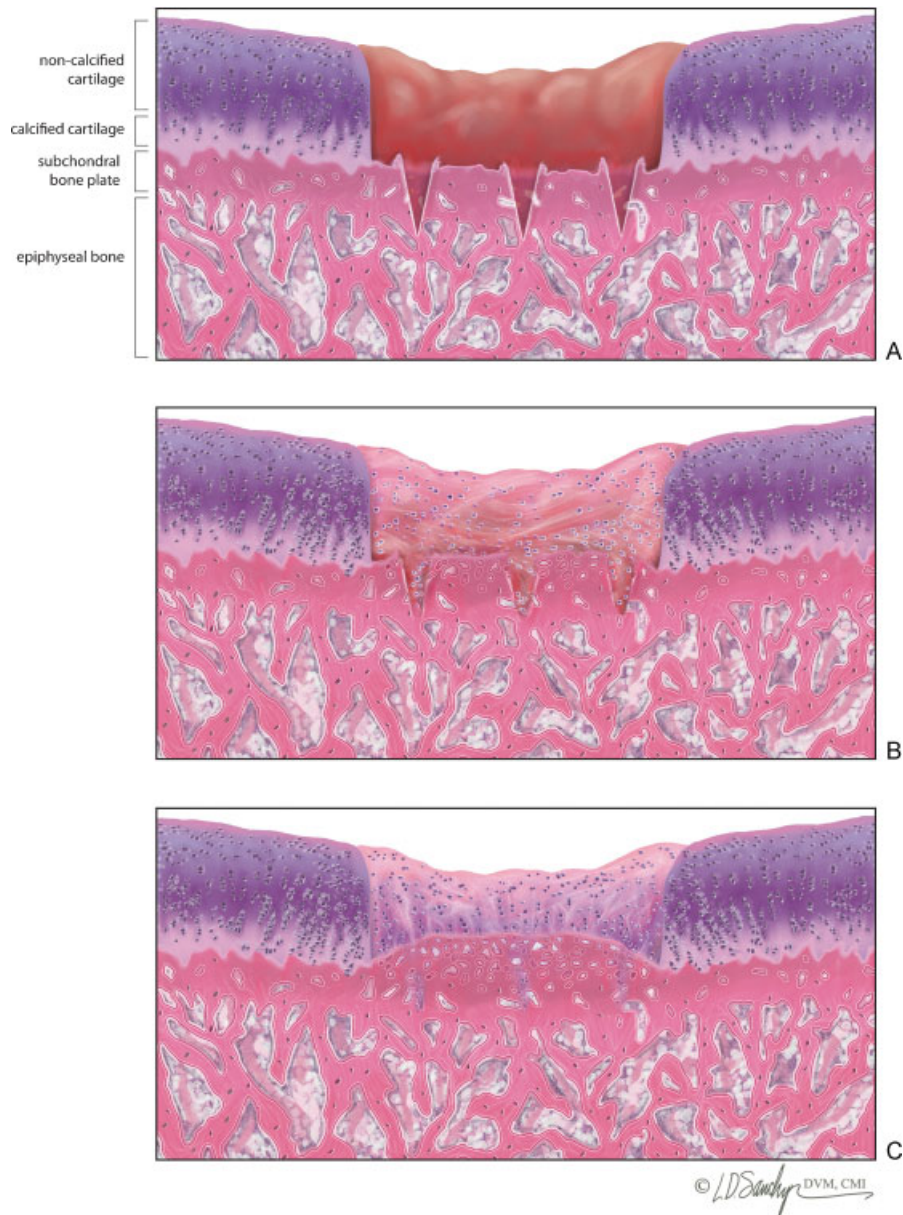
Animal model studies provide insight into temporal changes following microfracture (► **Fig. 1**). Early animal model studies

on microfracture repair were done in the horse.<sup>22,23</sup> The horse model was also used to validate the subjective clinical impression that removal of the calcified cartilage layer was important to optimize volume and attachment of repair tissue.<sup>24</sup> Further equine studies indicated that the volume of repair tissue did not change between 4 and 12 months postmicrofracture in direct weight-bearing sites (distal medial femoral condyle and distal radiocarpal bones), which at a minimum suggests that the repair tissue did not deteriorate by 12 months postoperatively.<sup>22</sup> Histologic assessment revealed that there was more type II collagen present at 12 months than at 4 months suggesting continued chondrogenic maturation of repair tissue to 12 months but the aggrecan content remained far below normal.

To provide information in a physiologic and anatomic environment more closely related to the human, similar studies were performed in cynomolgus macaques.<sup>5</sup> In this study, repair tissue was studied at 6 and 12 weeks postmicrofracture and indicated that the repair tissue underwent progressive chondrogenic remodeling during this time period based on post-mortem gross and histologic assessments. It is interesting to note that progressive maturation of microfracture repair tissue is not appreciated using arthroscopy with validated categorical scoring systems<sup>25</sup> which makes it difficult for a surgeon to make decisions regarding success based on arthroscopic observation only.<sup>26</sup> Noninvasive dGEMRIC and T2 mapping has been used to evaluate repair tissue following microfracture at 24 and 48 weeks postoperatively in a goat model.<sup>27</sup> The achieved objective of the study was to validate dGEMRIC and T2 mapping as surrogate markers of biochemical and histologic integrity of repair tissue. In addition, the study was the first to demonstrate increased glycosaminoglycan and total collagen content between 24 and 48 weeks postmicrofracture measured with both  $\Delta R1$  (1/s) and high performance liquid chromatography. Combined, these results suggest that microfracture continues to mature for the first 12 months after surgery, but the lack of normal matrix molecules translates to tissue with inferior biomechanical properties compared with normal cartilage, which renders the repair tissue prone to injury and deterioration. Based on animal model studies, it is unclear what biochemical or mechanical changes happen beyond 12 months and when, why, or how microfracture repair tissue fails or not. In an unpublished data by L.A.F, 2-year data are being analyzed in the horse. Clinically, it may have less to do with the breakdown of microfracture repair tissue than it does the ability of the repair tissue to “shield” the subchondral bone from load that is theoretically associated with the manifestation of symptoms. If this theory is correct, then methods to enhance or retain proteoglycan content in the repair tissue would increase the compressive stiffness of the repair tissue and should improve long-term results.

### Central Osteophyte Formation and Subchondral Bone Sclerosis

Microfracture has long been thought of as a “can’t hurt,” or “burn no bridges” type of procedure. However, in more recent years, there is heightened awareness and concern about the



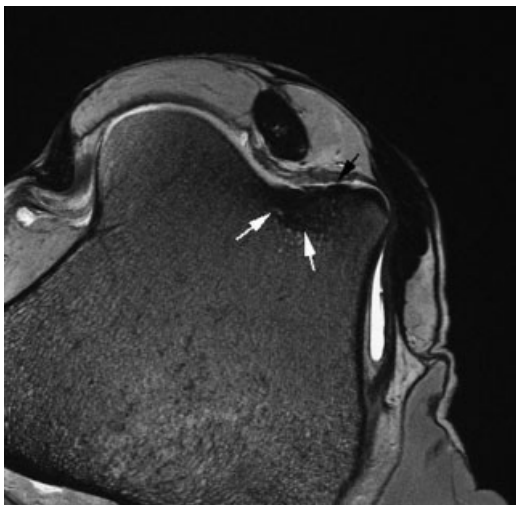
**Figure 1** Schematic representation of microfracture maturation over time. (A) At time 0, the cartilage defect is debrided to include removal of calcified cartilage. Microfracture is performed to a depth of 2 to 4 mm to penetrate the subchondral plate thereby allowing bone marrow to gain access to the cartilage defect forming a “superclot.” (B) At 4 to 6 months postmicrofracture, there is progressive chondrogenic remodeling of the fibrocartilage repair tissue filling the defect. The repair tissue is hypercellular. Proteoglycan (purple in base of repair tissue) and type II collagen content (not depicted) progressively increase, but remain low compared with normal tissue. Chondrocyte cloning is evident in the adjacent host cartilage. The microfracture holes progressively heal during this time period. (C) At 12 months postmicrofracture, the repair tissue has improved cellular organization and proteoglycan content, but not type II collagen. The microfracture holes are healed and in some instances, the subchondral bone is sclerotic and/or extends into the cartilage defect forming a “central osteophyte.”

formation of central/intralesional osteophytes, which are protrusions of subchondral bone extending above the level of the adjacent, normal subchondral plate (→ Fig. 2).<sup>28</sup> Formation of central osteophytes is not specifically investigated a priori or mentioned in most animal studies despite being quite obvious in figures contained in published articles, irrespective of the animal model studied. Figures presented in articles can be too high in magnification or focused on the repair-host tissue interface to appreciate central osteophyte formation. It should be noted that central osteophyte forma-

tion has been observed in microfracture defects in the horse model in both the distal femur (→ Fig. 3)<sup>22,29</sup> and lateral trochlear ridge (→ Fig. 2)<sup>30</sup> in ovine,<sup>14</sup> and in nonhuman primates.<sup>5</sup> Central osteophyte formation clearly does not occur in every case of microfracture and there are too few instances in the animal model studies for robust observations into causality.

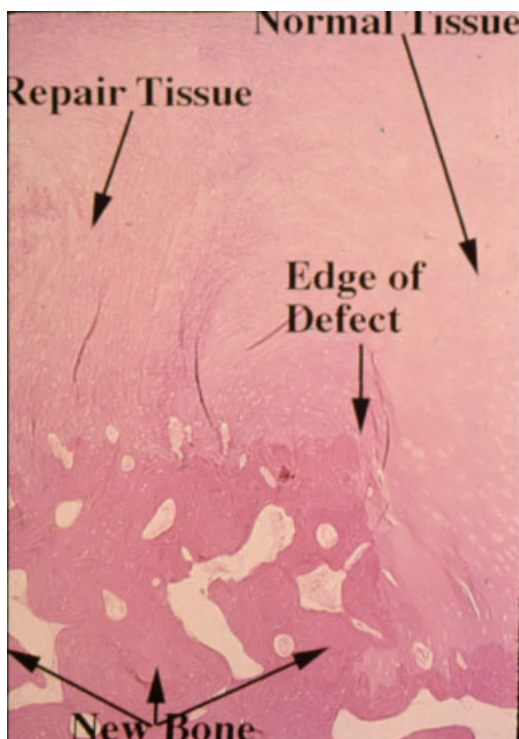
Subchondral bone sclerosis has also been noted following microfracture in horses when the repair tissue was assessed with radiographs or magnetic resonance imaging (MRI).<sup>26,30</sup>





**Figure 2** Fast-spin echo magnetic resonance image (MRI) of a microfracture-treated defect on the lateral trochlear ridge of the femur, 12 months after surgery. Subchondral bone sclerosis (white arrows) and protrusion of the subchondral plate into the cartilage defect (black arrow) are evident.

Most animal studies evaluate repair with histology and not with radiographs or MRI making assessment of subchondral bone sclerosis difficult and subjective. Sclerosis of the subchondral bone has been postulated as an initiating event in the development of osteoarthritis.<sup>31–33</sup> It should be restated that the animal model studies are limited to 1 year duration



**Figure 3** Histologic appearance of a microfracture-treated defect on the medial femoral condyle, 12 months after surgery. The fibrocartilage is well adhered to the surrounding normal cartilage tissue and to the underlying, protruding new subchondral bone. (Reproduced with permission from Frisbie DD, et al. *Vet Surg* 1999;28(4):242–255.)

so the long-term presence or consequences of this subchondral bone sclerosis on the microfracture repair tissue or clinical outcome of the patient is not evident.

Microfracture by definition is fracturing of the subchondral bone, and the results of subchondral bone sclerosis or central osteophyte formation might be anticipated knowing the natural course of healing following microfracture of cancellous subchondral bone. Trabecular microfractures of the femoral head, spine, patella, acetabulum have been studied since the 1960s.<sup>34</sup> These naturally occurring microfractures heal with woven bone microcallous. It is reasonable to presume that penetration of the subchondral plate with a microfracture awl to gain access to bone marrow elements stimulates a similar bone repair response. What circumstances lead to an overexuberant reaction with resultant central osteophyte formation is not clear. Bone repair/regeneration is complex and is influenced by many factors including age, mechanical and cellular environments, bone mineral content, and genetics.<sup>34,35</sup> There are also differences in the response of cells to mechanical loading and this too might influence cells in the superclot to differentiate down osteogenic or chondrogenic lineages.<sup>33,36</sup> The ability of progenitor cells to differentiate into osteogenic or chondrogenic cell lines should be remembered and investigated simultaneously when developing technologies for augmentation of microfracture.

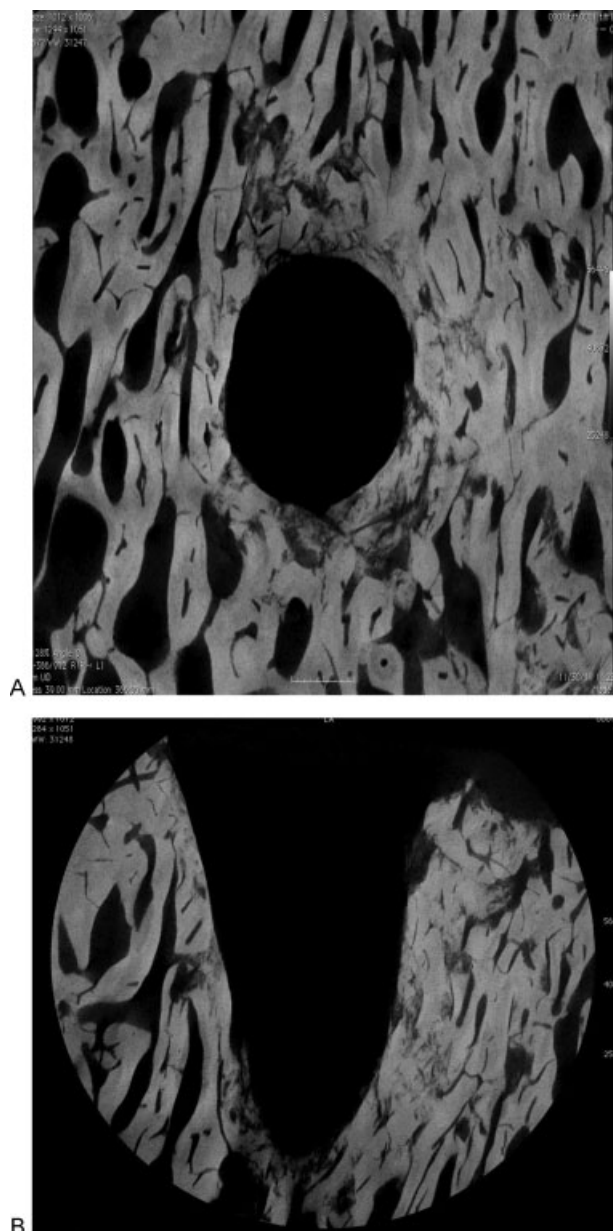
### Subchondral Cystic Formation

In animal models when using the medial femoral condyle as the treatment site, violation of the subchondral bone plate can result in formation of subchondral bone cysts.<sup>37–39</sup> In preparation of a cartilage bed for microfracture, overexuberant debridement of the calcified cartilage layer to include removal of the subchondral bed can lead to subchondral cyst formation.<sup>39</sup> Precise attention to the technical aspects of microfracture and the use of skeletally mature animals where the tidemark is formed and the calcified cartilage layer is visibly different that the overlying normal cartilage and underlying subchondral bone may be associated with reduced cyst formation. Radiolucent “cyst-like” areas in the medial femoral condyle have been observed following microfracture, but there was no evidence of a cyst on histologic analysis.<sup>22</sup> Although MRI was not performed, the authors were of the opinion that the radiolucency represented bone edema.

### Microfracture Compared with Microdrilling

In a rabbit study comparing microdrilling to microfracture at a depth of 2 mm, microcomputed tomography imaging performed 1 day postoperatively indicated that microfracture leads to more compaction of bone in the holes than did microdrilling.<sup>40</sup> The authors concluded that this impaction of bone might impede the ability of bone marrow to reach the articular defect and thereby might negatively affect repair. Bleeding in only one of four microfracture holes was observed intraoperatively, but all defects were filled with a blood clot. The lack of bleeding from the microfracture holes has not

been reported, nor is it consistent with the clinical experiences of the authors in humans or horses. Thus, it is likely a flaw of the rabbit as an animal model or more likely, as the authors suggested, a result of the type of homemade microfracture awl specifically created for the study, which had a collar to limit the depth of penetration to 2 mm. The collar likely restricted movement of bone from the microfracture holes, creating impaction fractures in the subchondral bone. However, impaction of subchondral bone surrounding the microfracture hole is seen using standard arthroscopic microfracture awls without a collar (►Fig. 4; ►Videos 1, 2). Microdrilling might be as effective as microfracture, but obviously



**Figure 4** Microcomputed tomography of normal equine lateral trochlear ridge subjected to microfracture. (A) Axial view of a microfracture hole demonstrating impaction of surrounding subchondral bone. (B) Sagittal view of a microfracture hole demonstrating impaction of surrounding subchondral bone. Minimum intensity projection of Micro-CT data acquired with 4  $\mu$ m x-y-z voxel size.

#### Video 1

Continued impaction of bone from the depth to the surface of the microfracture hole.

Online content including video sequences viewable at: [www.thieme-connect.com/ejournals/html/jks/doi/10.1055/s-0032-1310389](http://www.thieme-connect.com/ejournals/html/jks/doi/10.1055/s-0032-1310389)

#### Video 2

Impacted bone surrounding the entire circumference of the microfracture hole.

Online content including video sequences viewable at: [www.thieme-connect.com/ejournals/html/jks/doi/10.1055/s-0032-1310389](http://www.thieme-connect.com/ejournals/html/jks/doi/10.1055/s-0032-1310389)

requires more surgical instrumentation such as a drill compared with a hand-held awl to generate a superclot.

In summary, basic science and animal model studies indicate that microfracture results in improved repair tissue that continues to mature and becomes more cartilaginous for at least 1 year after surgery. The superclot clearly remodels, but does remain quite inferior to normal articular cartilage in matrix molecule composition and therefore biomechanical function. Numerous studies have been performed to augment microfracture even though we don't fully understand the fundamental biology of microfracture, and therefore how to improve upon current results. A potential detriment to the use of microfracture is the formation of central/intralesional osteophytes, which are unpredictable and have been associated with persistent or recurrent pain in human studies. Microfracture remains a commonly performed and investigated cartilage repair procedure because it is easy to do, requires minimal equipment, and clinical results in human patients are encouraging.

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