Editorial Commentary: Biological Cartilage Repair Technique—An "Effective, Accessible, and Safe" Surgical Solution for an Old Difficult Biological Problem

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Abstract: Achieving good long-term outcomes while treating chondral defects has always been a challenge. Several surgical techniques for regeneration of the articular cartilage have been proposed. Among them, osteochondral autograft transplantation and 2-step procedures such as autologous chondrocyte implantation have provided good results, promoting formation of new hyaline-like cartilage tissue, whereas other techniques such as microfracture result in fibrous cartilage and a less durable repair. Single-stage cell-based procedures are an attractive treatment option given the potential for cost savings and avoiding a second-stage procedure. We believe that 1-stage cartilage repair in the knee with a hyaluronic acid–based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate has a prominent role in treating chondral defects because this is a simple technique that could improve the care of patients and be cost-effective in the near future.

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High-quality studies such as systematic reviews, meta-analyses, and randomized clinical trials are critical to assess the long-term results and understand the real efficacy of a procedure. The study by Zamborsky and Danisovic[1] entitled "Surgical Techniques for Knee Cartilage Repair: An Updated Large-Scale Systematic Review and Network Meta-analysis of Randomized Controlled Trials" investigates the most appropriate surgical interventions for patients with knee articular defects from Level I randomized controlled trials. The authors reviewed 21 articles, including 891 patients.

We commend Zamborsky and Danisovic[1] for conducting a well-designed network meta-analysis of randomized clinical trials that helps to build the body of literature of different approaches that are readily available. We believe that this study can provide clinicians better insight into the pros and cons of widely performed cartilage repair techniques.

On the basis of the study by Zamborsky and Danisovic,[1] 2 important things can be concluded. First, microfracture (MF) results in poor long-term outcomes compared with advanced repair procedures such as autologous chondrocyte implantation (ACI), matrix-induced autologous chondrocyte implantation (MACI), and osteochondral autograft transplantation, which is in line with findings from a previous study from our institution.[2] Second, advanced cartilage repair techniques perform better than MF with a lower failure rate and a faster return to activity.

Moreover, Zamborsky and Danisovic[1] showed that osteochondral autograft transplantation had good to excellent results compared with MF whereas MF had poor results compared with ACI and MACI. Conversely, they did not find a significant difference among different interventions regarding reintervention, biopsy types, or adverse events. Finally, according to the *P* value scores for intervention ranking, there was a disagreement on the best intervention. However, MF was always ranked last.

Articular cartilage lesions are frequently found during knee arthroscopy. In a study of 1,000 patients who underwent arthroscopy, the prevalence of

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osteochondral defects was 61%.[3] In a review of a Polish registry, 5.2% of patients had Outerbridge grade III or IV lesions.[4] Curl et al.[5] found over 53,000 hyaline cartilage lesions in 31,516 knee arthroscopies. Hence, treating chondral defects of the knee with a durable repair tissue that can provide long-term results has remained the predictor of a successful repair procedure.

On the basis of our 25 years of experience performing cartilage repair procedures, MF has been the workhorse in treating cartilage defects, primarily because of its simplicity and cost-effective nature. After our series of studies, our approach toward managing chondral defects has constantly evolved. In our study in which we analyzed long-term results after MF, we found that patients treated with MF had deterioration in their activity level after 3 to 5 years and the results were short-lived.[6] Furthermore, in a nonrandomized controlled trial, we (Kon et al.[2]) compared patients who underwent treatment for chondral lesions with second-generation ACI (MACI) and MF. The MACI group of patients had superior clinical outcomes to the MF group. Although ACI and MACI provide good to excellent long-term outcomes,[7] the high cost and 2-stage procedure associated with these procedures make them unfavorable procedures for treating all chondral lesions. Hence, a single-stage cartilage repair evolved using cell-free 3-dimensional scaffolds. Since 2005, the role of stem cells in treating cartilage lesions has been explored, opening a new dimension of obtaining similar results to ACI but with less morbidity to the patients. In a 5-year follow-up prospective cohort study, we compared 50 patients who had a diagnosis of grade IV cartilage injury and were treated with a hyaluronic acid–based scaffold along with bone marrow aspirate concentrate (HA-BMAC) and MF.[8] A significant difference was found with better outcomes and a more durable cartilage repair at mid-term follow-up in the HA-BMAC group of patients.

We further investigated the need for cell culture to obtain optimal results by comparing the clinical outcomes of MACI with HA-BMAC using the same scaffold (Hyaff; Anika Therapeutics).[9] At 3 years' follow-up, we did not notice any statistically significant differences between the 2 groups and we concluded that both techniques were viable and effective. Furthermore, second-look arthroscopy after HA-BMAC treatment showed that the repaired lesions were filled with stable and well-integrated tissue that was nearly normal to normal according to the International Cartilage Repair Society visual scoring system. These findings were comparable with those of the MACI group that underwent second-look arthroscopy. Moreover, histologic evaluation after biopsy of the repair tissue indicated comparable success between HA-BMAC and MACI treatment regarding the ability to regenerate hyaline or hyaline-like tissue. Magnetic resonance imaging evaluation of the repaired lesions was also performed postoperatively and showed comparative success in the ability to completely fill the defects with well-integrated repair tissue in both groups.[9]

Recently, we analyzed the long-term outcomes after single-stage HA-BMAC repair of chondral defects based on the size and location of the lesion and showed positive outcomes at long-term follow-up in small and large lesions and in multiple-compartment lesions.[10] Hence, single-step cartilage repair eliminates the need for a 2-step procedure, thereby reducing the cost and morbidity to the patient.

Bone marrow–derived mesenchymal stem cells (BMDSCs) interact with a nonwoven hyaluronan-based scaffold that supports cellular adhesion, migration, and proliferation, promoting the synthesis of extracellular matrix components under static culture conditions.[11-13] Nejadnik et al.[14] compared the clinical outcomes of patients treated with first-generation ACI and patients treated with autologous BMDSCs, concluding that BMDSCs are as effective as chondrocytes for articular cartilage repair. In addition, many studies have shown multipotent mesenchymal stem cells sourced from bone marrow aspirate concentrate in combination with a biological scaffold to provide good to excellent clinical outcomes at long-term follow-up, as with ACI.[9,11,15]

Finally, as stated by Zamborsky and Danisovic[1] in the "Discussion" section and on the basis of the previous literature that showed inferior long-term outcomes after MF,[6,8,16] many surgeons are giving stronger consideration to alternative cartilage restoration procedures. However, to have an algorithm in choosing the treatment option for managing articular cartilage defects, it would be incomplete without comparing randomized controlled trials of single-stage cartilage repair procedures. High-quality randomized controlled trials are necessary to directly compare all cartilage restoration procedures to determine differential efficacy and cost-effectiveness. We believe that 1-stage cartilage repair in the knee with a hyaluronic acid–based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate has a prominent role in treating chondral defects because this is a simple technique that could improve the care of patients and be cost-effective in the near future.[10]

References

1. Zamborsky R, Danisovic L. Surgical techniques for knee cartilage repair: An updated large-scale systematic review and network meta-analysis of randomized controlled trials. *Arthroscopy* 2020;36:845-858.
2. Kon E, Gobbi A, Filardo G, et al. Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the

knee: Prospective nonrandomized study at 5 years. *Am J Sports Med* 2009;37:33-41.
3. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. *Arthroscopy* 2002;18:730-734.
4. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: Study of 25,124 knee arthroscopies. *Knee* 2007;14:177-182.
5. Curl WW, Krome J, Gordon ES, et al. Cartilage injuries: A review of 31,516 knee arthroscopies. *Arthroscopy* 1997;13:456-460.
6. Gobbi A, Karnatzikos G, Kumar A. Long-term results after microfracture treatment for full-thickness knee chondral lesions in athletes. *Knee Surg Sports Traumatol Arthrosc* 2014;22:1986-1996.
7. Gomoll AH, Gillogly SD, Cole BJ, et al. Autologous chondrocyte implantation in the patella: A multicenter experience. *Am J Sports Med* 2014;42:1074-1081.
8. Gobbi A, Whyte GP. One-stage cartilage repair using a hyaluronic acid—based scaffold with activated bone marrow—derived mesenchymal stem cells compared with microfracture five-year follow-up. *Am J Sports Med* 2016;44:2846-2854.
9. Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patello-femoral chondral lesions: A nonrandomized prospective trial. *Cartilage* 2015;6:82-97.
10. Gobbi A, Whyte GP. Long-term clinical outcomes of one-stage cartilage repair in the knee with hyaluronic acid-based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate. *Am J Sports Med* 2019;47:1621-1628.
11. Facchini A, Lisignoli G, Cristino S, et al. Human chondrocytes and mesenchymal stem cells grown onto engineered scaffold. *Biorheology* 2006;43:471-480.
12. Lisignoli G, Cristino S, Piacentini A, et al. Chondrogenic differentiation of murine and human mesenchymal stromal cells in a hyaluronic acid scaffold: Differences in gene expression and cell morphology. *J Biomed Mater Res A* 2006;77:497-506.
13. Pasquinelli G, Orrico C, Foroni L, et al. Mesenchymal stem cell interaction with a non-woven hyaluronan-based scaffold suitable for tissue repair. *J Anat* 2008;213:520-530.
14. Nejadnik H, Hui JH, Feng Choong EP, Tai BC, Lee EH. Autologous bone marrow-derived mesenchymal stem cells versus autologous chondrocyte implantation: An observational cohort study. *Am J Sports Med* 2010;38:1110-1116.
15. Dimarino AM, Caplan AI, Bonfield TL. Mesenchymal stem cells in tissue repair. *Front Immunol* 2013;4:201.
16. Goyal D, Keyhani S, Lee EH, et al. Evidence-based status of microfracture technique: A systematic review of level I and II studies. *Arthroscopy* 2013;29:1579-1588.