Editorial Commentary: Cartilage Restoration—What Is Currently Available?

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Abstract: In the past 30 years, bone marrow stimulation techniques such as microfracture (MF) have become a popular method to treat symptomatic focal articular cartilage lesions. Nonetheless, recent studies have not shown good long-term clinical outcomes, and MF has produced alterations in the subchondral bone architecture with degenerative changes. Autologous chondrocyte implantation (ACI) has shown good results at 20 years. Second- and third-generation ACI has shown superiority to MF and fewer complications than first-generation ACI. Each treatment option has its advantages and disadvantages. Recent research has shown that better filling of cartilage tissue occurs in patients treated with MF and collagen augmentation than in those treated with MF alone. Research from our clinic has shown that Hyaff scaffold combined with bone marrow aspirate concentrate in a 1-step technique yielded good results in patients with 10 years' follow-up. We believe that high-quality randomized controlled trials are necessary to directly compare all cartilage restoration procedures.

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When we face a biological problem, we should find a biological solution. There are different ways to treat a chondral defect, but there is only one target: re-create the normal hyaline tissue and restore the normal properties of the natural tissue. Despite many possible treatment options, a large number of cases are still treated with microfracture. Nonetheless, numerous studies have shown that microfracture leads to the formation of fibrocartilaginous tissue with a tendency to degenerate over time, especially in an active population.[1-3]

A recent study from our research center reported the long-term clinical outcomes of 1-stage cartilage repair in the knee with a hyaluronic acid–based scaffold embedded with mesenchymal stem cells sourced from bone marrow aspirate concentrate (BMAC) and showed positive outcomes in patients with 10 years' follow-up.[4] All scores were significantly increased at final follow-up ($P < .001$). The median Tegner, visual analog scale (VAS), and International Knee Documentation Committee scores were 4, 0.3, and 85, respectively. The final median subset scores of the Knee Injury and Osteoarthritis Outcome Score (KOOS) were as follows: pain, 94; symptoms, 89; activities of daily living, 99; sports/recreation, 85; and quality of life, 85.[4] Moreover, a study by Kon et al.[5] showed the beneficial effects of the treatment of osteochondral lesions of the patellofemoral joint using hyaluronan-based matrix-assisted autologous chondrocyte transplantation observed at long-term follow-up (10 years). Peterson et al.[6] evaluated a large group of patients who underwent autologous chondrocyte implantation (ACI) with 10 to 20 years' follow-up and found good to excellent clinical results. Saris et al.[7] showed that the treatment of symptomatic cartilage knee defects more than 3 cm^2 in size using matrix-induced autologous chondrocyte implantation (MACI) was clinically and statistically significantly better than treatment with microfracture. Kon et al.[8] compared the clinical outcomes of patients treated with second-generation ACI implants versus those treated with the microfracture repair technique. This study showed that patients with second-generation ACI (Hyalograft C; Fidia Advanced Biopolymers, Abano Terme, Italy) had statistically significantly better clinical results and the ability to return to more vigorous sports activity than patients after microfracture at 5 years' follow-up.[8,9] Furthermore, Minas et al.[3] reported that there is an increase in the failure rate of ACI after prior

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treatment with marrow stimulation techniques. We believe that microfracture has a strong negative effect on subsequent cartilage repair with ACI and therefore should be used judiciously in larger cartilage defects, especially given our finding that patients treated with microfracture have a higher incidence of intralesional osteophytes and subchondral cyst formation. The study in this issue by Kim, Chun, Wang, Kim, Kang, Yoo, Chon, Kim, Moon, Chang, Song, Ha, Choi, and In,[10] entitled "Is Microfracture Still the Gold Standard Treatment for Symptomatic Focal Cartilage Injuries or Should We Move to More Durable, Regenerative, and Less Invasive Approaches?," evaluated the clinical efficacy and safety of microfracture combined with a collagen-augmented chondrogenesis technique (C-ACT).

We commend Kim et al.[10] for this work because it represents a well-designed Level I, multicenter randomized controlled trial in 100 patients (all underwent microfracture and 52 received additional atelocollagen augmentation). Eighty-nine patients were evaluated at 2 years' follow-up. Both patients who underwent microfracture alone and those who underwent microfracture with atelocollagen augmentation were evaluated with the VAS score, KOOS, and International Knee Documentation Committee score and were noted to have significant improvement 2 years postoperatively. The authors concluded that the addition of C-ACT resulted in the better filling of cartilage defects of the knee joint on magnetic resonance imaging at 12 months and statistically higher results in terms of the VAS score at 24 months and KOOS pain subscore at 12 months postoperatively. As noted by Kim et al., the study had some limitations, such as short-term follow-up and lack of histologic analysis. Moreover, half of the patients undergoing the C-ACT procedure had this performed with a high tibial osteotomy, not in isolation, and the study was a single-blinded trial.

The limited repair potential of human articular cartilage contributes to the development of debilitating osteoarthritis and remains a great clinical challenge. This has led to the evolution of cartilage treatment strategies from palliative to either reconstructive or reparative methods in an attempt to delay joint replacement. Further development of tissue engineering–based cartilage repair methods has been pursued to provide a more functional and durable biological tissue.[11]

Cell-based therapy with ACI results in type II collagen production. First-generation ACI showed good outcomes in patients with femoral condyle lesions, but patients with patellofemoral defects were noted to have poor results.[12] This finding, combined with the uncertainty of the distribution of chondrocytes, in addition to complications including periosteal graft hypertrophy and arthrofibrosis, as well as other complications, led to the development of second-generation ACI techniques.[8]

Studies of MACI for patellofemoral osteochondral lesions have shown comparable results to those in the tibiofemoral location when appropriate concomitant procedures are performed.[13] Filardo et al.[14] reported differences in outcomes between trochlear and patellar lesions when treated by MACI. Moreover, some studies have shown better results with MACI than with ACI for the patellofemoral joint.[15,16]

However, MACI remains a 2-step procedure including an arthroscopic biopsy and subsequent implantation of the cultured chondrocytes. Donor-site morbidity, the risk of 2 surgical procedures, and the total cost of surgery, as well as scaffold and in vitro culture, still represent the major limitations of this technique.[17-19]

With the aim to avoid 2 surgical procedures, tissue biopsy and cell cultivation, the senior author (A.G.) started using BMAC and a scaffold in a 1-step technique in 2004. After visiting Alan Nixon at Cornell University, where animal studies were performed and interesting animal results were produced, the senior author was led to the concept that BMAC with a scaffold in a 1-step procedure could be an attractive treatment option. This allowed the patient to undergo only 1 operation, with the possibility of cost savings.

The senior author elected not to use the microfracture technique to avoid any possible osteophyte formation or overgrowth. Deterioration of the clinical outcome with microfracture was expected at 2 and 5 years after treatment, with degenerative changes being noted at long-term follow-up.[1,19,20] Following the same indication of a standard ACI procedure, the senior author elected to remove the damaged tissue and the calcified layer but did not violate the subchondral bone. Finally, to achieve a more reproducible preparation of the peripheral edge of the lesion, we developed, in Poland, special instruments to properly prepare the lesion to obtain sharp vertical edges or shoulders.[21]

Initially, we used porcine-derived type I–type III collagen (Chondro-Gide; Geistlich Pharma) with BMAC with an arthrotomy to treat large chondral defects. However, it was technically demanding to stabilize the membrane on the defect owing to the characteristic of the membrane itself, requiring the use of fibrin glue and implant suturing. We noted that the nonporous side should be placed facing away from the subchondral bone and the porous side should be in contact with the BMAC suspension.[19,22]

Given our extensive experience with the Hyaff membrane (3-dimensional hyaluronan-based scaffold; Fidia) using the Hyalograft technique, we decided to use the Hyaff scaffold combined with BMAC (HA-

BMAC).[4] We compared 2 groups of patients treated with the Hyaff membrane; in 1 group, this membrane was seeded with chondrocytes, whereas the other group received BMAC. A summary of the results showed that both techniques resulted in satisfactory results that were not statistically different.[23] Moreover, in another study, we showed that HA-BMAC can be successfully used in patients older than 45 years.[24]

In our technique, all cartilage lesions are identified during diagnostic arthroscopy. At the time of the procedure, it is necessary to decide whether the procedure should be performed arthroscopically or via an arthrotomy. The crucial part of the procedure is to perform appropriate preparation of the base of the lesion prior to implant placement because achieving good implant stability is critical.[25]

Moreover, just as techniques with MACI have progressed to be minimally invasive when arthroscopic access is adequate, the HA-BMAC technique may be performed arthroscopically to repair cartilage defects in appropriately located lesions.[4] Furthermore, we have developed the so-called dry arthroscopy for graft implantation.[25]

Finally, given the previous literature that shows inferior long-term outcomes after microfracture, many surgeons are giving stronger consideration to alternative cartilage restoration procedures. However, future high-quality randomized controlled trials are necessary to directly compare all cartilage restoration procedures to determine differential efficacy and cost-effectiveness. An individualized approach based on the patient's goals and surgeon's preferences is necessary.

References

1. 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.
2. Steadman JR, Rodkey WG, Rodrigo JJ. Microfracture: Surgical technique and rehabilitation to treat chondral defects. *Clin Orthop Relat Res* 2001;-S369:S362 (suppl).
3. Minas T, Gomoll AH, Rosenberger R, Royce RO, Bryant T. Increased failure rate of autologous chondrocyte implantation after previous treatment with marrow stimulation techniques. *Am J Sports Med* 2009;37:902-908.
4. 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.
5. Kon E, Filardo G, Gobbi A, et al. Long-term results after hyaluronan-based MACT for the treatment of cartilage lesions of the patellofemoral joint. *Am J Sports Med* 2016;44:602-608.
6. Peterson L, Vasiliadis HS, Brittberg M, Lindahl A. Autologous chondrocyte implantation: A long-term follow-up. *Am J Sports Med* 2010;38:1117-1124.
7. Saris D, Price A, Widuchowski W, et al. Matrix-applied characterized autologous cultured chondrocytes versus microfracture: Two-year follow-up of a prospective randomized trial. *Am J Sports Med* 2014;42:1384-1394.
8. Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M. 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.
9. Gobbi A, Kon E, Berruto M, et al. Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation. *Am J Sports Med* 2009;37:1083-1092.
10. Kim MS, Chun CH, Wang JH, et al. Is microfracture still the gold standard treatment for symptomatic focal cartilage injuries or should we move to more durable, regenerative, and less invasive approaches? *Arthroscopy* 2020;36:1612-1624.
11. Haleem AM, Chu CR. Advances in tissue engineering techniques for articular cartilage repair. *Oper Tech Orthop* 2010;20:76-89.
12. Brittberg M, Nilsson A, Lindahl A, Ohlsson C, Peterson L. Rabbit articular cartilage defects treated with autologous cultured chondrocytes. *Clin Orthop Relat Res* 1996;326:270-283.
13. Ebert JR, Fallon M, Wood DJ, Janes GC. A prospective clinical and radiological evaluation at 5 years after arthroscopic matrix-induced autologous chondrocyte implantation. *Am J Sports Med* 2017;45:59-69.
14. Filardo G, Kon E, Andriolo L, Di Martino A, Zaffagnini S, Marcacci M. Treatment of "patellofemoral" cartilage lesions with matrix-assisted autologous chondrocyte transplantation: A comparison of patellar and trochlear lesions. *Am J Sports Med* 2014;42:626-634.
15. Macmull S, Jaiswal PK, Bentley G, Skinner JA, Carrington RWJ, Briggs TWR. The role of autologous chondrocyte implantation in the treatment of symptomatic chondromalacia patellae. *Int Orthop* 2012;36:1371-1377.
16. Nawaz SZ, Bentley G, Briggs TWR, et al. Autologous chondrocyte implantation in the knee: Mid-term to long-term results. *J Bone Joint Surg Am* 2014;96:824-830.
17. Henderson I, Francisco R, Oakes B, Cameron J. Autologous chondrocyte implantation for treatment of focal chondral defects of the knee—A clinical, arthroscopic, MRI and histologic evaluation at 2 years. *Knee* 2005;12:209-216.
18. Minas T, Peterson L. Advanced techniques in autologous chondrocyte transplantation. *Clin Sports Med* 1999;18:13-44.
19. Gobbi A, Karnatzikos G, Sankineani SR. One-step surgery with multipotent stem cells for the treatment of large full-thickness chondral defects of the knee. *Am J Sports Med* 2014;42:648-657.

20. 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. *Am J Sports Med* 2016;44:2846-2854.
21. Blasiak A, Whyte GP, Matlak A, Brzóska R, Sadlik B. Morphologic properties of cartilage lesions in the knee arthroscopically prepared by the standard curette technique are inferior to lesions prepared by specialized chondrectomy instruments. *Am J Sports Med* 2018;46:908-914.
22. Lee YHD, Suzer F, Thermann H. Autologous matrix-induced chondrogenesis in the knee: A review. *Cartilage* 2014;5:145-153.
23. 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.
24. Gobbi A, Scotti C, Karnatzikos G, Mudhigere A, Castro M, Peretti GM. One-step surgery with multipotent stem cells and hyaluronan-based scaffold for the treatment of full-thickness chondral defects of the knee in patients older than 45 years. *Knee Surg Sports Traumatol Arthrosc* 2017;25:2494-2501.
25. Whyte GP, Gobbi A, Sadlik B. Dry arthroscopic single-stage cartilage repair of the knee using a hyaluronic acid-based scaffold with activated bone marrow-derived mesenchymal stem cells. *Arthrosc Tech* 2016;5:e913-e918.