Dry Arthroscopic Single-Stage Cartilage Repair of the Knee Using a Hyaluronic Acid-Based Scaffold With Activated Bone Marrow-Derived Mesenchymal Stem Cells

Graeme P. Whyte, M.D., M.Sc., F.R.C.S.C., Alberto Gobbi, M.D., and Boguslaw Sadlik, M.D., Ph.D.

Abstract: Cartilage lesions of the knee are a frequent finding; however, treatment options that are capable of restoring hyaline-like tissue are not routinely used. Cell-based technology such as autologous chondrocyte implantation may in some cases provide durable cartilage repair, but availability of this procedure is often restricted due to cost constraints. There have been promising outcomes reported with the use of scaffolds seeded with activated bone marrow aspirate concentrate in cases of chondral injury. There are clear advantages to cell-based cartilage repair techniques that are performed as a single-stage procedure, particularly when the repair technology can be used in a minimally invasive manner. We present an arthroscopic technique of cartilage repair using a hyaluronic acid-based scaffold associated with activated bone marrow aspirate concentrate. This technique is a cost-effective, minimally invasive, single-stage procedure that has the potential for routine use in a wide range of cartilage lesion types and locations.

Cartilage injury of the knee joint is a common source of pain and dysfunction, and is often encountered during arthroscopic procedures. Currently, reliable methods of treatment that provide long-lasting cartilage repair are lacking. Marrow stimulation techniques such as microfracture are frequently used. Although there may be a short-term benefit provided to patients treated with microfracture, these procedures typically lack medium- to long-term durability, particularly in cases of larger lesions.[1]

A number of advances in cartilage restoration have been developed in an attempt to prolong the durability of cartilage repair. Cell-based procedures such as autologous chondrocyte implantation (ACI) have been shown to better stimulate the production of hyaline-like repair tissue, and provide the patient with longer-lasting clinical improvement.[2,3] In addition, ACI in conjunction with a preseeded scaffold has been used arthroscopically, with encouraging success.[4,5] Although the success of marrow stimulation techniques is often related to lesion size and location, cell-based repair procedures have shown good clinical outcomes in cases of large, and even bipolar lesions.[6]

A major drawback to autologous chondrocyte procedures is the 2-stage nature of the technique, due to the requirement of off-site isolation and culturing of the chondrocyte cell line. The use of activated bone marrow aspirate concentrate (BMAC) in conjunction with scaffold implantation is a form of cell-based cartilage restoration that has been shown to provide durable repair, and has the added benefit of being single staged.[7]

Should cell-based cartilage repair be performed in a minimally invasive fashion that is cost effective, there is great potential for the expansion in use of such procedures. The following technique will detail arthroscopic cartilage repair using a hyaluronic acid-based scaffold seeded with activated bone marrow aspirate concentrate (HA-BMAC). This procedure is expected to provide many features of an ideal cartilage repair technique, such as hyaline-like repair tissue, longer-term

From the Orthopaedic Arthroscopic Surgery International (OASI) Bioresearch Foundation (G.P.W., A.G.), Milan, Italy; and Orthopaedic Department, St. Luke's Clinic (B.S.), Bielsko-Biala, Poland.

The authors report that they have no conflicts of interest in the authorship and publication of this article.

Received January 28, 2016; accepted April 21, 2016.

Address correspondence to Graeme P. Whyte, M.D., M.Sc., F.R.C.S.C., Orthopaedic Arthroscopic Surgery International (OASI) Bioresearch Foundation, Via Amadeo 24, Milan 20133, Italy. E-mail: gphwhyte@gmail.com

2212-6287/1687/$36.00

http://dx.doi.org/10.1016/j.eats.2016.04.020

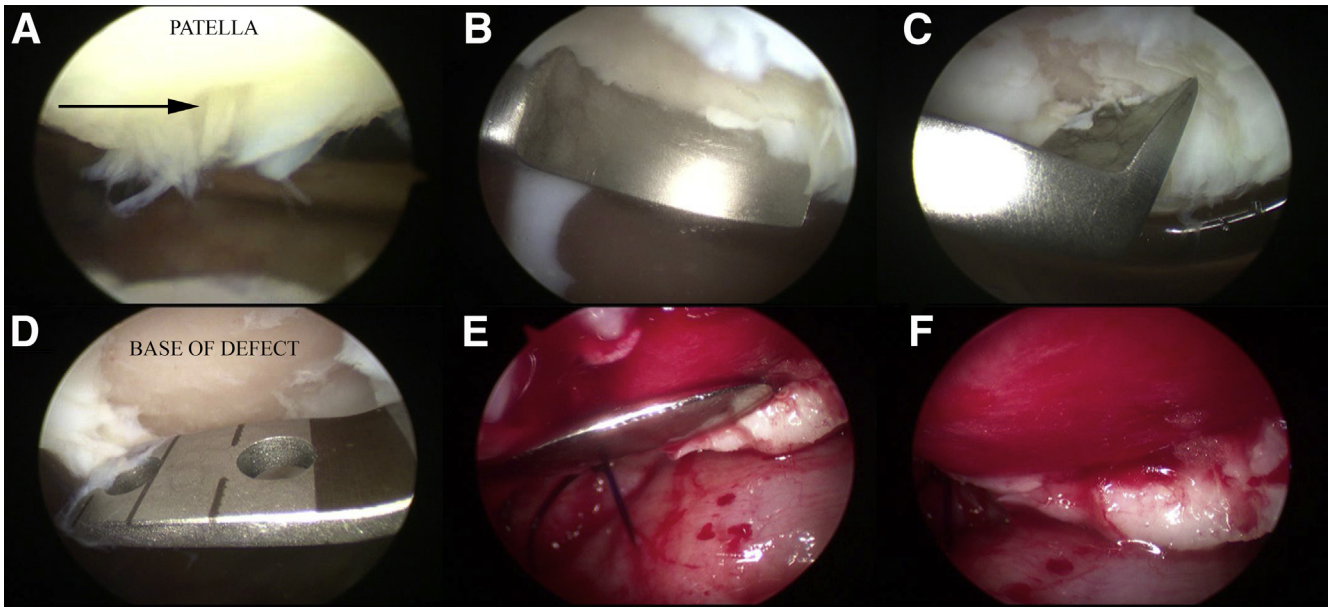

Fig 1. Patient in supine position, view of the left patellofemoral compartment through anterolateral portal and instrumentation inserted via the anteromedial working portal. Arthroscopic visualization of (A) full-thickness patellar chondral injury (arrow), (B, C) curettage of chondral defect to create contained lesion with vertical walls circumferentially, (D) measurement of chondral defect, (E) application and press fitting of a hyaluronic acid-based scaffold combined with activated bone marrow aspirate concentrate (HA-BMAC) under dry arthroscopy, and (F) seating of HA-BMAC implant into patellar chondral defect after cycling the knee to confirm stability of the graft.

improvement in patient outcomes, minimally invasive, and single stage.

Surgical Technique

Patient Positioning and Arthroscopic Evaluation

The patient is positioned supine as for standard knee arthroscopy. The ipsilateral iliac crest is also exposed and prepped in anticipation of bone marrow aspiration. The procedure is typically performed under general anesthesia. A thorough examination of the knee joint under anesthesia is performed to confirm and identify pathology associated with the cartilage defect, and concurrent treatment of associated injury may proceed as indicated. A diagnostic arthroscopy is performed to visualize all cartilage injury and characterize those lesions suitable for repair (Fig 1A). Specially designed instruments may help to optimize access and curettage of cartilage lesions, particularly in cases of patellar or trochlear injury (Chondrectomes Set, ATMED-Z. Rafalski, Katowice, Poland; Fig 1 B and C). Loose chondral tissue associated with the lesion is excised, and curettes are used to create a contained lesion with vertical walls circumferentially. Care is taken to remove the calcified cartilage layer overlying the subchondral bone, without violating the subchondral plate (Fig 1 B-D).[8]

HA-BMAC Preparation

A dedicated aspiration kit is used to harvest approximately 60 mL of bone marrow from the ipsilateral iliac crest (Fig 2A). A commercially available system is used to centrifuge the aspirate and concentrate the bone marrow cells (Angel, Cytomedix, Gaithersburg, MD). Cartilage lesion dimensions are estimated with an arthroscopic measurement device (Fig 1D). A template may be created from aluminum foil and inserted into the chondral defect to confirm correct sizing if needed. According to the defect dimensions, an appropriately sized implant is fashioned from the 3-dimensional hyaluronic acid-based scaffold (Hyalofast, Anika Therapeutics, Srl, Abano Terme, Italy; Fig 2C). The BMAC is activated using batroxobin enzyme (Plateltex Act, Plateltex SRO, Bratislava, Slovakia), forming a sticky clot substance (Fig 2B). The activated BMAC is applied to the scaffold, which is subsequently absorbed by the graft, creating a malleable implant (Fig 2D).

Dry Arthroscopic HA-BMAC Technique

Arthroscopic fluid is drained from the working articular space and a valveless cannula or skid is placed into the working portal. Particularly in cases of dry arthroscopic visualization of patellofemoral compartment lesions, exposure may be improved by retraction of the joint capsule and synovium, using a specially designed retracting plate (Arthroscopic Retracting System, ATMED-Z. Rafalski; Fig 3).[9] Dry arthroscopic examination confirms that the perimeter of the lesion has been appropriately prepared and that there is a stable rim of cartilage circumferentially. When undertaking arthroscopic cartilage repair of a femoral condyle or

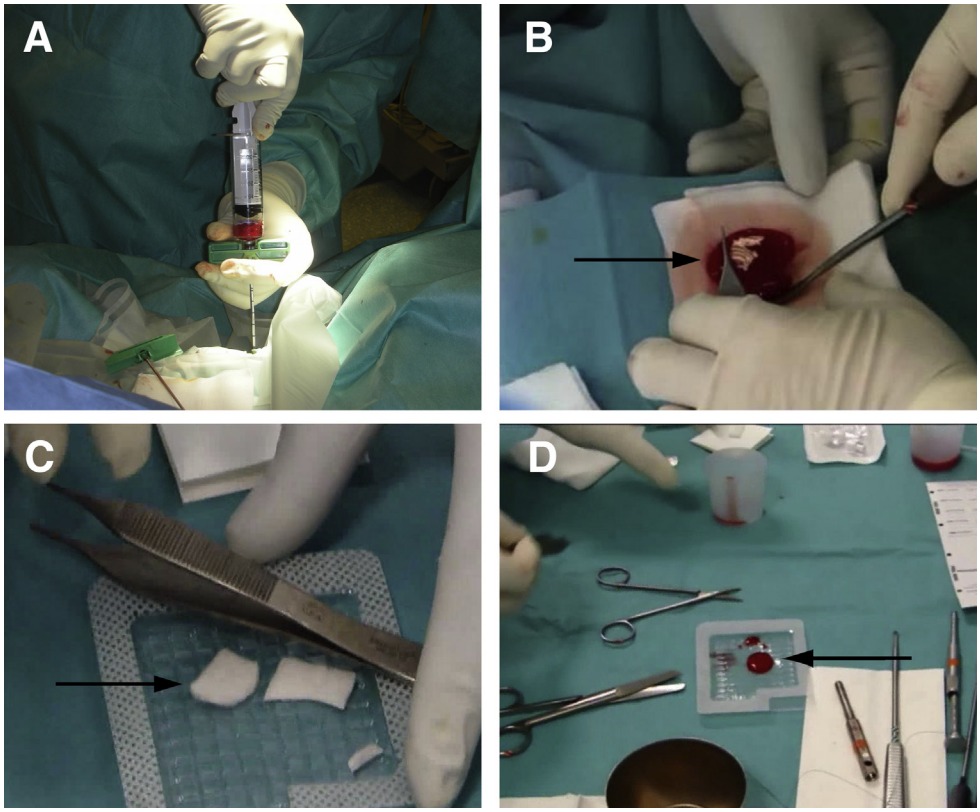

Fig 2. (A) Aspiration of bone marrow from the left iliac crest, patient in supine position. (B) Activation of bone marrow aspirate concentrate to produce congealed clot material (arrow) after application of batroxobin. (C) Hyaluronic acid-based scaffold (arrow) being fashioned to size of chondral defect. (D) Hyaluronic acid-based scaffold combined with activated bone marrow aspirate concentrate (HA-BMAC; arrow).

tibial plateau, full appreciation of the extent of the lesion should be assured; otherwise an open technique is preferred. The HA-BMAC implant is inserted through the working portal into the appropriate compartment. Using a grasper or nontoothed forceps, the implant is gently placed into the cartilage defect and is then press-fit (Fig 1 E and F). The knee is cycled while visualizing the implant arthroscopically to confirm stability of the graft. Fibrin glue may be applied for improved stability at the discretion of the surgeon. The remaining activated BMAC solution is injected into the knee joint and the portals are closed. Bracing is optional, although often preferred in cases of associated injury. Arthroscopic cartilage repair of a patellar lesion is shown in Video 1.

Step-by-Step Technique Summary

1. Position the patient supine, and expose the operative knee and ipsilateral iliac crest.
2. Examine the knee under anesthesia, and identify or confirm associated pathology.

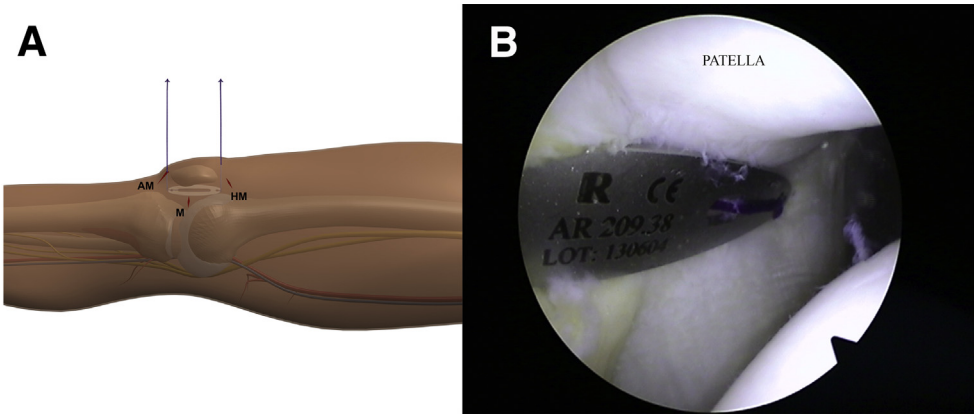

Fig 3. (A) Retraction plate positioning to improve arthroscopic visualization of the patellofemoral compartment. (B) Arthroscopic view of plate positioning to retract capsule and synovial tissue adjacent to patella to improve access to chondral lesions of the patella or trochlea; arthroscopic view from the anterolateral portal, patient in supine position. (AM, anteromedial portal; HM, high medial portal; M, medial portal.)

Table 1. Postoperative Rehabilitation Protocol

0-6 wk	• Focus on maintaining range of motion, reduction of effusion, minimization of muscular atrophy • Continuous passive motion begins postoperative day 2, 6 h per day until 90° of knee flexion is regained • For medial/lateral compartment lesions, weight-bearing is restricted for first 4 wk, and then touch-down weight-bearing with crutches begins • For patellofemoral compartment lesions, partial weight-bearing with knee braced in full extension begins postoperative day 1 • Early isometric and isotonic exercise
6-12 wk	• Unrestricted weight-bearing by 6 wk • Pool-based therapy • Active functional training begins at 9 wk
3-8 mo	• Progression to straight-line running • Proprioceptive exercises • Strength, endurance, aerobic training • By 8 mo, goal is to be pain free at moderate running pace and going up/down stairs
8-10 mo	• Agility and sport-specific training • Return to sport by 10 mo

3. Perform diagnostic arthroscopy, ensure complete visualization of cartilage lesion(s), and confirm appropriateness of arthroscopic treatment.
4. If suboptimal visualization of patellofemoral compartment pathology, use traction sutures or a retraction plate to retract the joint capsule and associated synovium to further open the compartment.
5. Address associated pathology with the arthroscopic procedure or osteotomy as indicated.
6. Prepare cartilage lesion(s) by excising loose chondral tissue and curetting the lesion(s) to ensure vertical walls circumferentially.
7. Remove the calcified cartilage layer at the base of defect without violating the subchondral plate.
8. Use an arthroscopic measuring device to obtain accurate dimensions of cartilage lesion(s).
9. Aspirate bone marrow from iliac crest and prepare BMAC with a commercially available system of choice.
10. Create size-matched hyaluronic acid-based scaffold(s) on the back table using recorded dimensions of cartilage lesion(s).
11. Activate BMAC using batroxobin to create clot and combine with scaffold(s) to create HA-BMAC graft(s) on the back table.
12. Drain remaining arthroscopic fluid from knee joint and ensure complete visualization of chondral lesion(s) under dry arthroscopy.
13. Insert the HA-BMAC graft through a valveless cannula or skid via the working portal into the relevant knee compartment.
14. Place the graft into the cartilage defect using a grasper or nontoothed forceps and press-fit securely to the base of the defect.
15. Fibrin glue may be added to further secure the graft.
16. Cycle the knee under arthroscopic visualization to ensure secure seating of HA-BMAC.
17. Remove instrumentation and apply dressing after closure of surgical wounds.

Postoperative Rehabilitation

Weight-bearing is restricted for the first 4 weeks postoperatively after the treatment of medial or lateral compartment lesions. After the treatment of isolated patellofemoral compartment lesions, the patient is allowed to partially weight-bear with crutches initially, unless there is an associated surgical procedure that requires greater restriction. Continuous passive motion is begun on the second postoperative day, until 90° of flexion is restored. Partial weight-bearing commences at 4 weeks, with expected unrestricted weight-bearing by week 6. After 3 months, patients progress to straight-line running, with an emphasis on strength, endurance, and aerobic training. Sports-specific training typically begins at 8 months, with expected return to competition by 10 months postoperatively. Rehabilitation is summarized in Table 1. Pearls/pitfalls and advantages/limitations of the technique are highlighted in Table 2 and Table 3, respectively.

Discussion

This technique details dry arthroscopic implantation of a stable HA-BMAC construct into a chondral lesion of the patella. Minimally invasive cartilage repair using cell-based technology has previously been studied at our center and others; however, these procedures were

Table 2. Pearls and Pitfalls of HA-BMAC Cartilage Repair

Pearls	• Complete exposure of the cartilage lesion is essential, and may be problematic in the patellofemoral compartment. Use traction methods as needed to provide a comfortable working space. • If dimensions of the prepared cartilage defect are difficult to measure, use an aluminum foil template or similar material to assist with accurate scaffold size matching. • The hyaluronic acid-based scaffold composition is symmetrical; after creation of the HA-BMAC graft, implantation may proceed with either side placed against the subchondral bone.
Pitfalls	• Arthroscopic cartilage repair should proceed only in cases where the entirety of the defect can be appreciated and treated in a minimally invasive manner; repair should be performed in an open manner otherwise. • Confirm secure graft seating within the cartilage defect by cycling the knee under arthroscopic visualization; failure to do so may increase the risk of graft delamination in the postoperative period.

HA-BMAC, hyaluronic acid-based scaffold associated with activated bone marrow aspirate concentrate.

Table 3. Advantages and Limitations of HA-BMAC Cartilage Repair

Advantages	• Cell-based cartilage repair performed as a single-stage procedure • HA-BMAC has been shown to provide durable cartilage repair • Low morbidity, minimally invasive approach • Attractive cost profile compared with autologous chondrocyte implantation
Limitations	• Larger cartilage lesions may not be amenable to the arthroscopic technique • Long-term outcome data of HA-BMAC cartilage repair are limited compared with autologous chondrocyte implantation at this time

HA-BMAC, hyaluronic acid-based scaffold associated with activated bone marrow aspirate concentrate.

2-stage in nature, using the resource-intensive matrix-assisted ACI.[4,5]

Both matrix-assisted ACI and HA-BMAC procedures result in hyaline-like cartilage restoration and have been shown to provide similar clinical outcomes.[10] Considering durability of repair, cell-based cartilage restoration using autologous chondrocytes has been studied more extensively in the literature. This technology has been examined both in conjunction with scaffolding and bone grafting,[11] and longer-term outcome data are widely available.[12] Similar outcome studies can be expected to become available for procedures using mesenchymal stem cell preparations, as this technology evolves.

Comparing these techniques, we find that a single-stage cartilage repair procedure using such technology as HA-BMAC has clear advantages over more expensive 2-stage procedures. In addition to cost savings, the patient is exposed to reduced surgical risk, and socioeconomic impacts to the patient are also lessened.

There are a number of potential risks associated with various methods of cartilage repair that should be considered. Marrow stimulation techniques, while simply performed and low cost, typically lead to predominantly fibrous type cartilage tissue at the repair site, and perforation of the subchondral plate may accelerate the development of intralesional osteophytes. With regard to ACI, in addition to the risks that accompany a second surgical procedure, the retrieval of chondrocytes is not always benign, and functional knee scores may be affected, depending on the intra-articular harvest site chosen.[13] In cases of repair techniques that rely on the procurement of autologous mesenchymal stem cells, such as the HA-BMAC technique presented, there is risk of donor site morbidity. Although our institution has not had experience with serious postoperative complication resulting from iliac crest marrow aspiration, the possibility of such an adverse event should be discussed with the patient before undergoing the procedure.

As opposed to some open techniques of cell-based cartilage repair, where the scaffold may be sutured flush with the superficial cartilage layer, the arthroscopic HA-BMAC technique places the graft securely adjacent to the subchondral bone of the defect. This is analogous to techniques of matrix-assisted chondrocyte implantation, where the impregnated scaffold is placed overlying the subchondral bone to allow transfer of chondrocytes to the bony articular surface, with expected seeding and chondrocyte proliferation. With regard to the arthroscopic technique presented, there is a similar reliance on proliferation of chondrocytes and production of cartilage matrix from the seeded subchondral surface, after differentiation of multipotent stem cells into native chondrocytes.

In order for successful dry arthroscopic implantation of a cell-seeded scaffold to be achieved, the physical properties of such a construct must be appropriate. The hyaluronic acid-based scaffold we use in combination with the activated BMAC becomes both malleable and adherent. Although fibrin glue may be applied arthroscopically to improve stability, this is not routinely necessary. Although Whyte et al.[14] have shown potentially clinically relevant improvement in fixation of a type I/III collagen patch with the use of fibrin glue and suture, collagen scaffolds have notable differences compared with hyaluronic acid-based material. The hyaluronic acid-based graft was considered to be ideal for this arthroscopic technique given the physical characteristics, and the clinical success that has been shown when using this scaffold in conjunction with both activated BMAC and ACI.[3,10]

The clinical outcomes that have been achieved with the use of HA-BMAC in open cases of cartilage repair have been encouraging, and the arthroscopic technique presented here may be an important step in the advancement of this technology. Medium- to long-term follow-up data from this arthroscopic HA-BMAC procedure will need to be analyzed to confirm restoration of hyaline-like cartilage, and the achievement of successful clinical outcomes similar to that achieved by HA-BMAC implantation performed in an open manner. Single-stage cell-based cartilage repair procedures, such as the technique presented, have the potential for routine use in a wide range of cartilage lesion types and locations.

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. Marcacci M, Berruto M, Brocchetta D, et al. Articular cartilage engineering with Hyalograft(R) C: 3-year clinical results. *Clin Orthop Relat Res* 2005;435:96-105.

3. Gobbi A, Kon E, Berruto M, et al. Patellofemoral full-thickness chondral defects treated with second-generation autologous chondrocyte implantation: Results at 5 years' follow-up. *Am J Sports Med* 2009;37:1083-1092.
4. 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 non-randomized study at 5 years. *Am J Sports Med* 2009;37:33-41.
5. Cortese F, McNicholas M, Janes G, et al. Arthroscopic delivery of matrix-induced autologous chondrocyte implant: International experience and technique recommendations. *Cartilage* 2012;3:156-164.
6. 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.
7. 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.
8. Drobnic M, Radosavljevic D, Cör A, Brittberg M, Strazar K. Debridement of cartilage lesions before autologous chondrocyte implantation by open or transarthroscopic techniques: A comparative study using post-mortem materials. *J Bone Joint Surg Br* 2010;92:602-608.
9. Sadlik B, Wiewiorski M. Dry arthroscopy with a retraction system for matrix-aided cartilage repair of patellar lesions. *Arthrosc Tech* 2014;3:e141-e144.
10. Gobbi A, Chaurasia S, Karnatzikos G, Nakamura N. Matrix-induced autologous chondrocyte implantation versus multipotent stem cells for the treatment of large patellofemoral chondral lesions: A nonrandomized prospective trial. *Cartilage* 2015;6:82-97.
11. Bhattacharjee A, McCarthy HS, Tins B, et al. Autologous bone plug supplemented with autologous chondrocyte implantation in osteochondral defects of the knee. *Am J Sports Med* 2016;44:1249-1259.
12. Rosa D, Balato G, Ciaramella G, Soscia E, Improta G, Triassi M. Long-term clinical results and MRI changes after autologous chondrocyte implantation in the knee of young and active middle aged patients. *J Orthop Traumatol* 2016;17:55-62.
13. McCarthy HS, Richardson JB, Parker JCE, Roberts S. Evaluating joint morbidity after chondral harvest for autologous chondrocyte implantation (ACI): A study of ACI-treated ankles and hips with a knee chondral harvest. *Cartilage* 2016;7:7-15.
14. Whyte GP, McGee A, Jazrawi L, Meislin R. Comparison of collagen graft fixation methods in the porcine knee: Implications for matrix-assisted chondrocyte implantation and second-generation autologous chondrocyte implantation. *Arthroscopy* 2016;32:820-827.