

EXHIBIT SELECTION

How to Treat Osteochondritis Dissecans of the Knee: Surgical Techniques and New Trends

AAOS Exhibit Selection

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Background: Osteochondritis dissecans is a relatively common cause of knee pain. The aim of this study was to describe the outcomes of five different surgical techniques in a series of sixty patients with osteochondritis dissecans.

Methods: Sixty patients (age 22.4 ± 7.4 years, sixty-two knees) with osteochondritis dissecans of a femoral condyle (forty-five medial and seventeen lateral) were treated with osteochondral autologous transplantation, autologous chondrocyte implantation with bone graft, biomimetic nanostructured osteochondral scaffold (MaioRegen) implantation, bonecartilage paste graft, or a "one-step" bone-marrow-derived cell transplantation technique. Preoperative and follow-up evaluation included the International Knee Documentation Committee (IKDC) score, the EuroQol visual analog scale (EQ-VAS) score, radiographs, and magnetic resonance imaging.

Results: The global mean IKDC score improved from 40.1 ± 14.3 preoperatively to 77.2 ± 21.3 (p < 0.0005) at 5.3 ± 4.7 years of follow-up, and the EQ-VAS improved from 51.7 ± 17.0 to 83.5 ± 18.3 (p < 0.0005). No influence of age, lesion size, duration of follow-up, or previous surgical procedures on the result was found. The only difference among the results of the surgical procedures was a trend toward better results following autologous chondrocyte implantation (p = 0.06).

Conclusions: All of the techniques were effective in achieving good clinical and radiographic results in patients with osteochondritis dissecans, and the effectiveness of autologous chondrocyte implantation was confirmed at a mean follow-up of five years. Newer techniques such as MaioRegen implantation and the "one-step" transplantation technique are based on different rationales; the first relies on the characteristics of the scaffold and the second on the regenerative potential of mesenchymal cells. Both of these newer procedures have the advantage of being minimally invasive and requiring a single operation.

steochondritis dissecans is an acquired, idiopathic lesion of subchondral bone characterized by osseous resorption, collapse, and sequestrum formation with possible involvement of the articular cartilage^{1,2}. The most frequently affected sites are the medial femoral condyle (involved in 70% of cases), the lateral femoral condyle (in 20%), the patella (in 5% to 10%), and the femoral trochlea (in <1%). Bilateral involvement has been reported in up to 25% of cases². The etiology remains controversial and endocrine disorders, familial predisposition, vascular insufficiency, epiphyseal abnormalities,

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TABLE I Details of the Case Series*								
Treatment	No. of Knees	Age† (yr)	Sex	Lesion Site	Lesion Area† (cm²)	Previous Surgery	Associated Surgery	Follow-up† <i>(yr)</i>
Massive osteochondral autologous transplantation	9	21.7 ± 6.1	5 F, 4 M	8 MFC, 1 LFC	2.4 ± 1.0	1 bone-cartilage paste graft	1 meniscectomy, 1 patellar realignment, 1 tibial plateau drilling	12.2 ± 9.5
Bone-cartilage paste graft	10	24.4 ± 9.0	3 F, 7 M	7 MFC, 3 LFC	2.9 ± 1.0	2 loose-body removal, 1 meniscectomy, 1 ACL, 1 microfracture	4 loose-body removal	3.8 ± 0.4
Second generation ACI + bone graft	28	19.8 ± 4.6	8 F, 20 M	19 MFC, 9 LFC	2.6 ± 0.9	8 loose-body removal, 1 meniscectomy, 2 patellar realignment	1 ACL, 2 meniscectomy	5.2 ± 1.3
Biomimetic osteochondral scaffold	8	27.5 ± 6.4	4 F, 4 M	4 MFC, 4 LFC	3.0 ± 1.0	2 loose-body removal, 2 meniscectomy, 2 shaving, 1 fragment fixation	1 meniscal allograft, 1 tibial osteotomy, 1 femoral osteotomy	2.6 ± 0.5
Bone-marrow- derived cell transplantation	7	25.4 ± 12.6	3 F, 4 M	7 MFC	2.7 ± 0.9	None	1 ACL, 2 meniscectomy, 1 tibial osteotomy	2.3 ± 1.4

*ACI = autologous chondrocyte implantation, MFC = medial femoral condyle, LFC = lateral femoral condyle, and ACL = anterior cruciate ligament surgery. †The values are given as the mean and the standard deviation.

and repetitive trauma are among the possible causes that have been suggested³⁻⁶. A variety of classifications have been proposed over time according to anatomical location, scintigraphic findings, age of occurrence (juvenile and adult forms), and anatomical pathology³⁻⁹.

The biomechanical abnormalities caused by untreated osteochondritis dissecans may contribute to the development of early osteoarthritis^{2,3}. Although some studies have shown good results with nonoperative management of osteochondritis dissecans of a femoral condyle, especially in skeletally immature patients, juvenile forms with the presence of a sclerotic rim have a tendency to fail to heal¹⁰⁻¹². Furthermore, the adult form, and in particular a lesion rated as stage 3 (having an unstable but not dislocated fragment) or stage 4 (having a loose body) according to the International Cartilage Repair Society (ICRS) classification⁹, typically requires surgery^{11,13-20}. Drilling, open or arthroscopic fixation, fragment excision, microfracturing, osteochondral grafting (with autograft or allograft), and autologous chondrocyte implantation have been described as viable surgical procedures to treat osteochondritis dissecans^{11,13-20}.

More recently, newer procedures based on the transplantation of bone-marrow-derived cells or on the use of a nanostructured scaffold alone have been proposed for repair of osteochondral lesions and have subsequently also been indicated for osteochondritis dissecans^{14,21,22}. The rationale for bone-marrow-derived cell transplantation is based on the capability of these multipotent cells, transferred along with their microenvironment to differentiate and to regenerate both the subchondral bone and the cartilaginous layer. The rationale for use of a nanostructured scaffold is based on the capability of an innovative three-layer collagen-hydroxyapatite biomaterial to induce in situ regeneration carried out by stem cells originating from the surrounding bone marrow. The aim of the present study was to describe five different surgical techniques for the treatment of osteochondritis dissecans performed in a series of sixty-two knees at the authors' institution. The advantages and disadvantages of each technique will be highlighted and the clinical results will be analyzed.

Materials and Methods

Sixty-two knees (sixty patients; mean age and standard deviation, 22.4 ± 7.4 years) with osteochondritis dissecans rated as ICRS⁹ stage 3 or 4 were treated between 1986 and 2009 (Table I). General or spinal anesthesia was used. Patients were placed in a supine position and a thigh tourniquet was applied. An open arthrotomy, a mini-arthrotomy, or a standard arthroscopic approach was used. In all cases, the osteochondritis dissecans lesion was identified and the fragment was removed along with fibrous tissue and degenerated bone until healthy, bleeding bone was reached.

Seventeen of the knees were considered to have the juvenile form of osteochondritis dissecans on the basis of skeletal immaturity at the time of diagnosis. All patients were examined clinically prior to surgery, at twelve months postoperatively, and at the latest follow-up visit (1.5 to 24 years post-operatively). The clinical outcome of each patient was assessed with use of the standard cartilage evaluation form developed by the ICRS, a functional knee test was performed according to the examination procedure developed by the International Knee Documentation Committee (IKDC)²³, and the patient was asked to evaluate his or her functional level with use of the EuroQol visual analog scale (EQ-VAS)²⁴ and activity level with use of the Tegner score²⁵. The postoperative Tegner score was also compared with the preoperative score and the pre-injury score. Radiographs were made and magnetic resonance imaging (MRI) scans were acquired.

Statistical Analysis

All continuous variables were expressed in terms of the mean and the standard deviation. The paired t test was used to test differences between preoperative and final values. The Kruskal-Wallis nonparametric test followed by the Mann-Whitney test for multiple comparisons were used to test differences among the means of different groups. The Pearson correlation coefficient was calculated to

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 $e_1(3)$

Fig. 1

Schematic representation of five surgical treatments for osteochondritis dissecans of the knee: massive osteochondral autologous transplantation (**Fig. 1-A**), bone-cartilage paste graft (**Fig. 1-B**), second-generation autologous chondrocyte implantation plus bone graft (**Fig. 1-C**), biomimetic osteochondral scaffold (**Fig. 1-D**), and bone-marrow-derived cell (BMDC) transplantation (**Fig. 1-E**).

assess the relationships between continuous variables. A p value of <0.05 was considered significant for all tests. The statistical analyses were performed with use of SPSS software (version 15.0; SPSS, Chicago, Illinois).

Massive Osteochondral Autologous Transplantation

The site of the lesion was prepared with squared margins with use of a chisel and was measured (Figs. 1 and 2-A). An osteochondral graft of appropriate size was harvested from a non-weight-bearing area on the superior aspect of the lateral femoral condyle, preserving the patellar groove (Fig. 2-B). The graft was carefully contoured so that it fit precisely into the recipient bed, and press-fitting was used

to insert the graft (Fig. 2-C). Screw fixation was used if the stability was judged to be insufficient (six of nine cases). Screw removal was performed arthroscopically two months postoperatively, before weight-bearing was permitted²⁶.

Advantages

This procedure requires a single surgical session and has the capability to transplant mature autologous bone and cartilage; the rate of osseous consolidation and the rate of cartilage survival are excellent. Bone-to-bone healing allows for a faster recovery compared with procedures involving cartilage regeneration.



Fig. 2

Massive osteochondral autologous transplantation. The images show the site of the lesion (Fig. 2-A), harvesting of the osteochondral graft from a nonweight-bearing area on the superior aspect of the lateral femoral condyle (Fig. 2-B), and press-fit implantation (Fig. 2-C). The Journal of Bone & Joint Surgery · JBJS.org Volume 94-A · Number 1 · January 4, 2012

Disadvantages

The amount of graft that a donor site can provide is limited, an arthrotomy is needed, and there may be an anatomical discrepancy between the shapes of the donor and recipient sites.

Pearls

Care should be taken to harvest the graft with use of perpendicular cut and to obtain a graft that has an appropriate thickness and a curved surface that matches that of the recipient area as closely as possible.

Pitfalls

The graft should be inserted with a press-fit technique; it should never be impacted forcefully, since this could jeopardize chondrocyte survivorship. Instead, a screw should be used if necessary to achieve good stability. The graft surface should not be either above or below the level of the surrounding articular cartilage.

Bone-Cartilage Paste Graft

Once the site of the lesion was prepared, the subchondral bone was penetrated multiple times with an arthroscopic awl until bleeding occurred (Fig. 1). Cartilage was harvested from the margin of the intercondylar notch with use of an 8-mm trephine, and cancellous bone was harvested from the proximal aspect of the tibia through a mini-incision. Both cartilage and bone were morselized to obtain a paste that was used to cover the osteochondral defect²⁷.

Advantages

This procedure involves a single surgical session, is inexpensive, uses an arthroscopic approach (with the exception of the mini-incision used to obtain bone from the proximal aspect of the tibia), and has minimal donor site morbidity. The composite may act as a cap to contain the mesenchymal stem cells that are derived from the subchondral bone.

Disadvantages

Regeneration of cartilage with hyaline features was observed in only a limited number of biopsy samples obtained during follow-up²⁷. The actual advantage provided by the addition of morselized cartilage matrix remains unclear.

Pearls

Cartilage may also be harvested from the margins of the lesion and from the detached fragment 28 .

Pitfalls

Only cover the bottom of the defect with paste; do not attempt to fill the defect. Impact the paste graft so that it penetrates into the bone, and maintain the pressure for one to two minutes.

Second-Generation Autologous Chondrocyte Implantation Plus Bone Graft

This procedure involved two surgical sessions²⁹. In the first session, a 150 to 200-mg biopsy sample of healthy cartilage was harvested from the ipsilateral knee and sent to a facility that cultured chondrocyte cells and seeded them onto a hyaluronic acid scaffold (Hyalograft C; Fidia Advanced Biopolymers, Abano Terme, Italy). During the same surgical session, cancellous bone graft was harvested from the medial side of the proximal aspect of the tibia through a small incision. The bone chips obtained were used to fill the osseous defect of the osteochondral lesion and were impacted arthroscopically (Figs. 1 and 3-A). In the second session, which was performed four to six months later to allow the bone graft to have become integrated, implantation of the Hyalograft C bioengineered scaffold was performed arthroscopically. After the lesion site had been prepared, a variable-diameter de-

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Fig. 3

Second-generation autologous chondrocyte implantation plus bone graft. In the first surgical session, the osseous defect is filled with autologous cancellous bone graft (**Fig. 3-A**). In the second session, performed four to six months later to allow integration of the bone graft, implantation of the Hyalograft C bioengineered scaffold is performed arthroscopically (**Fig. 3-B**).

livery device was used to evaluate the size of the defect, to size the scaffold, and to place the scaffold in the lesion site (Fig. 3-B).

Advantages

The capability of autologous chondrocyte implantation to regenerate hyaline cartilage has been well proven^{30,31}. There is minimal donor site morbidity. The implantation is performed arthroscopically (with the exception of the bone harvesting performed through the mini-incision on the proximal aspect of the tibia) and yields results similar to those of the open autologous chondrocyte implantation procedure and less morbidity³².

Disadvantages

Two surgical sessions are required, and the cost of this procedure is high.

Pearls

The use of dedicated instrumentation permits easy implantation of the biomaterial. Because of the adhesive properties of the biomaterial, no suture is required for graft stability. If one scaffold stamp is not sufficient, multiple stamps can be added, and even overlapped, to cover the entire lesion area. It is necessary to remove all of the intra-articular irrigation fluid before positioning the biomaterial.

Pitfalls

Improper preparation of the lesion site will compromise the stability of the implant.

Biomimetic Osteochondral Scaffold

The lesion site was prepared by creating a 9-mm-deep defect with stable shoulders into which the scaffold could be placed (Figs. 1 and 4-A). The lesion was templated with use of aluminum foil, and MaioRegen scaffold (Fin-Ceramica Faenza, Faenza, Italy) was cut to the exact size of the defect and implanted by press-fitting (Figs. 4-B and 4-C). This osteochondral biomimetic scaffold has a porous three-dimensional composite three-layer structure that mimics the osteochondral anatomy²².

Advantages

This technique involves a single surgical session, with no need for harvesting of autologous material and no need for any fixation device. The structure of this scaffold mimics the osteocartilaginous anatomical structure, confining bone formation to the deepest portion and cartilage regeneration to the surface without the need for any cell or growth-factor supplements. The Journal of Bone & Joint Surgery .jbjs.org Volume 94-A · Number 1 · January 4, 2012 How to Treat Osteochondritis Dissecans of the Knee: Surgical Techniques and New Trends



 $e_{1}(5)$

Fig. 4

Biomimetic osteochondral scaffold. The images show preparation of the defect (**Fig. 4-A**), cutting of the scaffold (**Fig. 4-B**), and press-fit implantation (**Fig. 4-C**).

Disadvantages

Clinical results are still preliminary, and formation of hyaline-like cartilage has been documented only in an animal model³³. The cost of this procedure is high, and an arthrotomy must be performed to implant this material.

Pearls

Because this technique takes advantage of the plasticity of the scaffold, even a large osteochondral lesion can be treated with use of a small incision.

Pitfalls

Stable defect shoulders, especially in locations such as the edge of the condyle, are important for implant stability. Implant fit must be checked after tourniquet removal since the scaffold size increases when blood flow is restored.

Bone-Marrow-Derived Cell Transplantation

This technique consists of three phases performed during a single surgical session: preparation of platelet gel, preparation of bone marrow aspirate, and implantation³⁴ (Fig. 1). In the first phase, 120 mL of the patient's venous blood was harvested and was processed with the Vivostat System (Vivolution, Alleroed, Denmark) one day before surgery to provide 6 mL of platelet-rich fibrin gel.

In the second phase, 60 mL of bone marrow aspirate was harvested from the posterior iliac crest with the patient in the prone decubitus position. The harvested bone marrow was processed in the operating room by removing most of the erythrocytes and plasma with use of a cell separator (SmartPReP; Harvest Technologies, Plymouth, Massachusetts) to obtain 6 mL of concentrate containing nucleated cells (stem cells, monocytes, lymphocytes, and other cells resident in the bone marrow). This concentrate was then loaded onto a hyaluronic acid membrane (HYAFF-11; Fidia Advanced Biopolymers) that provided support for the cells (Fig. 5-A).

In the third phase, the lesion site was prepared and multiple overlapping stamps of the membrane were positioned in the defect (Fig. 5-B). A layer of platelet-rich fibrin was finally applied over the membrane to provide growth factors.

Advantages

This procedure is entirely arthroscopic and involves a single surgical session. The entire pool of regenerative cells is concentrated directly in the operating room, eliminating the need for cell selection and expansion. This technique's capability to regenerate cartilage with hyaline features has been confirmed histologically. Good clinical, histological, and qualitative MRI results have been reported at two years postoperatively in both the knee and the ankle^{21,34,35}.

Disadvantages

It is necessary to perform harvesting of bone-marrow-derived cells from the iliac crest as a preliminary procedure. A recent MRI study raised the concern that regeneration of the subchondral bone may take longer than expected, and this may justify the use of cancellous or demineralized bone to fill the lesion before implantation of the biomaterial³⁵. The cost of the biomaterial is high.

Pearls

The application of platelet-rich fibrin to the biomaterial after it has been positioned within the lesion enhances the stability of the implant.

Pitfalls

The membrane becomes spongy and less easy to manage once it has been loaded with cells. It is important to remove all of the intra-articular irrigation fluid and to quickly position the biomaterial and cover it with platelet gel.

Results

 \mathbf{N} o severe adverse events were reported intraoperatively or postoperatively in this series. A marked improvement was noted in the IKDC and EQ-VAS clinical scores and the Tegner activity level between the preoperative assessment and the latest follow-up visit (5.3 ± 4.7 years postoperatively) in each of the



Fig. 5

Bone-marrow-derived cell transplantation. The images show loading of the hyaluronic acid membrane with the bone marrow concentrate (**Fig. 5-A**) and arthroscopic implantation of the biomaterial into the defect (**Fig. 5-B**).

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The IKDC subjective score for the entire study cohort preoperatively and at the time of the latest follow-up. The yellow bar indicates the median, the box indicates the interquartile range, and the whiskers indicate the farthest data points less than 1.5 times the interquartile range from the median.

treatment groups. The mean EQ-VAS score improved from 51.7 ± 16.9 preoperatively to 83.5 ± 18.3 at the time of the latest follow-up (p < 0.0005). The percentage of knees with a normal

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or nearly normal IKDC objective score increased from 37% preoperatively to 97% at the time of the latest follow-up (p < 0.0005); preoperatively, four knees had been rated as A, nineteen as B, twenty-three as C, and sixteen as D, whereas at the time of the latest follow-up forty-three were rated as A, seventeen as B, and two as C. The mean IKDC subjective score exhibited a general improvement from 40.1 ± 14.3 preoperatively to 77.2 ± 21.3 at the time of the latest follow-up (p < 0.0005) (Fig. 6). The improvement in the IKDC subjective score was significant for each of the surgical techniques (Fig. 7). The mean Tegner score improved from 1.9 ± 1.6 preoperatively to 4.8 ± 2.6 at the time of the latest follow-up, although it did not reach the pre-injury level of 6.3 ± 1.9 (p < 0.0005) (Fig. 8).

Further analyses were performed to assess the effect of various parameters on the results. When knees with juvenile and adult osteochondritis dissecans were analyzed separately, a tendency toward better IKDC scores in the knees with the juvenile form was evident, although the difference did not reach significance. Nevertheless, age had a significant effect on the IKDC subjective score, with older patients achieving less improvement (r = 0.307, p = 0.015) (Fig. 9). Sex had a significant effect on the IKDC subjective improvement, with female patients having less improvement than male patients (p = 0.04). The lesion size, lesion site, history of previous surgical procedures, and duration of follow-up did not have a significant effect on the results. The surgical technique also did not have a significant effect on the results, but there was a trend



Fig. 7 The IKDC subjective score in each treatment group preoperatively and at the time of the latest follow-up. 1 = massiveosteochondral autologous transplantation, 2 = bone-cartilage paste graft, 3 = second-generation autologous chondro cyte implantation plus bone graft, 4 =biomimetic osteochondral scaffold, and 5 = bone-marrow-derived cell transplantation. The yellow bar indicates the median, the box indicates the interquartile range, the whiskers indicate the farthest data points less than 1.5 times the interquartile range from the median, and the circles indicate outliers. Fig. 8 The mean pre-injury, preoperative, and final postoperative Tegner score (activity level) in each treatment group. 1 = massiveosteochondral autologous transplantation, 2 = bone-cartilage paste graft, 3 = second-generation autologous chondrocyte implantation plus bone graft, 4 = biomimetic osteochondral scaffold, and 5 = bone-marrow-derived cell transplantation. CI = confidence interval.

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Fig. 9

The improvement in the IKDC subjective score according to age at the time of the surgery, showing that a younger age was associated with a better outcome. On the y axis, 0% represents no change in the patient's score and 100% represents the maximum possible improvement (i.e., improvement to a perfect score).

toward better results following autologous chondrocyte implantation compared with nonregenerative techniques (massive osteochondral autologous transplantation and bone-cartilage paste graft) (p = 0.06).

Discussion

This study assessed the clinical outcomes of five different surgical techniques in patients treated for osteochondritis dissecans of the knee at a mean of five years of follow-up. Although primary fixation of the loose fragment may be desirable, it may not be possible to preserve the fragment, or the fragment may fail to heal after initial fixation (especially in patients who are more than fifteen years old, in whom sclerosis around the lesion is often observed)^{13,36}.

Recently published studies suggest that pain relief after simple loose-body removal may be temporary³⁷. When recommending treatment for osteochondritis dissecans, emphasis should be placed on the need to restore cartilage and subchondral bone as a unique functional unit³⁷. All of the treatments used in the present series aim to treat both cartilage and subchondral bone, and all yielded clinically satisfactory results in patients with osteochondritis dissecans. A reduction in symptoms and an increase in function occurred following treatment with each technique, and the improvement was maintained over time. When choosing a surgical management technique for osteochondritis dissecans, it is necessary to consider that each of the techniques has advantages and disadvantages, and awareness of pearls and pitfalls for a technique may help in obtaining better results.

Massive osteochondral autologous transplantation and use of bone-cartilage paste graft are reasonably simple techniques involving a single surgical session, are inexpensive, and can be readily performed in any surgical center. Disadvantages include donor site morbidity and the risk of a mismatch between the shape of the autograft and that of the lesion site; in addition, hyaline-like cartilage may not necessarily result after bone-cartilage paste grafting. Second-generation autologous chondrocyte implantation is an expensive technique that is not available at all surgical centers, and the need for two separate surgical sessions is a major drawback. Nevertheless, the quality of the regenerated tissue and the excellent clinical results that are maintained over time provide strong support for this technique.

Cartilage repair has recently moved in two new and opposite directions to overcome the disadvantages of the above-mentioned techniques. The first involves use of bone-marrow-derived cells that are capable of differentiating into both cartilage and bone, and the second involves use of a biomimetic nanostructured scaffold alone to guide the growth of both cartilage and bone. Both of these new techniques have already shown promising results in animal studies and in clinical trials for the treatment of osteochondral lesions of the knee or the ankle joint^{21,22,33,44}. Furthermore, biopsy samples and T2-weighted MRI mapping have confirmed the quality of the resulting reparative tissue³⁵.

Although it must be emphasized that surgical techniques based on bone-marrow-derived cell transplantation or nanostructured osteochondral scaffold have a shorter duration of followup compared with the other techniques, their preliminary results are encouraging. Both procedures are simple, involve a single surgical session, and are capable of overcoming disadvantages of the previously developed treatments. No conclusive indication of the superiority of one technique over the others was demonstrated in this study. Nevertheless, second-generation autologous

 $e_{1}(7)$

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chondrocyte implantation in association with bone graft was confirmed to be an extremely promising and reliable technique for cartilage repair in knees with osteochondritis dissecans, with a trend toward achieving better results compared with the nonregenerative techniques (such as massive osteochondral autologous transplantation and bone-cartilage paste graft). However, this trend may be partially due to the greater proportion of younger male patients in this treatment group, since better results in such patients were evident for all of the surgical techniques used. To date, the new techniques (biomimetic osteochondral scaffolds and bone-marrow-derived cell transplantation) have shown results similar to those of autologous chondrocyte implantation, with the capability of overcoming some of the disadvantages of the older techniques. However, the small number of patients treated with the newer techniques and their still-short duration of follow-up do not permit any definitive conclusions. Further studies are required to confirm the results obtained for the newer techniques and to determine whether longer follow-up will demonstrate similar results for HOW TO TREAT OSTEOCHONDRITIS DISSECANS OF THE KNEE: SURGICAL TECHNIQUES AND NEW TRENDS

all of these techniques or evidence of the clear superiority of one technique.

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