Original Article With Video Illustration

High Tibial Osteotomy in Combination With Chondrogenesis After Stem Cell Therapy: A Histologic Report of 8 Cases

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Purpose: To histologically evaluate the quality of articular cartilage regeneration from the medial compartment after arthroscopic subchondral drilling followed by postoperative intra-articular injections of autologous peripheral blood stem cells (PBSCs) and hyaluronic acid with concomitant medial open-wedge high tibial osteotomy (HTO) in patients with varus deformity of the knee joint. **Methods:** Eight patients with varus deformity of the knee joint underwent arthroscopic subchondral drilling of International Cartilage Repair Society (ICRS) grade 4 bone-on-bone lesions of the medial compartment with concomitant HTO. These patients were part of a larger pilot study in which 18 patients underwent the same procedure. PBSCs were harvested and cryopreserved preoperatively. At 1 week after surgery, 8 mL of PBSCs was mixed with 2 mL of hyaluronic acid and injected intra-articularly into the knee joint; this was repeated once a week for 5 consecutive weeks. Three additional intra-articular injections were administered weekly at intervals of 6, 12, and 18 months postoperatively. Informed consent was obtained at the time of hardware removal for opportunistic second-look arthroscopy and chondral biopsy. Biopsy specimens were stained with H&E, safranin O, and immunohistochemical staining for type I and II collagen. Specimens were graded using the 14 components of the ICRS Visual Assessment Scale II, and a total score was obtained. **Results:** Second-look arthroscopy showed satisfactory healing of the regenerated cartilage. Histologic analysis showed significant amounts of proteoglycan and type II collagen. The total ICRS Visual Assessment Scale II histologic scores comparing the regenerated articular cartilage (mean, 1,274) with normal articular cartilage (mean, 1,340) indicated that the repair cartilage score approached 95% of the normal articular cartilage score. There were no infections, delayed unions, or nonunions. **Conclusions:** Chondrogenesis with stem cells in combination with medial open-wedge HTO for varus deformity correction of the knee joint regenerates cartilage that closely resembles the native articular cartilage. **Level of Evidence:** Level IV, therapeutic case series.

Medial-compartment osteoarthritis due to varus deformity of the knee joint is a common orthopaedic presentation. Because of varus malalignment, accelerated degeneration of the medial compartment occurs.[1] Left untreated, varus deformity progresses and leads to significant clinical symptoms and deformity that warrant surgical intervention.

Previous publications have investigated the morphologic and histologic results of cartilage regeneration after high tibial osteotomy (HTO) with variable results, including cohorts with and without concomitant cartilage repair techniques.[2-9] However, studies evaluating cartilage repair techniques with concomitant HTO are limited,[4-6,9,10] and research using the International Cartilage Repair Society Visual Assessment Scale II (ICRS II) grading system with comparison to normal cartilage is lacking.

Recent animal and clinical research has focused on the use of stem cells to augment cartilage repair techniques.[11-19] Studies have shown success with combining arthroscopic marrow stimulation and

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postoperative intra-articular injections of stem cells in combination with hyaluronic acid (HA).[14,19-25] We have previously published our clinical results involving a case series and a randomized controlled trial after arthroscopic subchondral drilling in combination with postoperative intra-articular injections of peripheral blood stem cells (PBSCs) and HA. The randomized controlled trial used all 14 parameters of the ICRS II and concluded that the intervention group with stem cell therapy (PBSCs plus HA) showed a statistically significantly higher ICRS II score compared with the control group (HA).[21] Our results have shown that this technique is able to regenerate repair tissue that resembles hyaline cartilage[20,21] as opposed to fibrocartilage or a hybrid of hyaline and fibrocartilage, which is produced after microfracture alone.[24,25] This paved the way to combine this developed technique addressing large and complex International Cartilage Repair Society (ICRS) grade 4 bone-on-bone kissing lesions of the medial compartment with concomitant medial open-wedge HTO in patients with varus deformity of the knee joint.

The purpose of this study was to histologically evaluate the quality of articular cartilage regeneration from the medial compartment after arthroscopic subchondral drilling followed by postoperative intra-articular injections of autologous PBSCs and HA with concomitant medial open-wedge HTO in patients with varus deformity of the knee joint. We hypothesized that combining HTO with the developed cartilage repair technique would regenerate repair cartilage that closely resembled the normal articular cartilage.

Methods

Patient Selection

This study was a retrospective study with data collected from the outpatient department of the first author (K-Y.S.). The cases selected for this histologic study satisfied all of the following inclusion criteria: preoperative medial-compartment ICRS grade 4 bone-on-bone lesions, previous chondrogenesis with stem cells over the medial compartment with concomitant open-wedge HTO, and willingness to provide informed consent for second-look arthroscopy with chondral biopsy during hardware removal. The exclusion criteria were cases in which chondrogenesis was limited to either the medial femoral condyle alone or the medial tibial plateau alone, cases in which the postoperative injection protocol was not adhered to, and the absence of informed consent for chondral biopsy.

Indications for HTO

Radiographs with standard weight-bearing anteroposterior (AP), lateral, and merchant views of the affected knee joint were taken. A weight-bearing longitudinal radiograph of the lower limb in the coronal plane was taken to assess the degree of varus deformity of the knee joint, as shown in Figure 1A. We assessed the longitudinal axis alignment by drawing a line from the center of the hip to the center of the ankle joint. The weight-bearing line drawn across the tibial plateau (Fig 1A) can be used to determine any change in the percentage of weight bearing, as well as the axis alignment[26] (Fig 2). HTO is indicated in patients with significant varus deformity defined as a weight-bearing longitudinal axis equal to or greater than the 50% mark,[26] as shown in Figure 2.

The surgical indications were as follows: symptomatic medial-compartment discomfort, varus deformity such that the weight-bearing longitudinal axis is equal to or greater than the 50% mark and equal to or less than the 100% mark as shown in Figure 2, ICRS grade 4 chondral lesions of either the medial femoral condyle or the medial tibial plateau (or both), and age 18 to 60 years. Contraindications included patients with ligamentous instability, advanced tricompartmental osteoarthritis with significant bone loss over the medial compartment such that total knee arthroplasty was indicated, a history of knee infection, gross bone defects, and

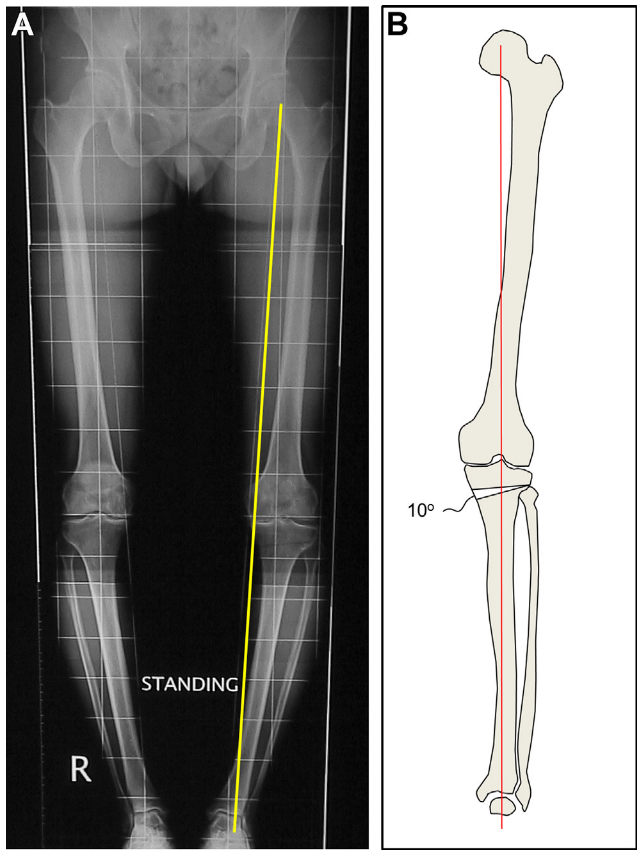


Fig 1. Preoperative planning showing (A) radiograph of long leg standing view to assess longitudinal axis alignment in the coronal plane as indicated by the yellow line and (B) traced longitudinal axis for planned open-wedge high tibial osteotomy.

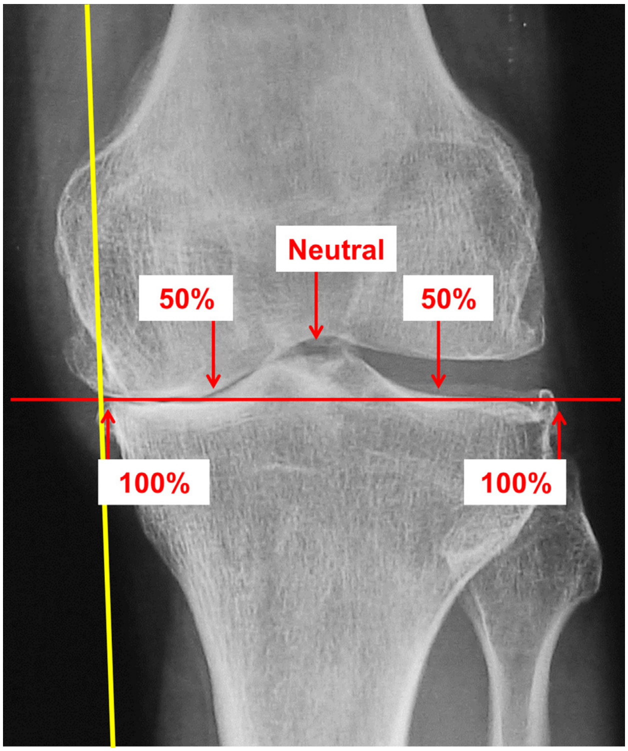


Fig 2. Radiograph showing significant varus deformity defined as the weight-bearing longitudinal axis in the coronal plane being equal to or greater than the 50% mark. The horizontal red line represents the point at which the longitudinal axis, as shown in Figure 1A, crosses the tibial plateau. The yellow line represents the axis alignment, as shown in Figure 1A.

rheumatoid arthritis. Chondral lesions were graded according to the ICRS Cartilage Injury Evaluation Package.[27] The diagnosis of chondral injury was made after clinical, radiographic, and magnetic resonance imaging (MRI) and was confirmed during arthroscopy. The advantages together with the disadvantages of HTO versus knee arthroplasty were discussed.

Preoperative Planning for HTO

Traditionally, overcorrection of the mechanical axis past neutral to the Fujisawa point has been recommended with HTO.[28] The necessary angular correction was calculated from the preoperative long leg radiographs (Fig 1B). With the ability to regenerate repair cartilage in the medial compartment,[20] the final longitudinal axis correction in this study was planned to neutral in the coronal plane (Fig 1B). The average open-wedge angular correction was 10° (range, 8° to 13°).

Filgrastim Administration, Apheresis, and Cryopreservation

Patients underwent stimulation with filgrastim, which is a granulocyte colony-stimulating factor; autologous PBSC harvesting by apheresis; and cryopreservation of the PBSCs at least 6 weeks before the surgical procedure. This is to allow recovery of the patient's own bone marrow before the major surgical procedure. The details of the harvesting procedure and cell preparation have been outlined in our previous publication.[20]

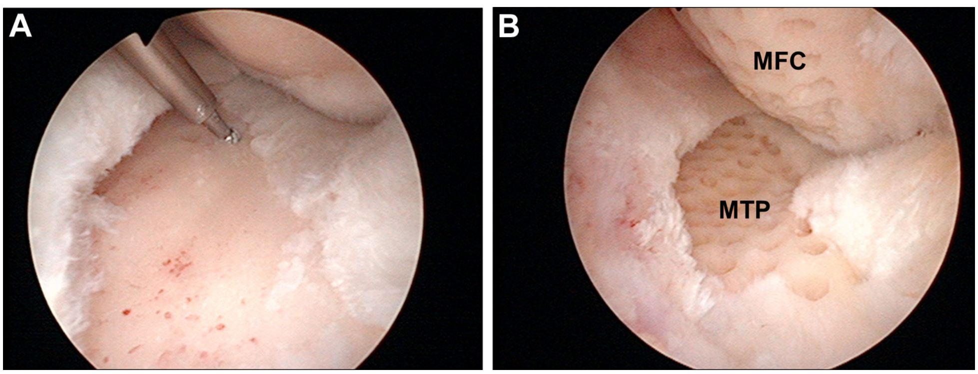
Surgical Procedures

All surgical procedures were performed by the first author (K-Y.S.)[20,21] with arthroscopic subchondral drilling of the chondral defects, meniscus surgery, and correction of lateral patellar maltracking by lateral patellar release when indicated. An example is shown in Figure 3, with Video 1 (available at www.arthroscopyjournal.org) showing the surgical technique of subchondral drilling in the medial compartment. The details of the surgical procedure have previously been published.[20,29] Concomitant open-wedge HTO was performed after the arthroscopic procedure, and an appropriate sized synthetic cancellous bone graft (chronOS; DePuy Synthes, Warsaw, IN) was inserted into the HTO site after Tomofix fixation with a medial high tibial plate (DePuy Synthes).

Intra-articular Injections

At 1 week after surgery, 8 mL of cryopreserved autologous PBSCs was mixed with 2 mL of HA (Hyalgan; Fidia Farmaceutici, Abano Terme, Italy) and injected intra-articularly into the operated knee joint

Fig 3. Intraoperative arthroscopic views of the medial compartment of the left knee (same patient shown in Figs 1 and 2) (A) before and (B) after subchondral drilling and abrasion chondroplasty of the medial femoral condyle (MFC) and medial tibial plateau (MTP).



under aseptic conditions (clean room environment) in the outpatient clinic. Hemarthrosis was aspirated before the injection. This was repeated once a week for 5 weeks. At 6, 12, and 18 months after surgery, 3 additional weekly intra-articular injections comprising 4 mL of PBSCs and 2 mL of HA were given.

Postoperative Rehabilitation

One hour of cold therapy 2 to 3 times per day was initiated after surgery and continued throughout the first month after surgery. On the first postoperative day, a continuous passive motion machine was applied on the operated knee for 2 hours. This was continued daily for a period of 4 weeks. The range of motion on the continuous passive motion machine was initially set at 0° to 30° for the first 2 days after surgery; it normally progresses beyond 90° at 2 weeks as the clinical situation improves. Patients were instructed on crutch-assisted progressive partial weight bearing (initially 15 to 20 kg) for the first 2 weeks. This progressed to full weight bearing at 3 to 6 months depending on the amount of bone healing over the osteotomy site. The rationale behind early partial weight bearing is that it is essential for chondrogenesis, as shown in our previous publication.[20]

Radiographs

Preoperative AP, lateral, and merchant views were taken. It is important to evaluate for lateral patellar maltracking; if present, this needs to be addressed with lateral patellar release at the time of arthroscopic surgery (Fig 4). Postoperative radiographs were taken on day 1; at 6 weeks, 3 months, and 6 months; and just before hardware removal. Serial radiographs were essential to visualize callus formation after osteotomy and to perform decision making as to the weight-bearing protocol.

We assess bone healing over the osteotomy site by the amount of bridging callus using standard weight-bearing AP and lateral radiographs. Bridging callus of more than 50% at the osteotomy site (AP view) from lateral to medial is deemed sufficient to allow full weight bearing on the operated leg. This is normally achieved at 3 to 4 months after surgery.

Fig 4. Preoperative radiographs showing (A) lateral patellar maltracking, (B) medial-compartment joint narrowing, and (C) intercondylar osteophyte blocking extension (arrow).

Second-Look Arthroscopy With Chondral Core Biopsy

Eight patients underwent second-look arthroscopy with chondral core biopsy. These were opportunistic biopsies performed during hardware removal. This is shown in Figure 5 A and B and Video 1 (available at www.arthroscopyjournal.org). Obtaining biopsy specimens from the medial femoral condyle was technically simpler compared with the medial tibial plateau because access to the medial femoral condyle is technically less challenging. For this reason, some cases only had biopsy specimens from the medial femoral condyle. Informed consent for chondral biopsy was obtained in addition to the consent for hardware removal.

Histologic Evaluation and Grading Using ICRS II

The staining method for the histologic samples has previously been described.[21] The biopsy specimens were graded by 2 independent blinded histopathologists (N.M., K.S.) using all 14 components of the ICRS II. Light and polarized microscopy was used during the grading process. For each of the 14 ICRS II parameters, a score between 0 and 100 was given as described in the initial ICRS II publication.[30] To obtain an overall histologic quality score of the repaired tissue, we calculated a total score by summation of these 14 histologic parameters for each of the biopsy samples. Summation of the scoring system yields a maximum score of 1,400.

Six normal articular cartilage biopsy specimens were also obtained from 4 different patients who gave informed consent during our previous randomized controlled trial.[21] Biopsy specimens were taken from areas deemed normal from preoperative MRI scans, as well as during arthroscopy. The biopsy samples were stained and graded according to the ICRS II for comparison.

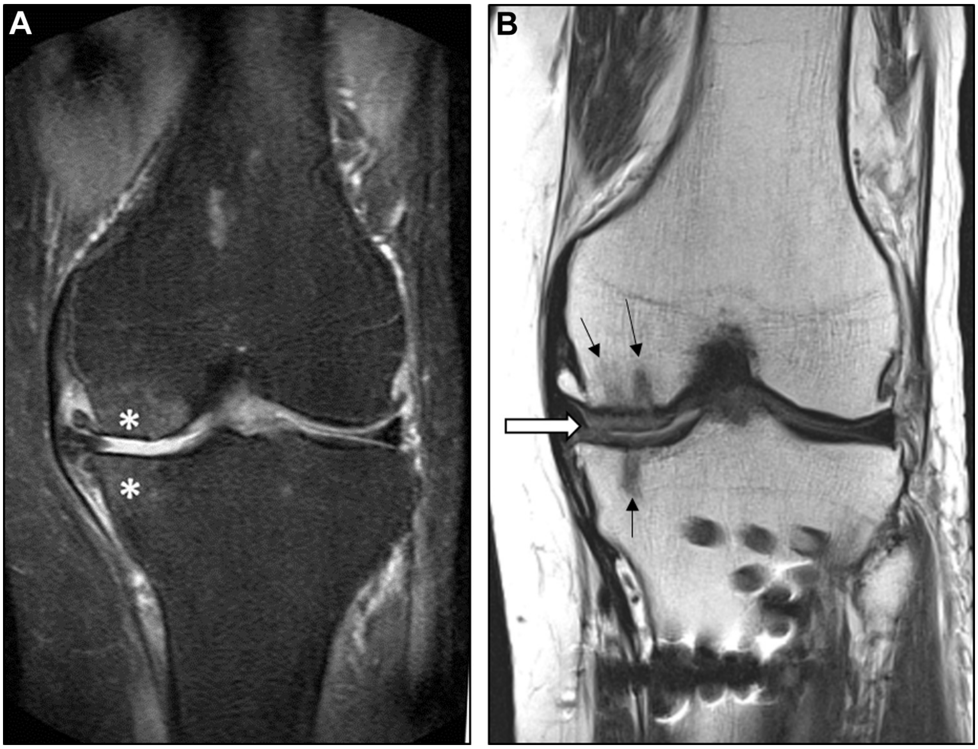


Fig 5. (A) A preoperative coronal proton density fat suppression magnetic resonance image (1.5 T) of the left knee shows full-thickness cartilage loss and subchondral edema (asterisks) of the medial tibiofemoral joint. (B) A coronal proton density magnetic resonance image (3 T) of the same knee at 15 months after chondrogenesis and high tibial osteotomy shows full-thickness articular cartilage regeneration with isointense cartilage signal intensity (white arrow). The 3 osteochondral tracks represent the location of the chondral biopsy (black arrows). The biopsy of this patient (case 5 in Table 2) is shown in Video 1 (available at www.arthroscopyjournal.org).

Statistics

Comparison of the total ICRS II score between the normal and HTO groups was evaluated with the nonparametric Wilcoxon (Mann-Whitney) test.

Results

Demographic Characteristics

The 8 patients in this case series were patients who gave informed consent to undergo hardware removal and opportunistic second-look arthroscopy for chondral biopsy. Institutional review board approval was obtained for the study. Preoperatively, the medial compartment of all knee joints involved ICRS grade 4 bone-on-bone lesions. The chondral defects were all diffuse large lesions involving at least one-third of the chondral surface of both the medial femoral condyle and medial tibial plateau (Figs 3 and 5A, and Video 1 [available at www.arthroscopyjournal.org]). The mean age at the time of surgery was 52.9 years, and there were 4 male and 4 female patients. The patients' demographic characteristics are presented in Table 1.

HTO was performed between the years 2008 and 2012 and biopsies between the years 2011 and 2014. During this period, 18 HTO cases were performed. At the time of biopsy, 6 cases still had the metalwork in place, 2 cases migrated abroad, 1 case only underwent subchondral drilling to the grade 4 medial femoral condyle lesion and had an intact medial tibial plateau (no subchondral drilling over the medial tibial plateau), and 1 case did not conform to the postoperative injection regimen. These 10 cases were therefore not included in the study.

Radiographs

Serial radiographs showed bone healing at the osteotomy site that was normally completed by 3 to 6 months. There was no evidence of delayed union or nonunion. A progressive reappearance of the medial compartment was observed up to the 2-year time point. A case example is shown in Figure 6.

Second-Look Arthroscopy With Chondral Core Biopsy

Arthroscopically, the regenerated articular cartilage appeared smooth and had excellent integration with the surrounding native cartilage without any delamination. Video 1 (available at www.arthroscopyjournal.org) illustrates a second-look arthroscopy with chondral biopsy; an example of this is shown in Figure 7. The mean time from surgery to hardware removal and biopsy was 25.9 months (range, 15 to 58 months).

Table 1. Demographic Characteristics (n = 8)

Characteristic	Mean	SD	Range
Age, yr	52.9	2.4	50.0-56.0
Height, m	1.7	0.1	1.6-1.8
Weight, kg	66.5	12.3	51.0-87.7
BMI, kg/m^2	24.2	3.3	20.7-30.4

BMI, body mass index.

Fig 6. Postoperative radiographs (same patient shown in Fig 4) at 4 years after high tibial osteotomy with chondrogenesis and 2 years after metalwork removal, showing (A) improved patellofemoral tracking after lateral patellar release and (B, C) reappearance of the medial-compartment articulation with bone healing of the osteotomy site.

Histologic Evaluation With Grading Using ICRS II

On evaluation of the histologic results, the mean ICRS II score of 1,274 for the regenerated articular cartilage approaches 95% of the normal articular cartilage core biopsy scores (mean, 1,340) (Fig 8). Table 2 shows data regarding the biopsy samples and the associated ICRS II scores.

Although the ICRS II scoring system does not involve immunohistochemical staining for type I and type II collagen, we included these data in our study. All 17 biopsy samples from the 8 cases showed an abundance of proteoglycan and type II collagen, with a minor presence of type I collagen. These characteristics closely resemble those of the native articular cartilage. Nevertheless, tissue morphologic assessment on polarized light microscopy indicated stromal collagen bundles in varying proportions (Fig 7), showing that the presence of type II collagen did not reflect 100% of nonfibrous tissue morphology.

Statistics

Figure 9 shows the mean and median ICRS II values of the HTO cases and normal cartilage core biopsy scores. There was a statistically significant difference between the regenerated cartilage and normal cartilage biopsy specimens, with $P = .0065$.

Complications and Adverse Events

None of the patients had immediate postoperative deep vein thrombosis as diagnosed by duplex ultrasonography performed 1 day after surgery. There were also no postoperative infections, cases of delayed postoperative deep vein thrombosis, vascular injuries, delayed unions, or nonunions.

Discussion

This case series shows that stem cell therapy with marrow stimulation may have the ability to regenerate high-quality repair cartilage that approaches the normal articular cartilage in medial-compartment ICRS grade 4 bone-on-bone lesions after HTO. A biological approach to treating medial-compartment osteoarthritis in a varus knee joint is appealing, especially in younger patients who may not do well in the long-term with total knee arthroplasty. For traditional isolated open-wedge HTO, cartilage regeneration has been documented; however, morphologic fill and cartilage quality are variable.[2,3,7,8] Previous histologic evaluations have documented that complete coverage can occur but fibrocartilage predominates.[3,7,8] Whereas one previous evaluation used the O'Driscoll histologic score, methods of histologic scoring have been simple and inconsistent, with none of the previous studies using the ICRS II scoring system.

With the advancement of cartilage repair techniques, clinicians have sought to combine HTO with biological joint resurfacing.[4-6,9,10] Akizuki et al.[9] compared combined HTO and arthroscopic abrasion arthroplasty versus HTO alone. Although better morphologic scores were seen in the abrasion arthroplasty group, no difference was found in clinical scores between the groups and histologic examination showed a predominance of fibrocartilage in both groups. Sterett and Steadman[10] evaluated clinical scores in patients treated with HTO and microfracture. Outcome scores were improved at 2 years, with no morphologic or histologic evaluation. Bauer et al.[6] evaluated 5-year clinical and MRI morphologic scores in 18 patients treated with HTO in combination with matrix-induced autologous chondrocyte implantation. Patients with lateral-compartment and patellofemoral lesions were excluded. Although the scores for 4 of the 5 Knee Injury and Osteoarthritis Outcome Score domains were maintained at 5 years, overall graft survival and cartilage infill were poor, with good cartilage fill in only 33% of patients.

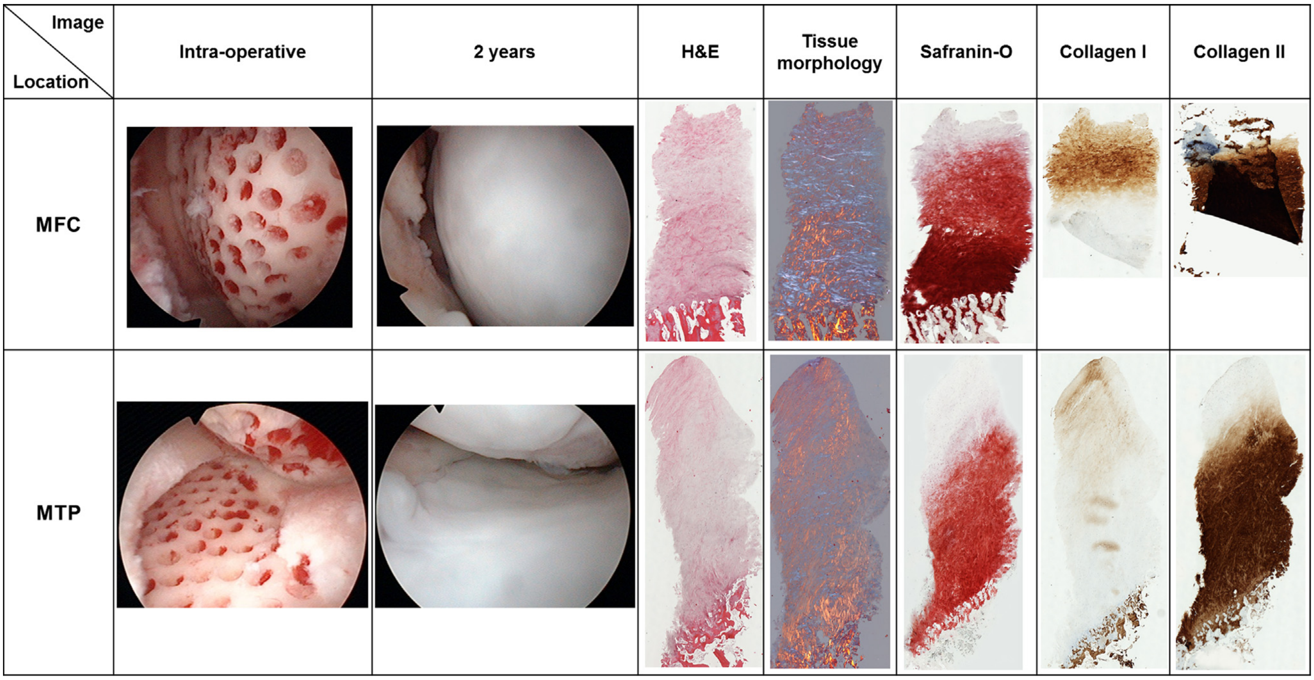


Fig 7. Findings of second-look arthroscopy and histologic assessment of medial femoral condyle (MFC) and medial tibial plateau (MTP) at 2 years in a 49-year-old male patient (same patient shown in Figs 4 and 6).

Two previous studies have investigated the addition of stem cells to HTO.[4,5] Wong et al.[4] compared the addition of 1 injection of cultured bone marrow–derived mesenchymal stem cells (MSCs) and HA at the 3-week time point versus 1 injection of HA. Magnetic Resonance Observation of Cartilage Repair Tissue MRI scoring at 1 year was better in the stem cell group, and International Knee Documentation

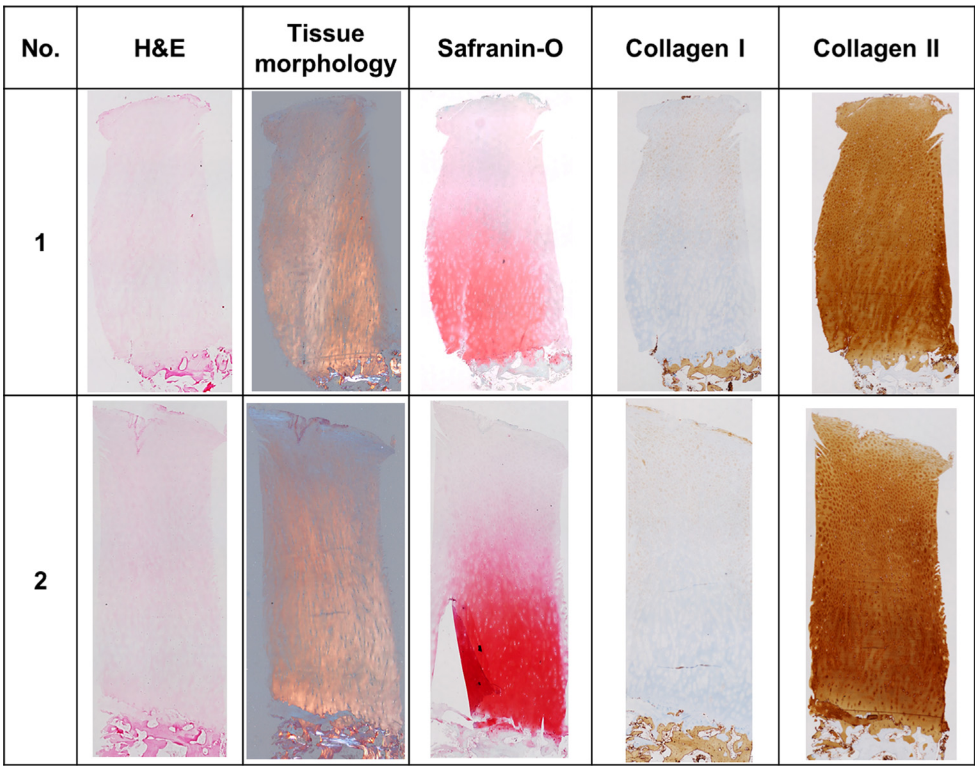


Fig 8. Examples of normal cartilage histologic findings.

Table 2. Data Regarding Biopsy Samples From MFC and MTP

Case No.	Time of Biopsy (After Initial Surgery), mo	Location of Biopsy	Mean ICRS II Score by Biopsy Site	Mean ICRS II Score Overall
1	30	MFC	1,250	1,250
2	58	MFC	1,230	1,230
3	15	MFC	1,285	1,270
		MTP	1,255	
4	25	MFC	1,265	1,258
		MTP	1,250	
5	15	MFC	1,300	1,318
		MFC	1,338	
		MTP	1,318	
6	21	MFC	1,263	1,286
		MFC	1,315	
		MTP	1,280	
7	22	MFC	1,278	1,260
		MFC	1,243	
8	21	MFC	1,320	1,321
		MFC	1,325	
		MTP	1,318	

ICRS II, International Cartilage Repair Society Visual Assessment Scale II; MFC, medial femoral condyle; MTP, medial tibial plateau.

Committee scores were better in the stem cell group after adjustment for age, baseline scoring, and time of assessment. Koh et al.[5] compared Knee Injury and Osteoarthritis Outcome Scores and morphologic scores by second-look arthroscopy in a group treated with HTO and a platelet-rich plasma injection at the end of surgery versus a group treated with HTO and an injection of adipose-derived stem cells and platelet-rich plasma at the end of surgery. Clinical scores and morphologic scores were mildly improved; however, coverage remained partial in most cases with repair tissue described as fibrocartilage.

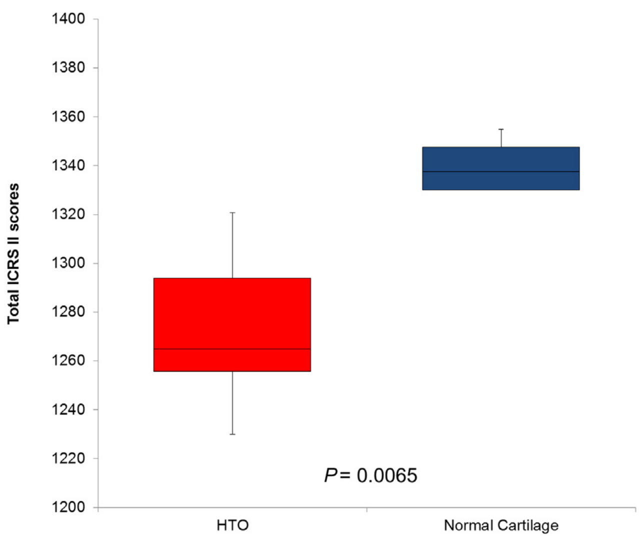


Fig 9. Box plot comparing International Cartilage Repair Society Visual Assessment Scale II (ICRS II) scores of high tibial osteotomy (HTO) cases versus normal articular cartilage ($P = .0065$).

The methods presented in our study differ from previous stem cell studies because the protocol involved multiple stem cell injections up to 18 months. Histologic studies involving cell therapy suggested that the process of chondrogenesis is still maturing at 24 months.[31] We theorize that the primary mechanism of delayed injections through the 18-month period in our case series involves the trophic paracrine benefits of PBSCs to enhance cartilage maturation. In our postoperative injection protocol, the delayed injections at 6 months and beyond involved 4 mL of PBSCs as opposed to 8 mL for the first 5 weeks. The rationale for this is that in the first 5 weeks after surgery, the volume of the hemarthrosis aspirated before injection is normally between 10 and 50 mL and therefore a 10-mL intra-articular injection (8 mL of PBSCs plus 2 mL of HA) does not result in significant discomfort. Beyond 6 months, synovial fluid aspiration is minimal, and in our experience, an intra-articular injection of 6 mL (4 mL of PBSCs plus 2 mL of HA) is generally more comfortable.

When PBSCs are harvested by apheresis, the product comprises hematopoietic stem cells (HSCs), MSCs, white blood cells, platelets, growth factors, and a small percentage of red blood cells.[32,33] PBSCs are able to differentiate into the mesenchymal lineage including cartilage, bone, and adipose tissue in vitro,[34,35] with clinical studies showing PBSCs' potential for cartilage repair.[14,15,20,21] The chondrocyte differentiation potential of stem cells derived from both peripheral blood and bone marrow has been shown to be similar in both in vitro and in vivo studies.[36,37] HSCs, MSCs, and growth factors in PBSCs play an important role in differentiating cells to initiate chondrogenesis, as well as providing paracrine effects to maturing repair tissue.[38,39]

Under normal situations, the bone marrow maintains the niche and equilibrium of stem cell production in the body,[40] and this balance of quiescent and activated stem cells is maintained throughout life. During injury, quiescent stem cells from tissue cell niches or bone marrow can be mobilized into the bloodstream or from neighboring stem cell niches to respond to injury signals and "home in" to the injury site. This is followed by events of proliferation, self-renewal, and differentiation to repair injured or regenerate damaged tissues.[41,42] This endogenous cell homing mechanism is naturally occurring, and it is the body's innate ability to regenerate. However, the potential for regeneration is limited without external stimulation,[41,43,44] possibly because of an age-related decline in the regenerative capacity of the endogenous stem cell population. When intra-articular PBSCs are injected into the knee joint, regeneration is initiated by exogenous HSCs in PBSCs, as well as from migrating endogenous bone marrow MSCs. The direct access channels to the bone marrow through subchondral drilling allow the endogenous bone marrow MSCs to migrate into the blood clot scaffold along the drilled channels and eliminate the difficulty in recruiting a sufficient number of MSCs traveling through the peripheral blood circulation to the injury site.[42,45,46] There is evidence that exogenous MSCs are able to augment endogenous MSC recruitment.[47,48] Similarly, we believe that the exogenous HSCs through intra-articular PBSC injections enhance endogenous MSC recruitment from the bone marrow to the drill sites. We theorize that HA enhances the matrix substance and continuous passive motion aids joint movement and provides chemical and cellular signals for chondrogenesis.[21,29,49] Early partial to full weight bearing is essential for remodeling and aligning the collagen fibrils along the axis of weight transmission.[20]

This study differs from previous studies in its use of the ICRS II grading system to evaluate cartilage repair tissue with normal cartilage for comparison. With increasing attention being paid to the improvement of cartilage repair techniques, the ICRS developed a grading system using a visual assessment scale in 2003, the ICRS I, for the purposes of evaluating cartilage repair. A modified version, the ICRS Visual Assessment Scale II (ICRS II) grading system, was proposed in 2010 to expand the scoring from 6 grading components to 14 components.[30] The use of the ICRS II grading system has been limited.[21,50-52] Cartilage grading systems attempt to quantify and compare the repaired tissue with normal cartilage (Fig 8, Table 3) by evaluating tissue morphology, integration, and composition. In contrast to articular hyaline cartilage, fibrocartilage is made up of disorganized type I collagen fibers with a heterogeneous background often including vascular channels. When chondral biopsy specimens are evaluated with the ICRS II grading system, chondrogenesis in the medial compartment after stem cell therapy and HTO can approximate 91% (range, 88% to 94%) of a perfect score (total score of 1,400 for the 14 parameters in the ICRS II combined) whereas normal cartilage approximates 96% (range, 95% to 97%) of a perfect score. Figure 9 shows a box-plot comparison of the ICRS II scores between the HTO cases and normal cartilage, with normal cartilage showing better scores with statistical significance of $P = .0065$.

Table 3. ICRS II Scores for Consented Normal Cartilage Biopsy Specimens

Age When Biopsy Sample Was Obtained, yr	Location of Biopsy	Mean ICRS II Score by Biopsy Site	Mean ICRS II Score Overall
39	MT	1,330	1,330
47	MFC	1,330	1,330
50	MFC	1,390	1,345
	MFC	1,300	
43	LPF	1,330	1,355
	LPF	1,380	

ICRS II, International Cartilage Repair Society Visual Assessment Scale II; LPF, lateral patellar facet; MFC, medial femoral condyle; MT, medial trochlea.

The long-term results of combining chondrogenesis with HTO for medial-compartment osteoarthritis remain to be seen. In addition to regenerating high-quality articular cartilage, neutral longitudinal axis correction in the coronal plane has the benefit of restoring normal alignment of the knee joint. Long-term results theoretically should not be worse than currently published results of standard HTO cases, whereby it has been reported that the survivorship of osteotomy ranges from 75% to 95% up to 5 years and from 51% to 98% at 10 years.[53-61]

The trial design for a phase II randomized controlled trial using the described technique has just been approved by the US Food and Drug Administration involving the institutions of the first and second authors (K-Y.S. and A.A.), the first author being the principal investigator. This trial will involve large chondral lesions, multiple lesions including ICRS grade 4 bone-on-bone chondral defects with comparison to a control group. Time will tell whether this technology will be efficacious as compared with the currently available methods for cartilage repair.

Limitations

This case series is a retrospective, nonrandomized histologic review, representing Level IV evidence. Although Level IV evidence is useful for making inferences about efficacy and determining the safety of a therapy, conclusions regarding efficacy are weak because of the lack of a control group. A second limitation is the small sample size. Because the technique is an evolving cartilage repair technology,[20,21,29,49,62] we found it difficult to recruit patients for biopsy, outside of patients presenting with hardware needing removal. Because the case series was obtained from opportunistic biopsies performed at different time points during metalwork removal, it was difficult to correlate the histologic findings with the functional clinical scores. The main focus of this case series is to share the knowledge that grade 4 bone-on-bone lesions are treatable arthroscopically while regenerating repair cartilage approaching normal articular cartilage histologically. Long-term follow-up is required for these patients to assess the longitudinal functional outcome of the regenerated articular cartilage.

Conclusions

Chondrogenesis with stem cells in combination with medial open-wedge HTO for varus deformity correction of the knee joint regenerates cartilage that closely resembles the native articular cartilage.

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