CASE REPORT

Osteochondral Regeneration in the Knee Joint with Autologous Peripheral Blood Stem Cells plus Hyaluronic Acid after Arthroscopic Subchondral Drilling: Report of Five Cases

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Background: Treatment of osteochondral defects (OCDs) of the knee joint remains challenging. The purpose of this study was to evaluate the clinical and radiological results of osteochondral regeneration following intra-articular injections of autologous peripheral blood stem cells (PBSC) plus hyaluronic acid (HA) after arthroscopic subchondral drilling into OCDs of the knee joint.

Case Presentation: Five patients with OCDs of the knee joint are presented. The etiology includes osteochondritis dissecans, traumatic knee injuries, previously failed cartilage repair procedures involving microfractures and OATS (osteochondral allograft transfer systems). PBSC were harvested 1 week after surgery. Patients received intra-articular injections at week 1, 2, 3, 4, and 5 after surgery. Then at 6 months after surgery, intra-articular injections were administered at a weekly interval for 3 consecutive weeks. These 3 weekly injections were repeated at 12, 18 and 24 months after surgery. Each patient received a total of 17 injections. Subjective International Knee Documentation Committee (IKDC) scores and MRI scans were obtained preoperatively and postoperatively at serial visits. At follow-ups of >5 years, the mean preoperative and postoperative IKDC scores were 47.2 and 80.7 respectively ($p = 0.005$). IKDC scores for all patients exceeded the minimal clinically important difference values of 8.3, indicating clinical significance. Serial MRI scans charted the repair and regeneration of the OCDs with evidence of bone growth filling-in the base of the defects, followed by reformation of the subchondral bone plate and regeneration of the overlying articular cartilage.

Conclusion: These case studies showed that this treatment is able to repair and regenerate both the osseous and articular cartilage components of knee OCDs.

Key words: Arthroscopic Subchondral Drilling; Bone and Articular Cartilage Regeneration; Bone Marrow Stimulation; Osteochondral Defects; Peripheral Blood Stem Cells

Introduction

Osteochondral defects (OCDs) of the knee joint are combined articular cartilage defects with damage to the underlying subchondral bone. When left untreated, further degeneration and deterioration may lead to an early knee arthroplasty. Clinical OCDs can be associated with acute traumatic knee injuries, subchondral insufficiency fractures, osteochondritis dissecans, avascular necrosis, localized early degenerative abnormalities and/or with previous failed cartilage repair procedures.[1–3] Surgical options include fixation of osteochondral fragments, transfer of autologous or allograft osteochondral grafts, and bone grafting combined with

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cellular therapies. The obvious benefit for combination therapy is harnessing the advantages offered by the surgical treatment while adding the regenerative power of cellular therapies. Algorithms are based on multiple factors, including size and location.[3] Preservation of patient's native cartilage and bone is preferred if a fragment can be salvaged with fixation. Regeneration of OCDs is perceived as challenging as it involves both bone and cartilage.[1]

Smaller cartilage lesions (<2 cm^2) are treated with a variety of options, for example microfracture, or osteochondral autograft or allograft. Microfracture has shown satisfactory short-term results,[4–6] but mid-term and long-term studies have demonstrated deterioration of function after 2 years.[5] Osteochondral autograft transfer has the benefit of transplanting autologous hyaline cartilage and the advantage of a single stage procedure. Results have shown improved subjective outcome scores and a higher rate of return to sports in athletes compared to microfracture. Unfortunately, results do deteriorate at longer follow-ups.[7,8] The failure rate of both the above-mentioned treatments was reported to be 50% at a 5-year follow-up study.[9] For the treatment of osteochondral allograft transplantation alone the failure rate is up to 46%.[10]

Larger lesions can be managed with osteochondral allograft transplantation or a cell-based option, such as matrix-induced autologous chondrocyte implantation (MACI). Although osteochondral allograft transplantation has shown good outcomes, most failures occur on an average of 42 months after surgery.[11,12] In addition, there are technical difficulties for performing surgery at sites involving tibial, deep-flexion femoral, and trochlear lesions. MACI has shown an estimated 9% to 10% revision surgery rate for symptomatic large lesions.[13,14] Even with these cell-based options, OCDs remain a difficult problem, with suboptimal results and outcomes.

Autologous peripheral blood stem cells (PBSC) have been used as a cellular therapy to augment knee articular cartilage repair with reported clinical outcomes. Several case series and randomized controlled trials (RCT) were published[15–17] using PBSC addressing massive chondral defects in the knee joint with statistically significant results, addressing both the safety and efficacy aspects of PBSC therapy on chondrogenesis.[17] PBSC have also been shown to have the ability to regenerate bone with encouraging clinical results.[18] In addition, an *in vitro* study has found PBSC to be pluripotent.[19]

The cases presented here include clinical and radiological results of successful osteochondral regeneration following intra-articular injections of autologous PBSC plus HA after arthroscopic subchondral drilling into OCDs of the knee joint. As shown in a previous study,[15] adjuvant HA injections are beneficial for cartilage repair. The published[15] benefits of HA have shown that it enhances differentiation to chondrocytes, decreased joint inflammation, increased proteoglycan content in repair cartilage, improved histologic scores after cartilage repair, improved defect filling/incorporation after cartilage repair, and decreased post-procedural coefficients of friction.

Case Reports

Five patients with OCDs of the knee joint were treated with arthroscopic subchondral drilling followed by post-operative intra-articular injections of autologous PBSC plus HA. The diagnosis of OCDs of the knee joint was based on history and clinical examination, followed by radiographs and MRI scans for confirmation. Weight-bearing radiographs with standard anteroposterior, lateral, and merchant views of the affected knee joint were taken. An additional full-leg anterior posterior radiograph was taken to assess the degree of varus or valgus deformity of the knee joint.

Informed consent was obtained prior to treatment with ethics approval (KLSMC Ethics Committee: KLSMC-012). Inclusion criteria were: (i) patients with bone and cartilage defects of the knee joint; (ii) patients with previous failed bone and cartilage procedures (for example, fixation of osteochondral fragments, transfer of autologous or allograft osteochondral grafts, MACI); and (iii) patients with "kissing" bone and cartilage defects. Exclusions were patients with varus or valgus deformity that would require osteotomy, and patients with contraindications for the PBSC harvesting procedure, for example, pregnancy, HIV, hepatitis, bleeding disorders and allergies to medications required for the harvesting process.

Arthroscopic procedures involved removal of loose bony fragments, debridement of underlying necrotic bone and soft tissue followed by subchondral drilling into the OCDs. The arthroscopic subchondral drilling procedure and chondrogenesis method for the knee joint has been described previously.[15–17,20]

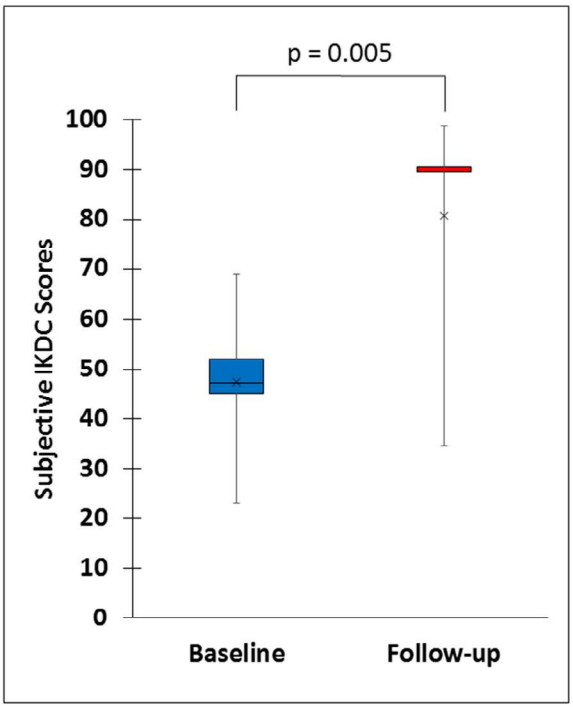
The details of PBSC harvesting procedure and cell preparation have been outlined in our previous publications.[15,16] In brief, filgrastim (Neupogen, Amgen, Thousand Oaks, CA, USA) were administered to mobilize the PBSC into blood stream and PBSC were harvested *via* apheresis using a Spectra Optia Apheresis Machine (CaridianBCT, Denver, CO, USA). The collected PBSC were then cryopreserved in 4 mL vials and stored in liquid nitrogen at −196 °C. PBSC administration and details of the physiotherapy regime have also been published.[17] In short, for the five cases presented here, each patient received a total of 17 injections. Intra-articular injections were given at week 1, 2, 3, 4, and 5 after surgery. This set of injections consisted of 8 mL of PBSC with 2 mL of HA. Then at 6 months after surgery, intra-articular injections consisted of 4 mL of PBSC with 2 mL of HA, were administered at a weekly interval for 3 consecutive weeks. These 3 weekly injections were repeated at 12, 18 and 24 months after surgery.

A 3T MRI scanner (Magnetom Spectra, Siemens, Erlangen, Germany) and a 1.5T extremity MRI scanner (ONI MSK Extreme; GE Healthcare, Waukesha, WI, USA) were used. The MRI protocol included multiplanar proton density-weighted with and without fat suppression, and T1-weighted.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA).

A two-tailed paired t-test was used to compare the Subjective International Knee Documentation Committee (IKDC) scores at baseline and latest follow-up. A p-value less than 0.05 was considered significant. Minimal clinically important difference (MCID) for IKDC scores was calculated using distribution-based method, where the MCID value is equal to half of the standard deviation of IKDC scores at baseline. Significant clinical outcome is defined as IKDC score improvement surpassing the calculated MCID value at follow-up for individual subjects.

The mean age and body mass index of all five patients at surgery were 29.6 ± 11.8 (range 16 to 47 years) and 23.7 ± 2.5 (range 20.0 to 26.6), respectively. At a mean follow-up of 8.9 ± 3.8 (range 5 to 11 years), the IKDC scores significantly increased from 47.2 ± 16.5 at baseline to 80.7 ± 26.1 with $p = 0.005$ (Figure 1). The difference in IKDC scores for all subjects surpasses the calculated MCID value of 8.3, indicating clinical significance. There were no documented infection or other major adverse events in this case series.



Case	Baseline	Follow-up	Improvement
1	45.0	90.8	45.8
2	69.0	98.9	29.9
3	23.0	34.5	11.5
4	52.0	89.7	37.7
5	47.0	89.7	30.0
Mean	47.2	80.7	33.5
SD	16.5	25.6	12.7

FIGURE 1 Box plot of Subjective International Knee Documentation Committee (IKDC) scores at baseline and latest follow-up.

The most important findings of this case series is the potential ability of autologous PBSC plus HA to repair and regenerate both the osseous and articular cartilage components of knee OCDs following arthroscopic subchondral drilling, without the need for bone grafting. Serial MRI scans provide an insight to the osteochondrogenesis process and allow assessment of the entire repair area non-invasively. There were no infections and the scans revealed no evidence of adverse articular or extra-articular abnormalities for all the cases reported here. The difference in IKDC scores for all subjects surpasses the calculated MCID value of 8.3, indicating clinical significance. Subjective IKDC scores showed improvements with statistical significance ($p = 0.005$) at a mid to long term follow-up period of 5.1 to 11.4 years (mean = 8.9 years). These scores suggested that the regenerated osteochondral components were resilient in nature. Similar scores were achieved in our previous published study where the cartilage biopsies of the regenerated cartilage approached 95% of normal articular cartilage score histologically.[20]

Articular cartilage is visible on most standard MRI sequences as a band of intermediate to high signal covering the articular aspect of the bone. Non-injured articular cartilage normally shows a continuous subchondral dark line (low-signal-intensity band) separating the underlying subchondral bone from the overlying articular cartilage (Figure 2B). This layer represents the calcified cartilage and the associated subchondral bone, referred to as the subchondral bone plate.[21] OCDs represent a combined injury of the articular cartilage, the subchondral bone plate and the underlying subchondral bone. The authors believe that the osteochondrogenesis process needs to document regeneration of these three essential layers. Our MRI scans performed on the first postoperative day following subchondral drilling into OCDs (Figures 2–4) showed the resultant defects well delineated from surrounding healthy cartilage. The defects were bare or partially filled-in with blood clots. Drill tracts and OCDs were observed, the subchondral bone area was disrupted and there was discontinuity of the subchondral bone plate. Over the course of 2 years, filling-in of bone and cartilage from the basal aspect paralleled the progressive resolution of marrow oedema, with re-establishment of the subchondral bone plate, accompanied by regeneration of the overlying articular cartilage. Histological evidence of this process can be seen in (Figures 2C and 3E) from a previous publication showing biopsy specimens from the femoral condyle illustrating ossification of regenerated cartilage and the re-establishment of the calcified cartilage layer.[15]

Case 1 is a 31-year-old woman who presented with a 13 years' history of progressive pain and swelling to the right knee. Ten years previously, she underwent two microfracture surgeries over the lateral femoral condyle and had a further microfracture surgery with autologous bone marrow aspirate concentrate (BMAC) injections 1 year prior to being seen. Arthroscopic subchondral drilling into the OCD was

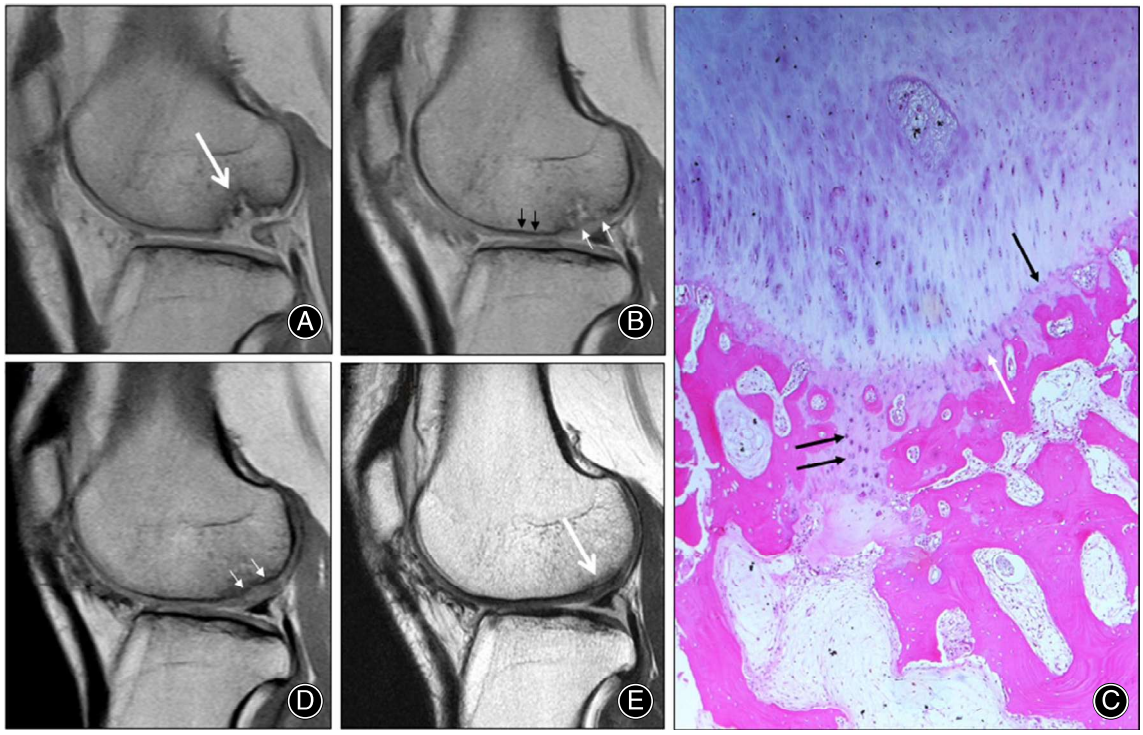


FIGURE 2 Sagittal proton density-weighted MR images of the right knee lateral femoral condyle showing the osteochondral defect with image (A) at 1 day after arthroscopic removal of necrotic and non-viable bone followed by multiple drilling into the osteochondral defect (white arrow). (B) Image at 3 months showing evidence of early bone and cartilage regeneration, with subtle restoration of the subchondral bone plate (white arrows). Black arrows depicting the existing subchondral bone plate, separating the underlying bony component from the overlying articular cartilage layer. (C) a previous publication with an example of the osteochondrogenesis process showing a biopsy specimen from the femoral condyle illustrating ossification of regenerated cartilage and the re-establishment of the calcified cartilage (white arrow) layer with tidemark (black arrow).[16] At the two-year time point, chondrocytes were still present from the drill hole below the calcified cartilage (double arrows) with areas of ossification. (D) Image at 1 year showing bone and cartilage regeneration with reappearance of the subchondral bone plate (white arrows), associated with hypertrophy of the overlying neocartilage. (E) Image at 2 years following remodeling of the underlying bone and overlying neocartilage resembling the native surrounding osteochondral structures (white arrow).

performed following removal of necrotic and non-viable bone. The resultant OCD measured 1.7 cm width (W) × 2.1 cm length (L) × 0.7 cm depth (D). Figure 2 shows progressive bone and cartilage regeneration following arthroscopic subchondral drilling and subsequent healing of the OCD. Follow-up period for Case 1 is 11 years.

Case 2 is a 22-year-old man who presented with a 2 years' history of progressive left knee pain secondary to osteochondritis dissecans with a follow-up period of 7 years. Radiographs and MRI scans revealed an osteochondral lesion measuring 1.3 cm (W) × 1.8 cm (L) × 0.8 cm (D) over the posterolateral weight bearing aspect of the medial femoral condyle. Arthroscopic removal of the osteochondral lesion was performed followed by subchondral drilling into the base of the defect. Figure 3 showed the osteochondral regeneration and remodeling process of the OCD following surgery.

Case 3 is a 32-year-old man who underwent left knee open fixation of a loose osteochondral fragment secondary to osteochondritis dissecans at age 16. At age 31, the osteochondral allograft transfer systems (OATS) procedure was performed over the medial femoral condyle. He remained asymptomatic for 9 months prior to being seen at the out-patient clinic. His pain returned and MRI revealed unincorporated osteochondral allograft cylinders. A knee arthroscopy confirmed loose and unhealed allografts. The resultant OCD measured 2.0 cm (W) × 4.0 cm (L) × 1.0 cm (D). Figure 4 also showed the breakdown of previous OATS procedure preoperatively and the subsequent healing with osteochondrogenesis. Follow-up period is 5 years.

Case 4 is a 16-year-old female teenager who fell and injured her left knee during a sprinting competition 18 months prior to being seen. Arthroscopic debridement was performed 6 months following the injury with no clinical improvement. She had progressive knee pain and was unable to weight bear on the injured knee for a period of 2 months before she was seen at the outpatient clinic. The OCD measured 1.2 cm (W) × 1.3 cm (L) × 0.8 cm (D) over the central lateral tibial plateau. Arthroscopic subchondral

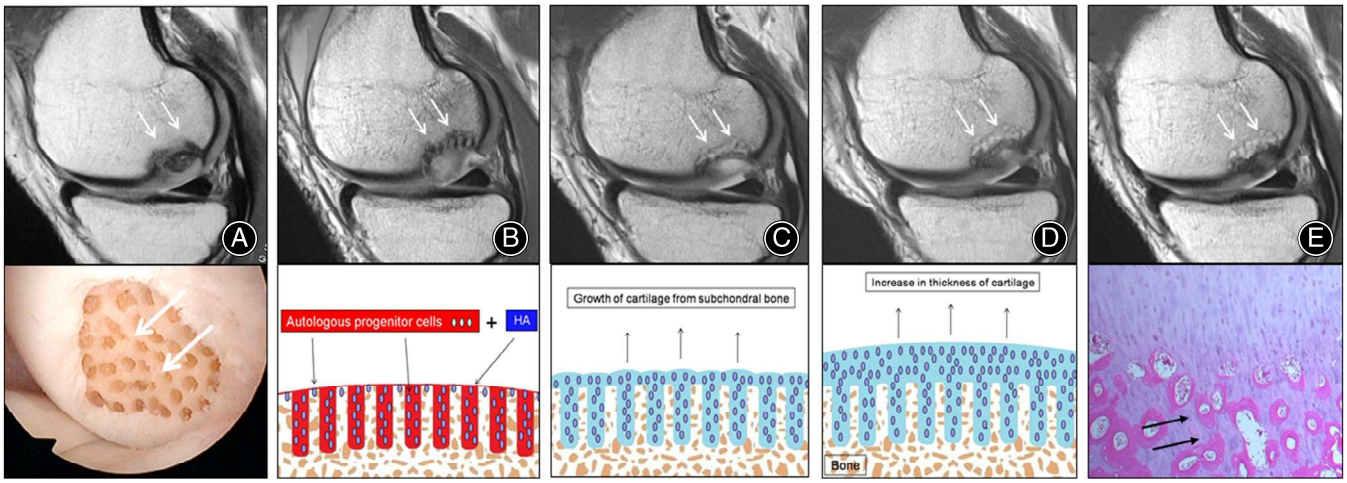


FIGURE 3 Sagittal proton density-weighted MR image (top row) with illustrations (bottom row). (A) MR image (top image) showing the osteochondritis dissecans over the posterolateral aspect of the left medial femoral condyle. Arthroscopic view (bottom image) after the removal of the osteochondritis dissecans and multiple subchondral drilling into the defect (white arrows). (B) Post-op day 1 revealed the evidence of multiple subchondral drilling into the base of the OCD with the resultant blood clot scaffold (white arrows). (C) At 6 months, the drill holes are gradually being replaced with bone, therefore less prominence of previous drill holes. (D) Evidence of cartilage growth from the periphery of the defect with increasing thickness of the regenerated cartilage at 1 year. (E) Progressive osteochondral regeneration showed bony in-fill of the osteochondral defect, reappearance of the subchondral bone plate and regeneration of the overlying articular cartilage at 2 years after surgery. The histology below is an example from our previous study with biopsy at 2 years showing the presence of chondrocytes (arrows) below the subchondral bone with areas of ossification. (Illustrations and histology adapted from Saw *et al.*[15])

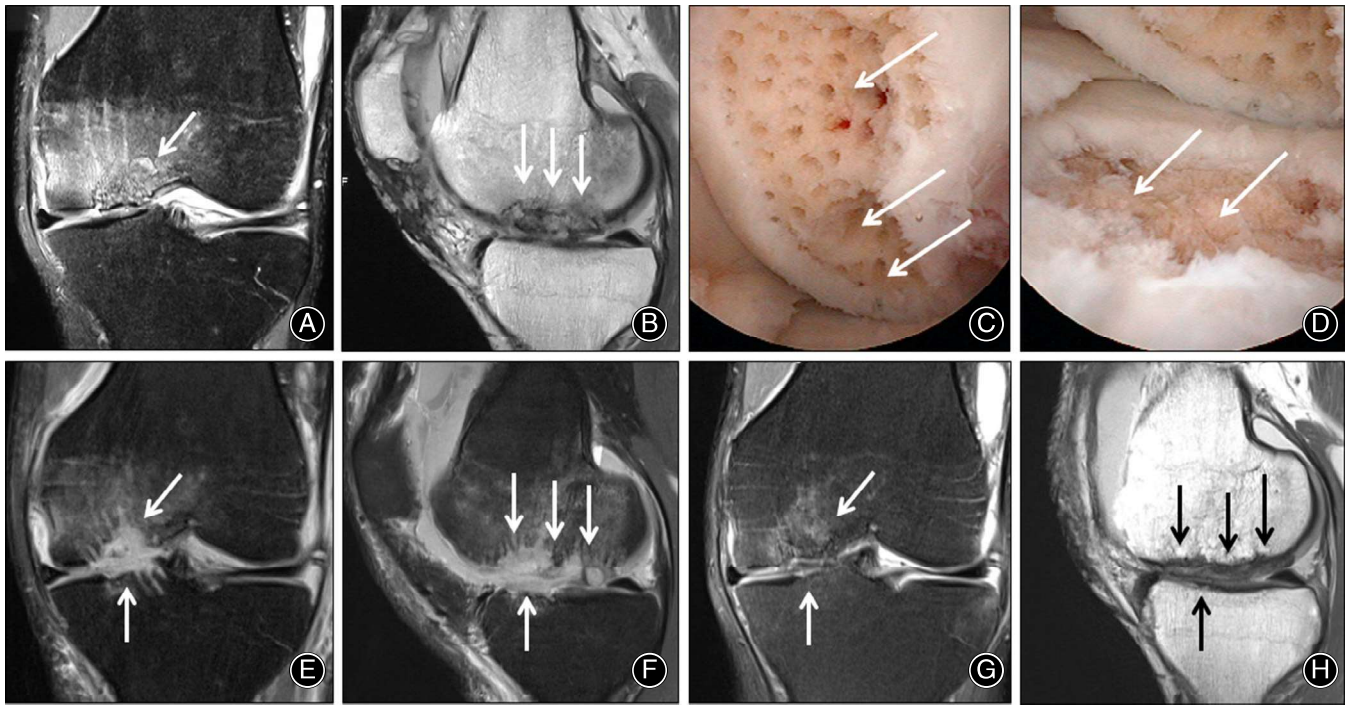


FIGURE 4 Coronal (A) and sagittal (B) MR images of the left knee showing breakdown of previous OATS procedure resulting in a large osteochondral lesion (white arrows) of the medial femoral condyle, associated with marrow oedema. (C) View following removal of previous OATS and subchondral drilling into the OCDs (white arrows). (D) View of the medial tibial plateau following subchondral drilling (white arrows). MR images with arrows at one (E, F) and 2 years (G, H) showing progressive bone and cartilage regeneration with resolution of marrow oedema. MR images are all fat-suppressed proton density-weighted except (B) & (H) which are proton density-weighted.

drilling into the lateral tibial plateau was performed as shown in Figure 5. Follow-up period is 10 years.

Case 5 is a 47-year-old man who presented with a 6 years history of right knee pain following a direct impact to the patellofemoral joint in flexion. Six weeks prior to being seen, he underwent arthroscopic debridement. MRI scan showed "kissing" OCDs of the central patella measuring 1.4 cm (W) × 1.1 cm (L) × 0.5 cm (D) and central trochlea measuring 2.0 cm (W) × 2.0 cm (L) × 0.5 cm (D). Arthroscopy showed lateral patellar maltracking with bone-on-bone lesion of the patellofemoral joint. Arthroscopic subchondral drilling was performed with lateral patellar release as shown in Figure 6. Follow-up period is 10 years.

Discussion

The OCDs in this case series were managed following the same principles as K.A.R.T.® (KLSMC Articular Regeneration Technology) procedure,[17] stressing the importance of motion and tailored weight-bearing to take advantage of the opposing articular cartilage to contour the healing OCDs, enabling the differentiation of PBSC into bone, re-establishing the subchondral bone plate and eventually forming a smooth articulating chondral surface.[16,20] The drill holes created from arthroscopic subchondral drilling surgery initially forms a blood clot scaffold, which contained endogenous stem cells. These drill holes provide a channel for access to the bone marrow. When seeded with exogenous stem cells from serial intra-articular PBSC and HA injections, chondrogenesis progresses evenly and the individual tufts of growing cartilage coalesce to form a new layer of articular hyaline cartilage.[15] As observed from previous histological evaluation of consented biopsy samples,[15] a linear pattern of chondrocytes formed from the subchondral bone region at the sites of subchondral drilling indicating early ossification originated within the tract. With external stimuli provided by the physiotherapy regime, this influences the differentiation of both endogenous stem cells and exogenous PBSC into bone, calcified cartilage layer and tidemark. A previous randomized controlled study[16] has also shown that intra-articular injections of PBSC plus HA after arthroscopic subchondral drilling gave rise to a significant statistical improvement in histologic and MRI scores as compared to HA injections alone.

Four of our five cases (except Case 2) had failures from previous debridement with/without microfracture or additional procedures. In combination, these cases included chondral/OCDs affecting the patellofemoral and medial/lateral femorotibial joints. Case 2 was the only previously un-operated knee in our series. Due to the success of the previously documented Case 1, a decision was made to not pin back the unstable osteochondritis dissecans and instead removed the loose fragment followed by osteochondrogenesis with PBSC plus HA. Case 3 was challenging as the patient had failure of previously fixed osteochondritis dissecans followed by disappointing results of subsequent surgery with multiple OATS. Options for him were either larger OATS which may have an even higher chance of failure or knee arthroplasty. Another point of note is that the patients in this case series are relatively young patients with an average age

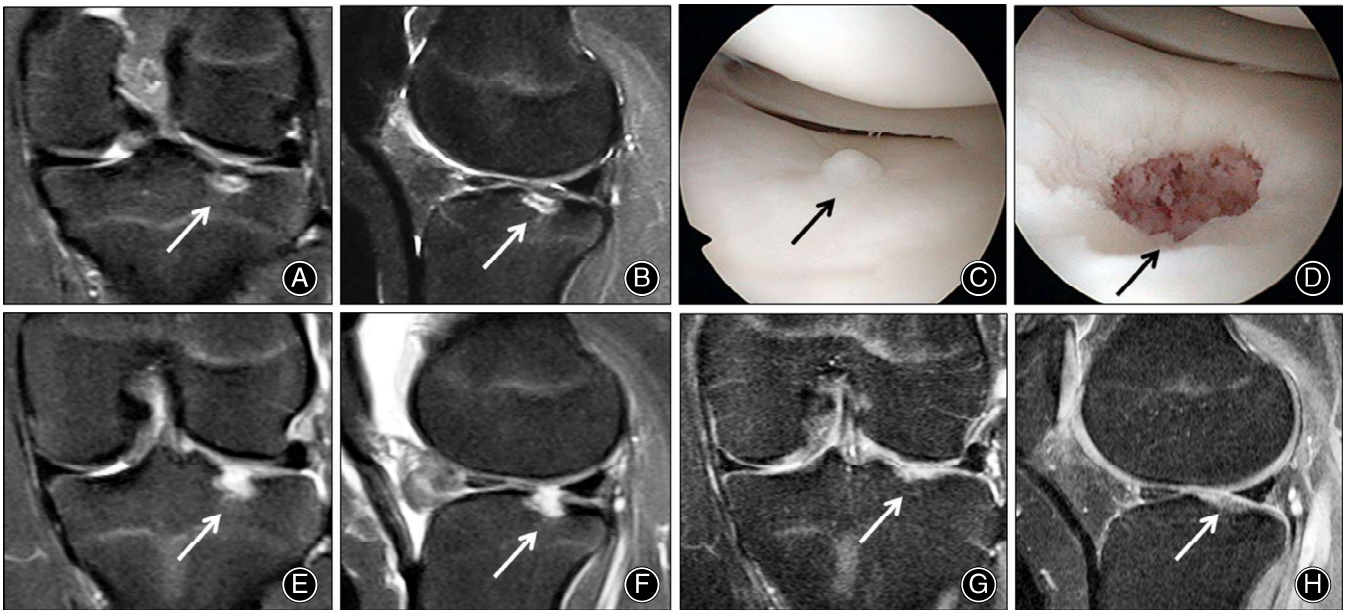


FIGURE 5 Coronal (A) and sagittal (B) MR images of the left knee showing an OCD (white arrows) over the central lateral tibial plateau. Arthroscopic view of the OCD before (C) and after debridement and drilling into the OCD (D). Coronal (E) and sagittal (F) MR images at post-op day 1 showing the resultant defect following drilling (white arrows). Coronal (G) and sagittal (H) MR images at 2 years following surgery showing full thickness osteochondral regeneration with normal signal intensity and intact cartilage surface (white arrows). MR images are all fat-suppressed proton density-weighted.

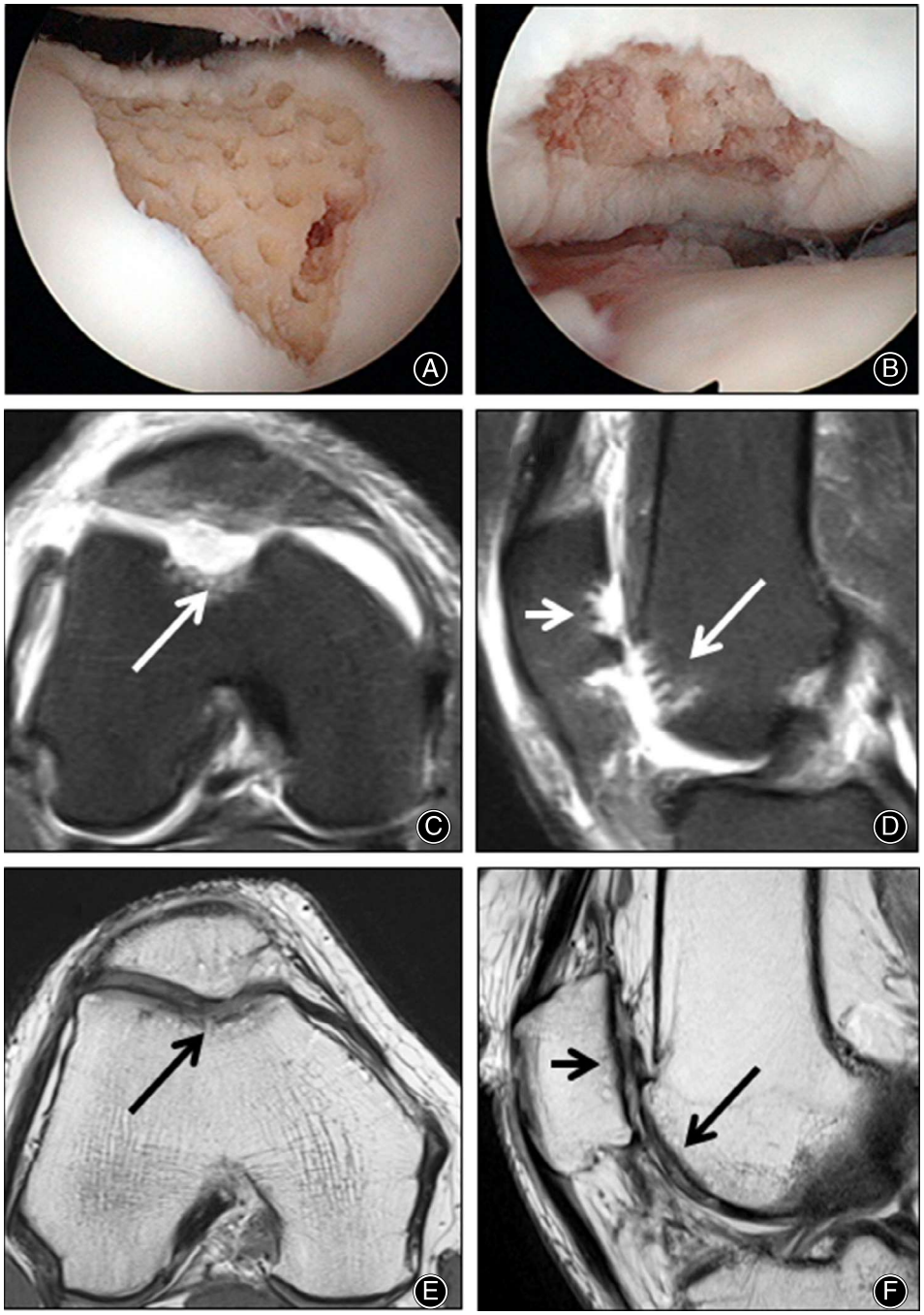


FIGURE 6 Arthroscopic view of central trochlear (A) and central patella (B) after subchondral drilling. Axial (C) and sagittal (D) fat-suppressed proton density-weighted MR images of the right knee showing 'kissing' OCDs with subchondral drilling at the central patella (short white arrow) and central trochlea (long white arrows) at post-op day 1. Axial (E) and sagittal (F) proton density-weighted MR images of the right knee at 7 years post-subchondral drilling showing full thickness osteochondral regeneration at the central patella (short black arrow) and central trochlea (long black arrows).

of 29.6 years old (16 to 47 years old) and knee arthroplasty is not an ideal long-term solution.

The limitations of this case studies include limited number of cases as only five are presented; the etiology of the cases is not all similar; and follow-up radiographs of the full leg view were not taken for further assessment.

The K.A.R.T.® procedure is not just limited to repair and regeneration of OCDs of the knee joint. Other applications to the musculoskeletal system with this technology have been published.[22] For example, addressing large osteochondral lesions of the talus,[23] reversal of end-stage ankle arthritis,[24] repair and regeneration of chronic Achilles tendinopathy[25] and regeneration of massive bone defects.[18] We are embarking on a phase 3 US-FDA clinical trial treating massive knee cartilage defects in the very near future. With the hope of a successful clinical trial, this technology will then be publicly available to address some of the "unmet medical needs" in orthopedic surgery. Delaying and reversal of osteoarthritis is possible with K.A.R.T.® procedure.

Conclusion

These case series showed that massive and "kissing" OCDs of the knee joint are treatable with arthroscopic subchondral drilling followed by postoperative intra-articular injections of autologous PBSC plus HA.

Author Contributions

Khay-Yong Saw: the treating surgeon involved in the management of the cases and the inventor of this technology. Adam W. Anz: the principal investigator involved in the development of this technology in the USA. Assisted in intellectual input of this manuscript. Caroline Siew-Yoke Jee: lead scientist involved in management of the project, stem cells harvesting and drafting of this manuscript. Soo-Fin Low: the radiologist contributed in analyzing the radiographs and MRI images. Amal Dawam: the scientist involved in data collection and quality control tests. Alisha Ramlan: biostatistician, contributed in MCID calculation and graph. All authors provided intellectual contribution and approval of this manuscript for publication. The authors consist of medical professionals and research scientists. The medical professionals are the orthopedic surgeons and radiologist involved in development of this technology, patient care, and analysis of radiographs and MRI images. The research scientists provided input related to the fundamental scientific knowledge in the field of stem cells and involved in the stem cells harvesting process, quality control, data collection and statistical analysis.

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Ethics Statement

Ethical approval is given by KLSMC Hospital Ethics Committee chaired by Dr. Yong Guan Tay. Informed consent was taken for all cases.

Conflict of Interest Statement

The authors declare no conflicts of interest in this case.

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