

Increased Failure Rate of Autologous Chondrocyte Implantation After Previous Treatment With Marrow Stimulation Techniques

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Background: Marrow stimulation techniques such as drilling or microfracture are first-line treatment options for symptomatic cartilage defects. Common knowledge holds that these treatments do not compromise subsequent cartilage repair procedures with autologous chondrocyte implantation.

Hypothesis: Cartilage defects pretreated with marrow stimulation techniques will have an increased failure rate.

Study Design: Cohort study; Level of evidence, 2.

Methods: The first 321 consecutive patients treated at one institution with autologous chondrocyte implantation for full-thickness cartilage defects that reached more than 2 years of follow-up were evaluated by prospectively collected data. Patients were grouped based on whether they had undergone prior treatment with a marrow stimulation technique. Outcomes were classified as complete failure if more than 25% of a grafted defect area had to be removed in later procedures because of persistent symptoms.

Results: There were 522 defects in 321 patients (325 joints) treated with autologous chondrocyte implantation. On average, there were 1.7 lesions per patient. Of these joints, 111 had previously undergone surgery that penetrated the subchondral bone; 214 joints had no prior treatment that affected the subchondral bone and served as controls. Within the marrow stimulation group, there were 29 (26%) failures, compared with 17 (8%) failures in the control group.

Conclusion: Defects that had prior treatment affecting the subchondral bone failed at a rate 3 times that of nontreated defects. The failure rates for drilling (28%), abrasion arthroplasty (27%), and microfracture (20%) were not significantly different, possibly because of the lower number of microfracture patients in this cohort (25 of 110 marrow-stimulation procedures). The data demonstrate that marrow stimulation techniques have a strong negative effect on subsequent cartilage repair with autologous chondrocyte implantation and therefore should be used judiciously in larger cartilage defects that could require future treatment with autologous chondrocyte implantation.

Keywords: cartilage; marrow stimulation; autologous chondrocyte implantation

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Full-thickness defects of articular cartilage have limited to no spontaneous repair potential⁴ and can compromise patients through symptoms such as activity-related pain and swelling.⁵ Various techniques have been developed to address these symptoms, including palliative procedures such as debridement and reparative procedures such as marrow stimulation techniques (MST). The latter include drilling¹⁷ and abrasion arthroplasty¹⁰ as well as the more recently developed microfracture procedure.²¹ All 3 attempt to effect filling of a chondral defect with reparative tissue

resulting from stimulation of the subchondral bone at the bottom of the defect. Blood and mesenchymal cells from the underlying bone marrow form a clot in the defect that over time differentiates into a fibrocartilaginous repair tissue.²¹ Marrow-stimulating technique procedures, in particular microfracture, are considered the first-line treatment for full-thickness cartilage lesions and have demonstrated good to excellent results in 60% to 80% of patients.^{13,20} There are, however, concerns over the durability of the repair tissue and hence the clinical outcome, especially in defects that are larger than 2 to 4 cm² and located in areas other than the femoral condyles.^{9,11,12} Autologous chondrocyte implantation (ACI)³ was developed in an attempt to improve on the early MST procedures that resulted in a predominantly fibrous repair tissue. Autologous chondrocyte implantation is a 2-stage procedure with considerable morbidity, complex rehabilitation, and long recovery and is therefore indicated as a second-line treatment after failure of other modalities, including microfracture. Conventional wisdom holds that the results of other cartilage repair procedures are not negatively influenced by previous treatment with MST, which has been called a “non-bridge-burning” procedure. More recent studies, however, have demonstrated subchondral changes in up to one third of patients treated with microfracture, such as thickening of the subchondral bone, osseous overgrowth, and formation of subchondral cysts.^{12,13} These findings are similar to those seen in chronic defects, which have yielded lower success rates after any type of cartilage repair, including ACI⁸; this has prompted concerns that treatment with MST could negatively affect later cartilage repair procedures. We therefore reviewed the results of all patients treated at our institution with ACI by the senior author to determine whether defects previously treated with marrow stimulation techniques failed at rates higher than those that were not.

MATERIALS AND METHODS

Study Design and Subject Selection Process

This cohort study using prospectively collected data was conducted to assess potential differences in failure rates of ACI depending on previous treatment with MST procedures affecting the subchondral bone, such as drilling, abrasion chondroplasty, and microfracture. The indications for treatment of cartilage defects with ACI were 1 or more full-thickness chondral defects of the knee with consistent history, physical examination, imaging, and arthroscopy; no inflammatory joint disease, unresolved septic arthritis, deficient soft tissue coverage, or metabolic or crystal disorders; no or correctable ligamentous instability, malalignment, or meniscal deficiency; and not more than 50% loss of joint space on weightbearing radiographs.

Three hundred thirty-two patients treated by the senior author between March 1995 and December 2004 were eligible for inclusion, because they had completed more than 2 years of follow-up by the time of data analysis for this study. One additional, international patient treated

during this time period did not return for follow-up and was therefore not included in this study. Eleven patients with potential confounders such as revision ACI, previous bone grafting, or osteochondral allograft transplantation were excluded, leaving 321 patients (325 knees) for analysis. More than 200 additional ACI procedures have been performed by the senior author since December 2004 that were not eligible because of shorter follow-up. Of the 332 patients, 289 (87%) are still being followed by our center and are current with their follow-up. All 332 completed 2 years of follow-up, whereas 43 failed to continue with their regular follow-up appointments after their 2-year appointment: 29 did not return after the 36-month mark, 3 after 48 months, 5 after 60 months, 4 after 72 months, and 1 patient each after 84 and 96 months.

Patients were assigned to 1 of 2 groups based on whether they had previously undergone MST for the treatment of cartilage defects of the same knee that later underwent ACI. When patients reported having undergone previous cartilage repair procedures, we obtained surgical records to confirm the type of procedure. Only patients with a verified history of MST were assigned to the respective group; all others were placed in the control group. Institutional review board approval was obtained to create a prospective database at its onset in March 1995. All patients provided informed consent at the time they were entered into the database, usually at the time of their index operation.

Autologous Chondrocyte Implantation

The details of the ACI procedure have been described elsewhere.¹⁵ In summary, patients received ex vivo cultured autologous chondrocytes (Genzyme Bio Surgery, Cambridge, Massachusetts) injected underneath a periosteal patch that had been secured with resorbable sutures and fibrin glue (Tisseel, Baxter Biosurgery, Deerfield, Illinois) sealant. We routinely delayed ACI for 9 to 12 months after previous MST to allow the subchondral bone to reconstitute and the subchondral edema commonly seen after MST to resolve. Defect sizes were measured intraoperatively, and concomitant procedures were recorded. Patients with defects of the weightbearing femoral condyles in the setting of 2° or more of malalignment from the neutral mechanical axis were treated with a concurrent valgus- or varus-producing corrective osteotomy. Patients with patellofemoral defects had a concurrent anteromedialization tibial tubercle osteotomy, lateral release, and vastus medialis obliquus advancement if there was evidence of patellar subluxation and tilt as noted by physical examination, radiographs, and/or CT scan assessment.

Intralesional osteophytes were commonly seen after previous MST; initially these were left untreated to avoid bleeding and admixture of marrow elements with end-differentiated articular chondrocytes. However, when large intra-articular osteophytes presented themselves above the level of the adjacent articular cartilage, these were impacted with a bone tamp flush with the adjacent subchondral bone, followed by a standard ACI. In both cases, failures at these sites were seen. The senior author then moved on to removing the osteophytes with a rongeur

and noticed no bleeding or minimal bleeding that was easily controlled with epinephrine or fibrin glue. The technique for intralesional osteophytes finally evolved into its current form of microburring to remove the stiffened subchondral bone.

Postoperative Rehabilitation

Principles of physical therapy were restoration of motion and muscle control and avoidance of ACI graft overload. Rehabilitation was progressed in stages: stage I (weeks 1-6 after surgery) included the use of continuous passive motion (CPM) for 6 to 8 hours per day, touchdown weight-bearing, range of motion (ROM), and isometric muscle exercises; stage II (7-12 weeks) included active ROM exercises, functional muscle use, and progression from partial to full weightbearing at 12 weeks after index surgery. Patients were restricted from inline impact activities (running) for 12 to 18 months and cutting sports for at least 18 months. The ACI rehabilitation protocol considered each patient's individual surgical reconstruction, graft maturation, and previous activity level, which were reflected in individualized variations in the rehabilitation protocol.

Outcome Criteria and Outcome Assessment

For statistical analysis, the cohort was subclassified on the basis of size, type, and location of the defect into Simple, Complex, and Salvage categories. Simple defects were defined as single lesions smaller than 4 cm² located on the femoral condyles; the Complex category included multifocal lesions as well as single lesions that were either larger than 4 cm² or situated on the trochlea, tibia, or patella; the Salvage category included all bipolar (kissing) lesions as well as all defects located in knees with early arthritic changes including osteophyte formation or Ahlback stage 0 to I changes (<50% joint space narrowing). Further subanalyses were performed based on whether the original defect was caused by osteochondritis dissecans (OCD), the type of MST procedure (microfracture, abrasion arthroplasty, or drilling), and whether the patient received workers' compensation payments.

Approximately half of patients who had failed ACI after having undergone prior marrow stimulation were found to have additional, not pretreated defects at the time of ACI. In further subanalysis, the failure rate of these lesions was assessed separately from the pretreated defects, acting as an internal control located in the same knee as the latter.

Failure was defined as persistent or recurrent symptoms and MRI evidence of graft delamination or surgical removal of more than 25% of the graft area; repeat ACI; additional surgical treatment violating the subchondral bone, such as microfracture; or prosthetic replacement.

Statistical Analysis

Data were collected independent of the surgeon by trained research staff using standardized case report forms or questionnaires, and statistical analysis was

conducted by an independent statistician. Statistical analyses were performed using the SAS 8.2 (SAS Institute Inc, Raleigh, North Carolina) software package. Student *t* test was used to assess potential differences between the 2 groups (MST or control) in regard to demographic characteristics, such as average defect size, number, and subject age. The chi-square test was used to detect differences between the 2 groups (MST or control) as well as between the 3 different MST procedures. The level of statistical significance was set at $P < .05$.

RESULTS

The 2 patient groups (control and MST) were not significantly different in regard to patient age at implantation ($P = .7$), gender ($P = .6$), follow-up time ($P = .4$), defect size ($P = .2$), and number of defects per joint ($P = .9$) (Table 1). Average follow-up was 55 months: 54 months (range, 24-132) in the control group and 56 months (range, 24-144) in the MST group. In the control group, there were 56 (26%) varus/valgus-producing osteotomies, 55 (26%) tibial tubercle osteotomies (TTOs), and 6 (3%) ligament reconstructions. This compares with 23 (21%) varus/valgus osteotomies, 30 (27%) TTOs, and 9 (8%) ligament reconstructions in the MST group. Average transplant area per knee was 8.2 cm² overall: 7.9 cm² in the control group and 8.6 cm² in the MST group ($P = .3$). For non-workers' compensation patients (83% of patients), the average transplant area per knee was 8.1 cm² in the control group and 8.5 cm² in the MST group ($P = .6$). For workers' compensation patients (17% of overall patients), the areas were 6.4 cm² and 8.2 cm², respectively ($P = .1$).

Joints in the control group failed at a rate of 8% (17/214), compared with a failure rate of 26% (29/111) in joints that had been pretreated with MST (chi-square test, $P < .001$).

With the exception of defects in the Simple category, subanalysis of the data demonstrated a fairly constant ratio of approximately 3:1 in failure rate between the MST and control groups for Complex- and Salvage-type defects, osteochondritis dissecans lesions, and patients receiving workers' compensation (Table 2). There were no significant differences in failure rates between the 3 types of MST (chi-square, $P = .5$), even though there was a trend toward a lower failure ratio in microfractured defects, which failed at only twice, rather than 3 times the rate of defects in the control group (Table 2).

Within the group of 29 knees that had failed ACI after prior treatment with MST, 14 were implanted for isolated defects and 15 for multiple defects. Among these 15 knees there were a total of 35 implanted defects, some of which had been marrow stimulated and some of which had not: specifically, 17 had previously been marrow stimulated (13 knees with 1 defect each and 2 knees with 2 defects each) and 18 lesions had not been treated before ACI. Because all knees had at least 1 marrow-stimulated defect and 1 untreated defect, we used the untreated defect as an internal control. Sixteen of the 17 marrow-stimulated defects failed compared with 2 of the 18 previously untreated lesions.

TABLE 1
Patient Demographics for the Control Group (No MST) and Previously Marrow-Stimulated Group (Prior MST)^a

	No MST	Prior MST	P
Knees (patients), n	214 (211)	111 (110)	
Average age, y (SD, range)	35.0 (9.2, 13-60)	35.4 (10.1, 14-55)	.7
Gender, men/women, n	124/87	61/49	.6
Average follow-up time, mo (SD, range)	54 (27, 24-132)	56 (30, 24-144)	.4
Average no. of defects per knee (SD, range)	1.7 (0.9, 1-5)	1.7 (0.8, 1-4)	.9
Average defect size, cm ² (SD, range)	4.6 (2.7, 0.5-21)	5.2 (3.1, 0.7-16.8)	.2
Average transplant area per knee, cm ² (SD, range)	7.9 (5.0, 1.0-28.3)	8.6 (5.9, 1.5-30.5)	.3
Workers' compensation patients, n (%)	28 (13)	24 (22)	.1
Patients lost to follow-up after 2 years by defect category, n (%)			
Simple	3 (1)	2 (2)	>.5
Complex	16 (8)	12 (11)	>.5
Salvage	6 (3)	4 (4)	>.5

^aMST, marrow stimulation technique.

TABLE 2
Failure Rates for Control (No MST) and Marrow-Stimulated Groups (Prior MST)^a

	No MST		Prior MST		P
	No.	No. of failures (%)	No.	No. of failures (%)	
Overall	214	17 (8)	111	29 (26)	<.001
Simple defects	18	2 (11)	9	1 (11)	NA
Complex defects	97	9 (9)	56	17 (30)	<.01
Salvage defects	99	6 (6)	46	11 (24)	<.01
Subanalyses					
OCD lesions	23	2 (9)	20	6 (30)	NA
WC patients	28	4 (14)	24	9 (38)	NA
Previous MFx			25	5 (20)	>.5
Previous AA			33	9 (27)	>.5
Previous drill			53	15 (28)	>.5

^aMST, marrow stimulation technique; NA, insufficient power to calculate; OCD, osteochondritis dissecans; WC, workers' compensation; MFx, microfracture; AA, abrasion arthroplasty; Drill, drilling.

DISCUSSION

Marrow-stimulation techniques, in particular microfracture, are an appropriate first line of treatment for full-thickness defects of the articular cartilage and have demonstrated good to excellent results in 60% to 80% of patients.^{13,20} These techniques have the low morbidity of an all-arthroscopic procedure with a comparatively quick recovery and low complication rate. Several studies have provided data enabling surgeons to better define patients and defects most appropriately treated with microfracture. The authors of a recent prospective randomized trial comparing microfracture with ACI reported that larger lesions, in particular those bigger than 4 cm², performed worse with microfracture, whereas no such size correlation was seen in the ACI group, and concluded that bigger

lesions might be better treated with ACI.¹¹ Another group reported on the outcomes of microfracture based on the location of the defect; only lesions of the weightbearing femoral condyles demonstrated lasting improvements, whereas tibial and patellofemoral defects deteriorated after 18 months.¹²

As our understanding of the underlying pathophysiological changes has increased, osteoarthritis has come to be considered a disease of the osteochondral unit and entire joint rather than a disorder limited to the articular cartilage.² Current data suggest that osteoarthritis could be initiated through activation of the secondary center of ossification attributable to microfractures and microcracks.⁶ This mechanism results in thickening of the subchondral bone attributable to advancement of the tidemark with corresponding thinning of the overlying cartilage, which is then more susceptible to damage and further degeneration.¹ A similar mechanism is potentially at work after marrow stimulation: MRI follow-up studies have demonstrated a 27% to 33% incidence of osseous overgrowth and intraleisional osteophytes in microfractured defects^{12,13} (Figures 1 and 2). Although the significance of these findings has not been conclusively proven, changes in the subchondral bone are regarded as a potential explanation for the deterioration and failure of microfracture: the regenerated tissue overlies a thickened, prominent, and stiff subchondral plate, a potential factor predisposing it to degeneration.^{7,18,19} As mentioned previously, similar changes are found in osteoarthritis and chronic chondral defects, which have demonstrated worse outcomes with cartilage repair procedures.⁸ It can be theorized that the altered subchondral plate is responsible for the worse outcomes both in chronic defects and in lesions treated with marrow-stimulation techniques. Interestingly, osteochondritis dissecans lesions, by definition associated with altered subchondral bone, have shown success rates after ACI similar to those for the treatment of conventional focal chondral defects.^{15,16} In our experience, ACI failure after marrow stimulation can be predictably classified in 1 of 3 ways: delamination, central

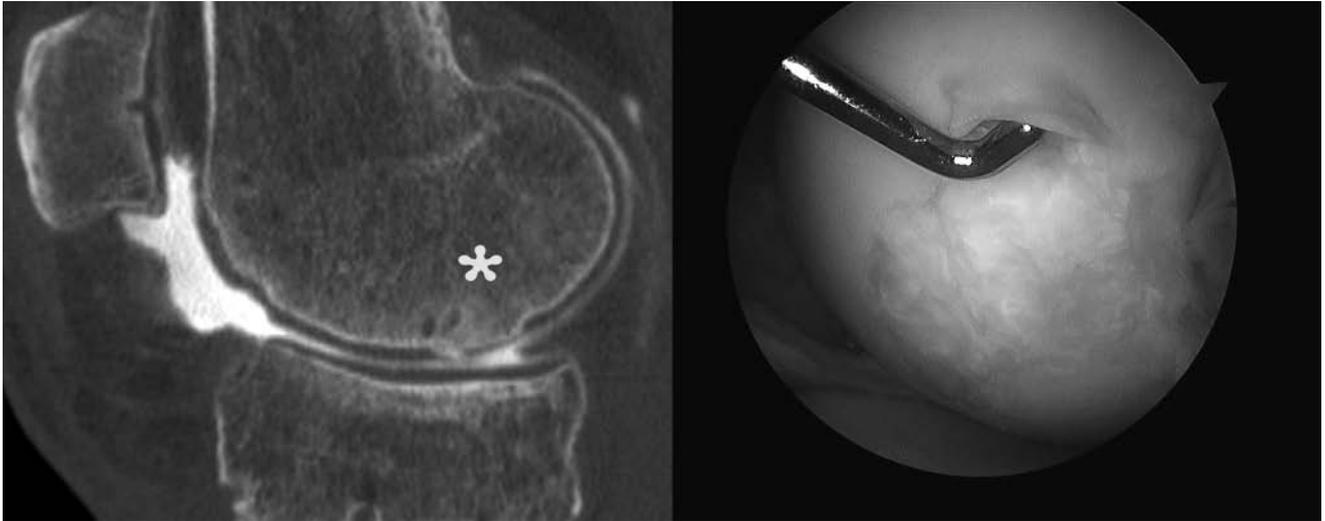


Figure 1. Left, preoperative CT arthrogram depicting a previously microfractured chondral defect on the medial femoral condyle. *An intralesional osteophyte is seen. Right, arthroscopic appearance of the same defect at the time of cartilage biopsy.

degeneration over an intralesional osteophyte, or formation of subchondral cysts (Figure 3).

Although previous studies have demonstrated detrimental effects of defect chronicity¹⁴ and patient age^{11,14} on the outcome of ACI, we are unaware of any published data on the consequences of prior procedures. Our review of 321 patients undergoing treatment with ACI demonstrated a failure rate in defects previously treated with marrow-stimulation 3 times that of untreated controls (26% vs 8%). This ratio remained remarkably stable during subanalyses according to defect severity (Complex vs Salvage), defect origin (OCD vs chondral defect), and workers' compensation claim status. Comparison of failure rates between the 3 different marrow-stimulation techniques showed a nonstatistical trend toward lower failure rates with microfracture (20%) than either abrasion arthroplasty (27%) or drilling (28%)—all 3, nonetheless, were significantly higher than the failure rate seen in defects that had not previously been treated with MST procedures (8%). We hope that microfracture, which was designed to be less traumatizing to the subchondral bone, will have less of a negative effect on subsequent ACI. However, the low numbers in each subgroup make it impossible, at this time, to conclusively determine whether microfracture indeed has fewer negative effects than the other MST.

There are valid concerns that patients with failed MST are somehow different, either because of currently unknown biological factors that might limit the success rate of cell-based reparative therapies or in regard to other issues such as compliance with rehabilitation. If this were the case, repeat treatment with another cell-based therapy (eg, ACI) would be expected to fail as well, the cause of failure not being a defect-specific factor such as pretreatment with MST but rather a patient-specific factor predisposing them to failure. To address these concerns, we analyzed a subgroup of 15 joints who had failed ACI. What distinguished

these joints was the presence of an internal control: each had multiple defects with at least 1 that had been pretreated with marrow stimulation and 1 that had not. We obtained the original operative notes for these patients to determine which of the multiple defects had previously been marrow stimulated. Among the 15 knees, a total of 35 defects were implanted with ACI: 17 defects that had been marrow stimulated and an additional 18 that had not been treated prior to ACI. We used these untreated lesions as internal controls to evaluate the influence of potential, unknown patient-specific factors: if patient-specific factors (eg, compliance, biology) were the cause for increased failure of ACI after MST, one would expect the additional defects to fail at a significantly increased rate as well. If, however, defect-specific factors (eg, prior MST) were responsible, then the failure rates should be different. Only 2 of the 18 previously untreated defects failed, compared with 16 of the 17 defects that had originally been marrow stimulated. One could argue that the additional defects were likely newer and therefore responded better to treatment, because defect chronicity has been identified as a negative predictor. The difference in failure rates between pretreated and not pretreated defects in the same joints, however, is larger than one would expect attributable to chronicity alone. It is therefore likely that the increased failure rate is indeed attributable to defect-specific factors rather than issues affecting the entire joint and/or patient.

Our study is not without limitations: it is not randomized, because this would not be feasible for this question; it is, however, a prognostic cohort study based on prospectively collected data in a large number of patients. The majority of marrow-stimulation procedures were either drilling or abrasion chondroplasty, techniques that are slowly being replaced by the more recently developed microfracture. It is possible that these older techniques induce more trauma to the subchondral bone than microfracture, thus leading

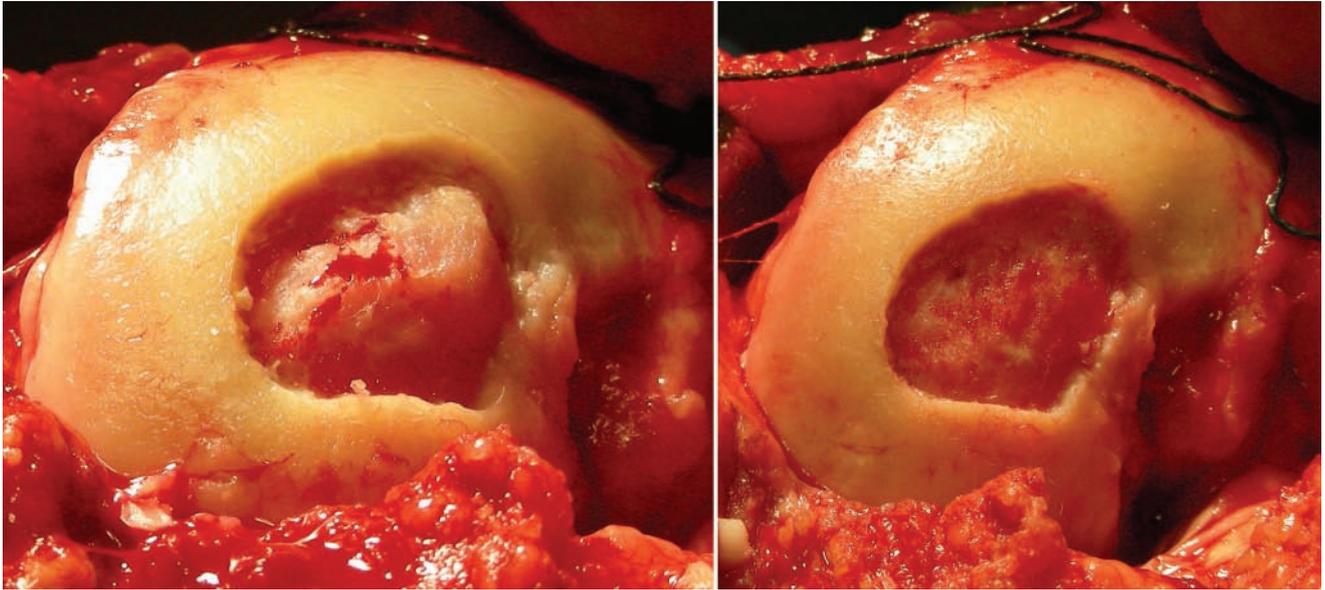


Figure 2. Intraoperative photographs of the same patient. Left, intralesional osteophyte after debridement of the overlying fibrocartilaginous tissue. Right, the osteophyte has been removed with the microbur.

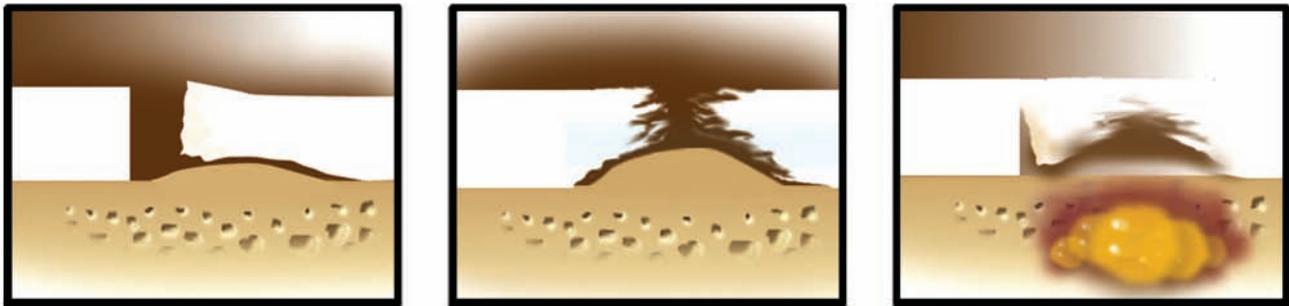


Figure 3. Modes of failure after marrow stimulation. Left, delamination; center, intralesional osteophyte; right, subchondral cyst.

to worse results. The strengths of this study lie in the long and complete prospective follow-up of a large patient group treated by a single experienced surgeon with a consistent approach to indication, technique, and rehabilitation.

Additional research is needed to identify the exact cause of failure, for example, the increased mechanical stiffness of the subchondral plate. In response to a subjective impression that defects pretreated with MST procedures failed more frequently, the senior author changed his technique for preparation of the subchondral bone. Originally, intralesional osteophytes were tamped down level with the surrounding subchondral plate. Currently, any osseous overgrowth is carefully debrided with a microbur, thus thinning the thickened bone plate. Although we do not yet have adequate numbers and follow-up to provide a statistically and clinically meaningful analysis of defects treated in this fashion, there appears to be a trend toward a lower failure rate than that seen in previously marrow-stimulated defects in this study.

CONCLUSION

Cartilage repair is an evolving field and as such is associated with substantial controversy, especially in regard to indications for microfracture and ACI. Our data demonstrated a 3-fold increase in failure rate of ACI after previous marrow stimulation. It is not our intention to take away from the good outcomes of microfracture but rather to investigate the current understanding that it is a non-bridge-burning procedure that does not negatively affect subsequent procedures. Smaller lesions of the weightbearing femoral condyles are appropriately treated with MST, ideally microfracture, which can be expected to result in good outcomes in a majority of patients. Larger lesions, however, seem less effectively treated with marrow stimulation, and our results suggest that its use will compromise subsequent revision cartilage repair with ACI. As our data on previously microfractured patients increase over time, we will be able to provide further subanalysis on whether

the failure rate in this group is significantly different from the other marrow-stimulation techniques and whether microbur treatment of intralesional osteophytes decreases the risk of failure. Additional research is necessary to further investigate the function of the osteochondral unit and the effects of preparing the defect bed to enhance integration of the cartilaginous repair tissue with the subchondral bone to form a functional unit. We should soon be able to answer the question whether in the presence of stiffened subchondral bone it will be most appropriate to perform microburring and ACI, removal of the altered subchondral bone with concurrent sandwich ACI and bone grafting to create a new osteochondral functional unit, or fresh osteochondral allograft transplantation.

We hope that these data will help orthopaedic surgeons select the appropriate first-line treatment for these difficult lesions with a view toward long-term options in case patients fail their initial intervention.

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