Chapter 12
Autologous Chondrocyte Implantation After Previous Treatment with Marrow Stimulation Techniques

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Abstract Full-thickness defects of articular cartilage have limited to no spontaneous repair potential and can compromise patients through symptoms such as activity-related pain and swelling. Various techniques have been developed toaddress these defects, including palliative procedures such as debridement and reparative procedures such as marrow stimulation techniques (MST). Marrow stimulation techniques result in changes to the subchondral bone, including osseous overgrowth and intralesional osteophytes. Defects that had prior treatment affecting the subchondral bone have a three to seven times higher failure rate after ACI procedure when compared with non-treated defects.

In this chapter we are going to discuss the role of previous bone marrow stimulation on subsequent cartilage repair and discuss possible surgical techniques to address the altered subchondral bone in order to restore the osteochondral functional unit.

Keywords Cartilage • Marrow stimulation • Autologous chondrocyte implantation

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Key Points

- Bone marrow stimulating procedures as drilling or microfracture may affect subchondral bone cause intralesional osteophytes formation.
- Intraleasional osteophytes and alterations in the subchondral bone unit increases autologous chondrocyte implantation failure rate.
- Intralesional osteophytes should be addressed during ACI surgery. High speed burr is effective to remove subchondral bone thickening and intralesional osteophytes.
- Sandwich ACI technique may be performed in the presence of bone cysts or after subchondral bone removal due to sclerotic aspect.
- Better understanding of the osteochondral unit, the subchondral bone itself, and the interface and interaction between cartilageandsubchondral-bone may help us improve surgical procedures after failed marrow stimulation procedures.

12.1 Introduction

Full thickness defects of articular cartilage have limited to no spontaneous repair potential [1] and can compromise patients through symptoms such as activity-related pain and swelling. Cartilage repair should restore joint function, ideally with a near-normal and durable tissue regenerate. Marrow stimulation techniques such as drilling, abrasion arthroplasty, or microfracture are frequently considered first-line treatment options for symptomatic cartilage defects [2, 3]. These techniques attempt to affect filling of a chondral defect with reparative tissue resulting from stimulation of the subchondral bone at the bottom of the defect [4]. Blood and mesenchymal cells from the underlying marrow cavity form a clot in the defect that gradually differentiates into a fibrocartilaginous repair tissue [5]. These techniques have the low morbidity of an all-arthroscopic procedure, with a comparatively quick recovery and low complication rate. Better results are obtained in younger patients, with lesions size smaller than 2–4 cm^2, and without previous surgeries [6]. Durability of the repair tissue, and hence the clinical outcome, is lower in defects that are larger than 2–4 cm^2 and/or located in areas other than the femoral condyles [7, 8]. Autologous chondrocyte implantation (ACI) may be performed as a second-line treatment after failed bone marrow stimulation, as well as first-line treatment in larger lesions [9]. Over the long-term, primary ACI is believed to demonstrate better outcomes, as microfracture-treated patients frequently seem to have recurrence of symptoms 2–5 years after surgery [10]. The ratio of patients maintaining sports activities after 5 years is higher in ACI treated patients compared to microfracture [11, 12].

Whenever a marrow stimulation procedure is chosen as the primary treatment, it is important to evaluate whether the results of a potentially subsequent procedure are not negatively influenced; essentially whether it can truly be considered a "non-bridge-burning" procedure. Recent studies have demonstrated subchondral

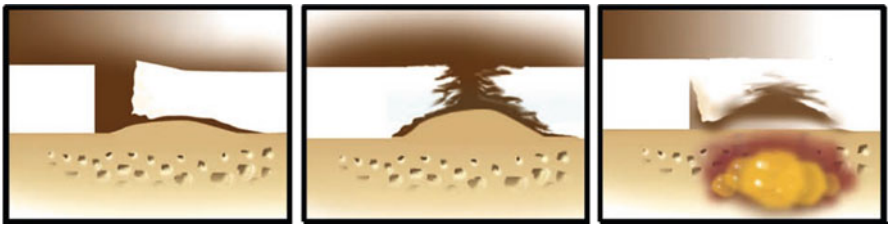

Fig. 12.1 Modes of failure after marrow stimulation. *Left* delamination, *center* intralesional osteophyte, *right* subchondral cyst

changes in up to half of patients treated with microfracture, such as thickening of the subchondral bone, osseous overgrowth and formation of subchondral cysts [8, 13, 14]. Therefore, the interaction of subchondral bone changes with ACI warrant further investigation [15]. This prompted us to review 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 defects that were treated previously with debridement alone.

12.2 Failure Rates of ACI Depending on Previous Treatment with MST Procedures

This cohort study utilizing 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.

Hypothesis: Cartilage defects pre-treated with marrow stimulation technique demonstrate an increased failure rate (Fig. 12.1).

Methods: This study reviewed prospectively collected data for 332 patients treated by the senior author between March 1995 and December 2004. Indications for treatment of cartilage defects with ACI were full-thickness chondral defect(s) of the knee with consistent history, physical examination, imaging and arthroscopy; no inflammatory joint disease, no unresolved septic arthritis, no deficient soft tissue coverage, no metabolic or crystal disorders; no or correctable ligamentous instability, malalignment or meniscal deficiency; not more than 50 % loss of joint space on weight-bearing radiographs. All patients had completed more than 2 years of follow-up by the time of data analysis for 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.

Patients were assigned to one of two groups based on whether they had previously undergone MST for the treatment of cartilage defects or not.

Patients received *ex-vivo* cultured autologous chondrocytes (Genzyme Bio Surgery, Cambridge, MA, USA) injected underneath a periosteal patch, which had

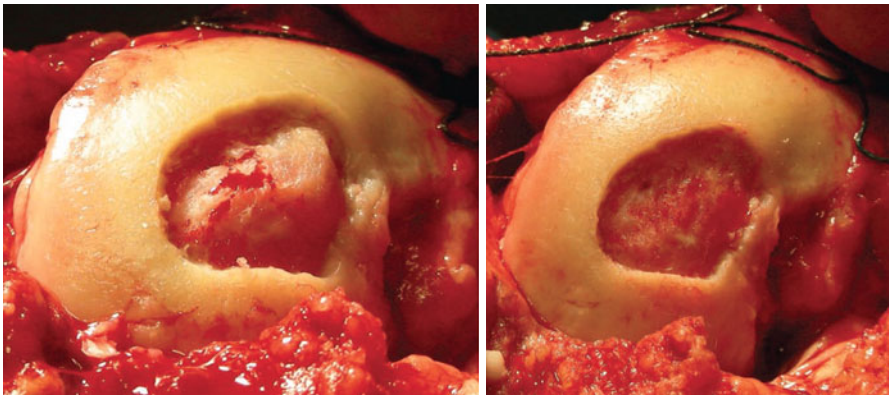

Fig. 12.2 Intralesional Osteophytebefore (*left*) and after debridement with a bur (*right*)

been secured with resorbable sutures and fibrin glue (Tissue Seal, Baxter Biosurgery, Deerfield, IL) sealant [16]. We routinely delayed ACI for 9–12 months after previous MST to allow the subchondral bone to reconstitute and the subchondral edema to resolve. Defect sizes were measured intra-operatively, 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 anteromedializationtibial tubercle osteotomy, lateral release and vastus medialis oblique muscle 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 so as to not create 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 or minimal bleeding 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 (Fig. 12.2).

Outcomes were classified as complete failure if more that 25 % of the grafted defect area had to be removed in later procedures due to persistent symptoms and MRI evidence of graft delamination, or surgical removal of more than 25 % of the graft area.

For statistical analysis, the cohort was sub-classified 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 cm^2 located on the femoral condyles; the Complex category included both multifocal lesions, as well as single lesions that were either larger than 4 cm^2 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 0–1

Table 12.1 Patient Demographics for Control Group (No MST) and Previously Marrow-Stimulated Group (Prior MST)

	No MST	Prior MST	P value
No. of knees/no. of patients	214/211	111/110	
Average age (years)	35.0 (9.2, 13–60)	35.4 (10.1, 14–55)	0.7
Gender (male/female)	124/87	61/49	0.6
Average follow-up time (months)	54 (27, 24–132)	56 (30, 24–144)	0.4
Average no. of defects per knee	1.7 (0.9, 1–5)	1.7 (0.8, 1–4)	0.9
Average effect size (cm^2)	4.6 (2.7, 0.5–21)	5.2 (3.1, 07–16.8)	0.2
Average transplant area per knee (cm^2)	7.9 (5.0, 1.0–28.3)	8.6 (5.9, 1.5–30.5)	0.3
Worker's compensation patients	28 (13 %)	24 (22 %)	0.1
Patient lost to follow-up after 2 years			
Simple	3 (1 %)	2 (2 %)	>0.5
Complex	16 (8 %)	12 (11 %)	
Salvage	6 (3 %)	4 (4 %)	

Data are given as (*SD* range) or number (%)

changes (<50 % joint space narrowing). Further sub-analyses were performed based on whether the original defect was caused by osteochondritisdissecans (OCD), by type of MST procedure (microfracture, abrasion arthroplasty or drilling) and whether the patient received worker's compensation payments.

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, N.C.) software package. The Student's *t*-test was used to assess potential differences between the two groups (MST or control) in regards to demographic characteristics, such as average defect size, number and subject age. The chi-square test was utilized to detect differences between the two groups (MST or control), as well as between the three different MST procedures. The level of statistical significance was set at $P < 0.05$.

Results: The patient groups (control and MST) were not significantly different in regard to patient age at implantation ($p = 0.7$), gender ($p = 0.6$), follow-up time ($p = 0.4$), defect size ($p = 0.2$) and number of defects per joint ($p = 0.9$) (Table 12.1). 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 (TTO), 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 cm^2 overall: 7.9 cm^2 in the control group and 8.6 cm^2 in the MST group ($p = 0.3$). For non-worker's compensation patients (83 % of patients), the average transplant area per knee was 8.1 cm^2 in the control group and 8.5 cm^2 in the MST group ($p = 0.6$). For worker's compensation (17 % of overall patients), the areas were 6.4 and 8.2 cm^2, respectively ($p = 0.1$).

Approximately half of patients that had failed ACI after having undergone prior marrow stimulation were found to have additional, not pre-treated defects at the time of ACI. In further sub-analysis, the failure rate of these lesions was assessed

Table 12.2 Failure rates for Control (No MST) and Marrow-Stimulated (MST) Groups

	No MST	Prior MST	P Value
Overall	214 (17, 8 %)	111 (29, 26 %)	<0.001
Simple defects	18 (2, 11 %)	9 (1, 11 %)	N/A
Complex defects	97 (9, 9 %)	56 (17, 30 %)	<0.01
Salvage defects	99 (6, 6 %)	46 (11, 24 %)	<0.01
Sub analyses			
Osteochondritisdissecans lesions	23 (2, 9 %)	20 (6, 30 %)	N/A
Worker's comp.	28 (4, 14 %)	24 (9, 38 %)	N/A
Previous microfracture		25 (5, 20 %)	>0.5
Previous abrasion arthroplasty		33 (9, 27 %)	
Previous drilling		53 (15, 28 %)	

separately from the pre-treated defects, acting as an internal control located in the same knee as the latter.

Overall, joints in the control group failed at a rate of 8 % (17 of 214), compared with a failure rate of 26 % (29 of 111) in joints that had been pre-treated with MST (chi-square test, $p<0.001$).

With the exception of defects in the "Simple" category, sub-analysis 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, osteochondritisdissecans lesions and patients receiving worker's compensation (Table 12.2). There were no significant differences in failure rates between the three types of MST (chi-square, $p=0.5$), even though there was a trend towards a lower failure ratio in microfractured defects, which failed at only twice, rather than three times the rate of defects in the control group (Table 12.2).

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 prior to ACI. Since all knees had at least one marrow-stimulated defect and one untreated defect, we utilized the untreated defect as an internal control. Sixteen of the 17 marrow-stimulated defects failed compared with 2 of the 18 previously untreated lesions.

Conclusion: Defects that had undergone to prior treatment affecting the subchondral bone failed at a rate three times that of nontreated defects (Fig. 12.3).

12.3 Subchondral Bone Unit

The articular cartilage varies throughout its depth from articular surface to subchondral bone. The cartilage can be divided into four zones: superficial, transitional, deep, and calcified cartilage zones. The deepest layer, the zone of calcified cartilage,

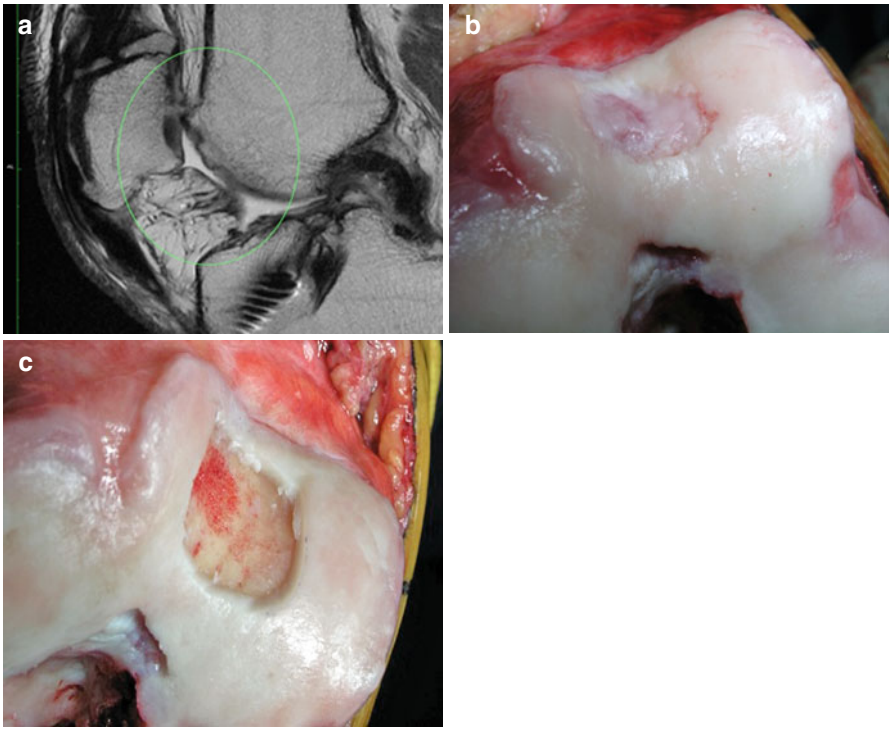

Fig. 12.3 (**a**) Preoperative magnetic resonance imaging (*upper left*), (**b**) intraoperative picture of intralesional osteophyte (*upper right*), (**c**) intraoperative picture of subchondral bone after intralesional osteophyte removal (*bottom*)

separates the hyaline cartilage form the subchondral bone, and it is characterized by small cells distributed in a cartilaginous matrix encrusted with apatitic salts. Histologically, the calcified cartilage zone may be distinguished from the deep zone by the tide-mark, which appears as a bluish line with hematoxylin/eosine staining. Lamellar bone is found throughout the mature skeletal in both trabecular and cortical bone, regardless of whether the bone was formed by intramembranous or endochondral ossification. Bone is a very dynamic and well-organized tissue, and trauma to cortical, trabecular or subchondral bone may activate healing process [17]. One theory suggests microfractures in subchondral bone or calcified cartilage are the potential trigger that provokes reactivation of the secondary center of ossification, with thickening of the subchondral plate and calcified cartilage, and causing the tidemark to advance with corresponding thinning of the overlying cartilage [18]. The activation of secondary centers of ossification in the subchondral plate is considered by some as the initiating event in osteoarthritis [19].

Recently, there has been an increasing interest and awareness of the importance of the subchondral bone and its role in the pathophysiology of osteoarthritis and chondral lesions. Furthermore, studies have demonstrated the necessity to carefully

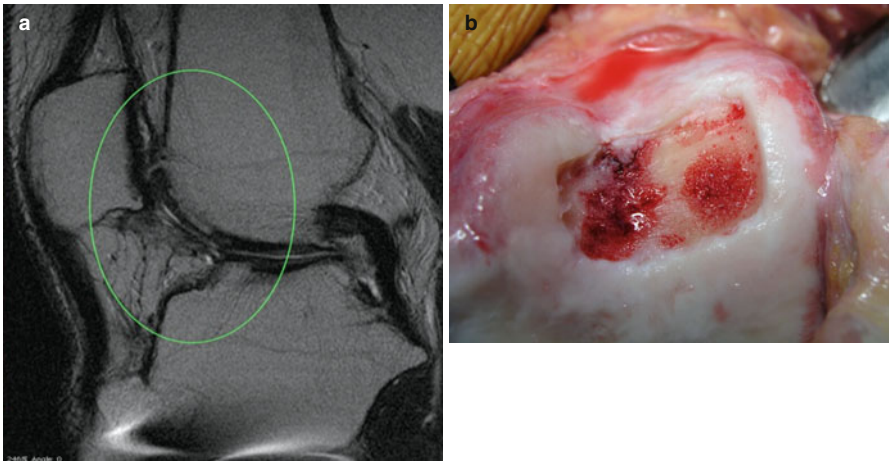

Fig. 12.4 (**a**) MRI scan of an intralesional osteophyte of the trochlea (*left*) and (**b**) intraoperative picture after debridement (*right*). Note the abnormal appearance of the subchondral bone and the holes from the previous microfractures

consider this structure in the treatment of articular surface damage, in the evaluation of the results over time, and in the determination of the patients' prognosis [20].

As our understanding of the underlying pathophysiological changes grow, we realize that cartilage lesions have to be evaluated as an osteochondral unit rather than a disorder limited to the articular cartilage. It is becoming apparent that without support from an intact subchondral bed, any treatment of the surface chondral lesion is likely to fail [20]. Subchondral bone may be affected primarily or secondarily in many diseases of the articular cartilage. Osteochondritis dissecans and spontaneous osteonecrosis of the knee both start in the subchondral bone and progressively affect the articular cartilage. Traumatic osteochondral fractures resulting from impacting may concomitantly affect both, articular cartilage and subchondral bone. Furthermore, several studies have demonstrated a 27–33 % incidence of thickening of the subchondral plate and intralesional osteophytes after microfractures [6, 8, 13]. Animal studies also have demonstrated a high incidence of subchondral bone cysts after microfracture procedures [21]. Finite element analyses suggest that subchondral stiffening and stress concentration causes an elevation in shear stresses in the deep cartilage layers [22, 23]. This thinner layer of viscoelastic cartilage overlies a thickened and stiffened subchondral plate and is therefore more susceptible to damage from shear forces.

In imaging evaluation of the subchondral bone, injury and OA-related changes in bone marrow are manifested by an increase in the signal intensity in bone marrow on fat-saturated T2-weighted images (bone marrow edema, BME). These hyperintense MR imaging abnormalities may be an expression of a number of noncharacteristic histological abnormalities that include bone marrow necrosis, bone marrow fibrosis and trabecular abnormalities [24, 25]. Bone marrow edema has been associated with severity and progression of OA. Evaluationof the subchondral bone after a previous microfracture procedure can be performed with MRI and

should include evaluation of the signal intensity, the appearance of the subchondral-lamina, the presence of intralesional osteophytes, granulation tissue, sclerosis, and cystic formations (Fig. 12.4) [26–28].

Better understanding of technical details to minimize the subchondral bone unit dysfunction after bone marrow stimulation should be pursued. To perform a microfracture technique, all unstable cartilage must be removed, stable perpendicular walls should be obtained at the edges of the lesion in order to contain the blood clot and allow proper edge healing. Currently, complete removal of all calcified cartilage is advised to obtain better filling with repair tissue [29]. Animal studies demonstrated that failure to completely remove the calcified cartilage layer leads to poor healing of the defect. However, Frisbie et al. observed significantly more new bone formation in defects in which the calcified cartilage had been removed completely at the time of surgery (26.5 % against 3.7 %). Subchondral bone cyst prevalence after microfracture was not affected by whether the calcified zone was removed or not [21].

12.4 Surgical Techniques for Autologous Chondrocyte Implantation After Bone Marrow Stimulation Procedures

Initially, a careful clinical history should be obtained, specifically focusing on previous knee surgery. The patient should be asked about any pain-free periods after the previous microfracture procedure to evaluate if they ever experienced pain relief or not. After microfracture, 60–80 % of patients have at least temporary symptomatic improvement, but some are worse even right after surgery.

Arthroscopic pictures of previous procedures help to evaluate the extent of the defect. Radiographic views should include weight-bearing anterior-posterior, 40° flexion weight-bearing posterior-anterior (Rosenberg view), lateral, and axial views. Long-leg weight-bearing views are important for alignment evaluation.

Any surgical intervention should include correction of all articular co-morbidities, such as malalignment, patellofemoralmaltracking, or meniscal and ligament insufficiency. As ACI is a two-stage procedure that requires an arthroscopic cartilage biopsy, we thoroughly evaluate all aspects of the knee during this stage.

During the implantation and after cartilage lesion debridement, the subchondral bone should be assessed for intralesional osteophytes and sclerosis of the subchondral plate. We found the use of a 5-mm bur under continuous irrigation helpful to gently take down any sclerotic cortical bone to the level of native subchondral plate, being mindful not to break into the subchondral bone itself. Bone bleeding may occur and should be addressed with fibrin glue, thrombin, or cauterization if there are distinct vessels. Standard collagen membrane or periosteal suturing is performed afterwards.

In the presence of bone cysts or when the subchondral bone is severely compromised, we elect to perform a sandwich technique. All sclerotic cortical bone and bone cysts are removed down to a healthy bed of subchondral bone, and the resulting defect is filled withautologous bone graft. When a closing wedge high

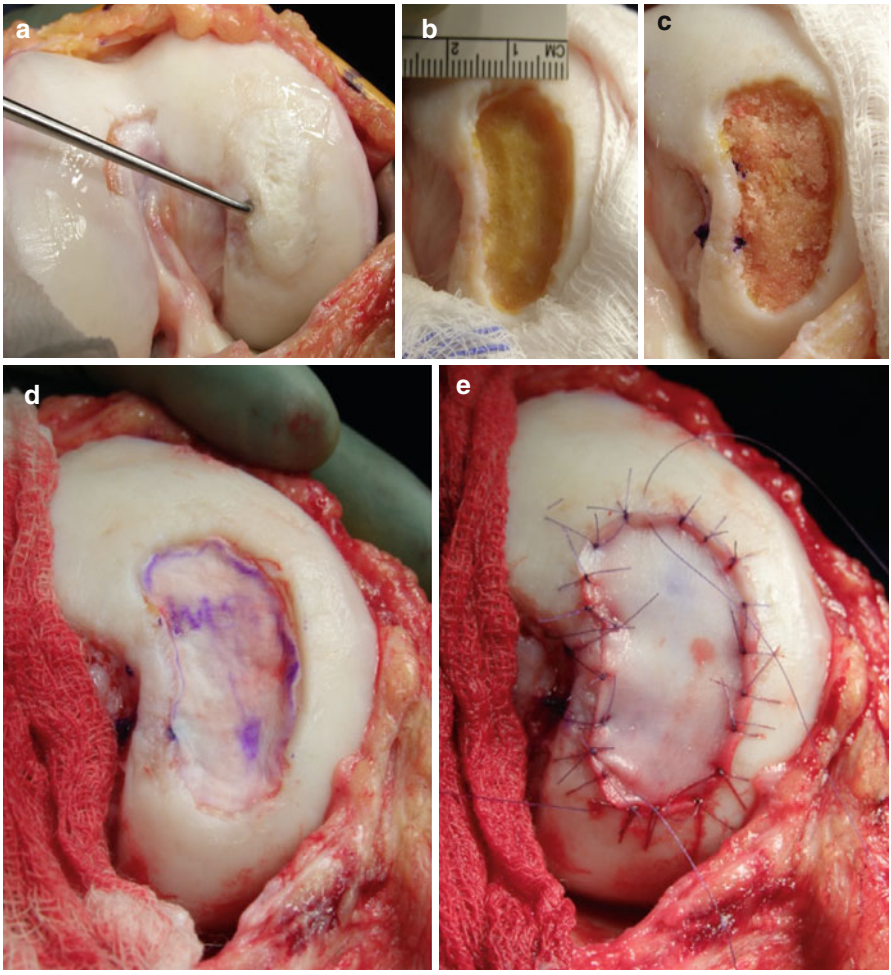

Fig. 12.5 Sandwich technique. Intralesional osteophyte (**a**), after complete debridment (**b**), bone grafting (**c**), membrane covering bone graft (**d**) and final appearance after ACI (**e**)

tibial osteotomy is performed concurrently, we utilize bone from the osteotomy site. Alternatively, bone can be obtained from the medial or lateral femoral or tibialcondyles. A small cortical window of approximately 1 by 1 cm is created with an osteotomeandremoved. Any cancellous bone attached to the cortex can be harvested for graft material. A curette can now be used to harvest as much graft as needed to fill the defect. Alternatively, it has been helpful to utilize a 10-mm harvesting tube from any of the available osteochondralautograft transfer systems by aiming in different directions; at least 3–4 cores of cancellous bone can be obtained. The harvest site can then be filled with allograft chips or putty and the cortical window is replaced. The graft material is now placed into the defect and compacted with a bone tamp. A layer of fibrin glue is placed on top of the bone graft, which is then covered by a size collagen or periosteal membrane. The graft is then compressed with digital

pressure and the tourniquet is released, waiting for the resulting blood clot to solidify and stabilize the graft. Conventional ACI technique is the used from here on. We found second generation ACI techniques simplify the procedure with marked advantages from a biological and surgical point of view (Fig. 12.5) [30, 31].

We are currently reviewing our data on patients with intralesional osteophytes where burring was performed during ACI surgery. We currently reviewed 85 patients that had an osteophyte formation that was removed with high-speed bur or curette prior to ACI. Magnetic resonance imaging at a minimum of 2 years was obtained in 46 patients. Intralesional osteophyte regrowth was observed in ten patients (22 %).

12.5 Conclusion

In cartilage repair, it can be theorized that the altered subchondral plate is responsible for the worse outcomes both in chronic defects, as well as in cartilage defects previously treated with marrow-stimulation techniques [20].

Better understanding of the osteochondral unit, the subchondral bone itself, and the interface and interaction between cartilage and subchondral bone may help us improve surgical procedures after failed marrow stimulation procedures.

Furthermore, future work is also needed to learn how to minimize disruption of the subchondral bone during microfracture, evaluate the subchondral bone before ACI, and treat the subchondral bone unit when necessary during ACI surgery.

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