1 The Evolution of Cartilage Restoration

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Case Example

A 42-year-old male had a remote history of medial femoral condyle osteochondritis fragments removed. He experienced progressive medial knee pain. In an outside facility, he underwent autologous chondrocyte implantation (ACI). He presented with persistent medial pain with minimal joint space narrowing, but a 4° varus alignment (Fig. 1.1). At staging arthroscopy, the bone base was noted to be sclerotic. He was treated with realignment into 2° of valgus with removal of basilar sclerotic bone at the time of revision ACI. This case illustrates the importance of optimizing the alignment and the importance of a healthy osteochondral unit. The role of recalibrating the anabolic/catabolic as well as proinflammatory/anti-inflammatory environment pre-salvage remains under evaluation.

Knee cartilage restoration can be traced to 1925, when Lexer reported the first osteoarticular transplant [1]. Since that time, contemporary methods slowly evolved from several different approaches. Dr. Allan Gross in Canada and Meyers [2] and Convery [3] in the United States popularized this historical concept of fresh osteochondral allograft transplantation [4, 5]. The classic Pridie drilling technique of the 1950s, later termed spongialization by Ficat, was modified with the advent of arthroscopy to abrasionoplasty by Johnson which morphed into the Steadman marrow stimulation technique [6, 7] that is currently returning to drilling based on the basic science work of Chen et al. [8–12]. Cell therapy cartilage restoration as we know it today began with the pioneering work of Dr. Lars Petersen over 30 years ago who was responsible for the first generation of cultured chondrocyte implantation [13]. Hangody, Morgan, and Bobic concurrently worked with autograft transfers in the 1990s, and slight modifications of the original techniques continue to be an important part of the cartilage restoration armamentarium [14, 15] for small lesions. While there are a number of new emerging technologies at various stages of preclinical and clinical development, most will have their lineage from one of these approaches. By learning from the history of cartilage repair solutions, it may be possible to better use current and future technology and avoid some of the past problems.

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Osteochondral Allografts

Drs. Gross, Convery, and Meyers began using fresh osteochondral allografts (OCA) in the 1970s for segmental loss of bone and cartilage

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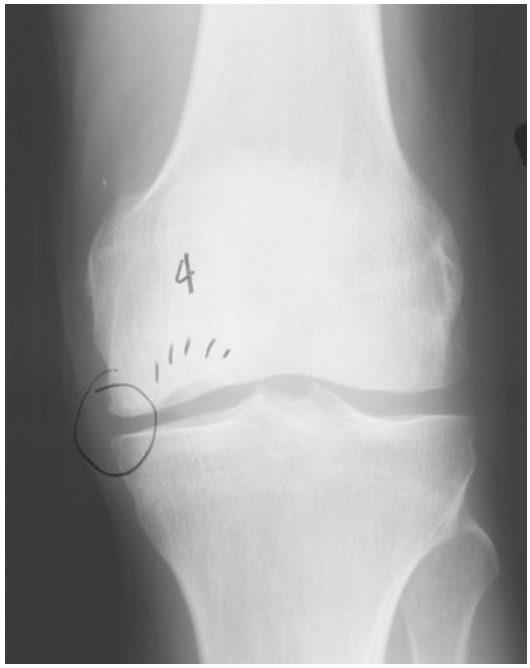

Fig. 1.1 Preoperative weight-bearing radiograph suggesting varus, which was measured at 4° varus on alignment radiograph. Joint space is near normal. Sclerosis is noted at the medial femoral condyle lesion site

after en bloc resection of knee tumors [2–5]. The success was supported by the separate works of Mankin and Friedlaender when reconstructing knees after tumor resection with approximately an 80% successful outcome with long-term follow-up [16, 17]. At the same time, frozen OCA were also being used, but over time, the matrix deteriorated due to the absence of viable chondrocytes [18]. This importance of viable cells remains a tenant of OCA as various forms of cryopreservation have largely been unsuccessful—most recently reiterated by Farr and Gomoll with their experience with preserved acellular OCA [18–21]. After problems with procurement-related infections surfaced in early 2000s, Kainer reviewed patients receiving allograft between 1998 and 2003 and reported 14 patients that had infections: 12 having *Clostridium septicum* and one death from *C. sordellii* [22]. In March 2002, the Food and Drug Administration (FDA) issued a new guidance document for tissue banks to improve safety from procurement to delivery [23]. As a result of this guidance, it was necessary to store the osteochondral allografts for adequate bacterial and viral testing. To maintain chondrocyte viability during this testing period, the allografts were stored in nutrient media. The thought at that time was that cooling the chondrocytes would decrease their metabolic needs and thus prolong viability. Several laboratories demonstrated sustained chondrocyte viability that rapidly decreased after a few weeks [18, 24]. Bugbee studied unused cool-stored OCA samples from actual patient surgery [25]. With a mean storage time of 20.3 days, the samples had significantly lower viability, cell density, and metabolic activity as compared to fresh allografts. However Riley, in a small short-term series, could not detect a difference in clinical outcomes between grafts stored 17 and 42 days [24].

Recently, Bugbee and Cook have challenged the storage technique temperatures and compared storage at 37 °C with the standard 4 °C and found improved chondrocyte viability in the warmer storage medium [26, 27]. Kim reported concepts on modulating apoptosis of chondrocytes (programmed cell death) through the use of apoptotic mediators [28]. At implant, several authors have shown in the laboratory that impaction energy can harm chondrocytes and thus, the call for finger-pressured placement [29, 30]. After the implant, the knee with hemarthrosis probably is not the optimal "medium" for the transplant, as shown by Williams, and this opens a new area for optimization of the entire transplant process [24]. That is, what is the role of postoperative environment optimization with platelet-rich plasma or bone marrow aspirate? Certainly, the goal remains to optimize chondrocyte viability at and after the time of transplantation.

The discussion above focused on the cartilage portion of the osteochondral transplant. However, the initial application of osteoarticular grafts was with large segmental joint transplantation with large portions of bone. This avascular bone requires a two-step process: first "fracture healing" at the host/allograft interface and then extensive time to be replaced or incorporated through creeping substitution. During the latter, bony collapse or insufficiency fractures were not uncommon in early cases [31]. Because chondral

and osteochondral nononcologic lesions of the knee typically are associated with minimal involvement of the subchondral bone, Bugbee, Convery, and Meyers recommended that the OCA graft have the least amount of bone possible to minimize these adverse consequences [15, 32]. Current constructs are 6–8 mm thick with 2–3 mm of that being articular cartilage [33, 34]. Although it is often stated that OCA are immunoprivileged, a percentage of patients become antibody positive after OCA transplantation [35–38]. It is generally believed that the antibodies form in response to the bony portion of the graft and more specifically, the vascular and marrow elements present within the subchondral bone. Comparing patient outcomes, those that were antibody positive have less favorable outcomes compared to those that were antibody negative [39, 40]. Therefore, thin "shell allografts" may potentially decrease the risk of immunogenicity as the total volume of bone is diminished and the thin bone shell can be better cleared of marrow elements by pulsatile lavage. Building up this, Bugbee has advocated meticulous attention at removing as much of the biologic load as possible, and many surgeons are exploring addition of platelet-rich plasma or optimized bone marrow aspirate to the bone portion to improve the healing process [41–43].

In recent years, cartilage with minimal bone allograft techniques have emerged and are under continued investigation. The two constructs currently available are proprietary and have only microscopic amounts of bone, which allows some degree of malleability during implantation (Cartiform®, Arthrex, Naples, FL and ProChondrix® AlloSource, Centennial, CO). An interesting expansion of the theme, but not independently confirmed technique, is partial thickness incision on the deep layers of cartilage only grafts (termed "hedgehog" after the appearance) [44].

Cartilage-only allograft involves the implantation of intact fragments of articular cartilage. Historically, this was first reported by Albrecht in 1983 in the rabbit with promising results [45]. The technique utilizes minced juvenile allogenic fresh-stored cartilage, which has been shown in the laboratory to form hyaline-like cartilage [46]. Though currently available in the United States as a "minimally manipulated tissue" (and as such, is not regulated by the FDA under HCT/P 361), there is a slowly increasing literature. Farr and Bonner first published peer-reviewed case reports followed by case series [47, 48], but randomized controlled series are not available or planned [49, 50]. Undoubtedly, there will continue to be further modifications and refinement in the OCA field. Fortunately, a group of surgeons is pursuing the goal of data collection from multiple centers under the umbrella of MOCA, Metrics of Osteochondral Allograft, funded by the Joint Preservation Foundation (nonprofit organization in Centennial, Colorado).

Marrow Stimulation

Open aggressive debridement of damaged cartilage and removal of subchondral bone to expose the cancellous bone as a means to treat cartilage lesions was first described by Pridie and later by Ficat [6, 7]. The clot formation with marrow elements gradually organized and remodeled to create fibrocartilage fill. The results were anecdotally reported as case series without a control group. The outcomes were highly variable, and the positive effects from debridement alone were unknown, especially when patients presented with the acute or subacute onset of mechanical symptoms (i.e., unstable osteochondritis dissecans). Nevertheless, Ficat reported good-to-excellent outcomes in 79% of patients treated with spongialization [6].

Using the principles of Pridie and Ficat, arthroscopists debrided cartilage lesions to subchondral bone, creating bleeding at the base of the lesion. The technique evolved from full removal of the subchondral plate to a more superficial burring, and Johnson coined the term "abrasion arthroplasty" [51]. Johnson's technique allowed formation of what he termed a "superclot" while still maintaining most of the integrity of the subchondral plate. Unfortunately, arthroscopists in that era thought more was better and often breached the subchondral plate.

Whether the widespread adaptation led to poor results in the community is unknown. Nevertheless, abrasionoplasty was abandoned in the 1990s as the technique of clot formation was modified by Steadman who kept the subchondral plate thickness intact except for punctuate holes [52]. Note that a more recent study of abrasionoplasty demonstrated "good" results, so it is important to keep the concept in mind. This points out the importance of adhering closely to the technique [53].

With the Steadman microfracture, the defect is prepared to a subchondral bone base cleared of calcified cartilage, as an equine model showed superior repair tissue formation and adherence compared to retention of the calcified cartilage layer [54]. After the calcified cartilage layer is removed, a small microfracture awl is used to create 1–2 mm fracture holes spaced 3–5 mm apart. These holes are said to allow "marrow-derived cells" to populate the blood clot, noting Mazzoca demonstrated that a femoral aspirate yielded a similar magnitude of pluripotential cells as the iliac crest [55], while others reported a tenfold difference (condyle less) [56]. Pluripotential cells are attracted by cytokines released during this clot formation and lead to formation of hyaline-like cartilage if exposed to the appropriate postoperative mechanical environment. Steadman empirically suggested that 6–8 weeks of non-weight-bearing and continuous passive motion is the key for positive outcomes and this is supported by the preclinical work of Gill who showed very immature tissue at 6 weeks, but more mature tissue at 12 weeks [57]. Nevertheless, Marder showed in a case series that good outcomes were possible with unlimited postoperative weight-bearing in lesions under 2 cm^2, yet caution should be exercised when extrapolating these data as the size of the lesion, age of the patient, comorbidities, and long-term outcomes may change the author's conclusions [58].

Marrow stimulation has become the most widely used cartilage restoration procedure in the United States, partly in light of the ease of performing it arthroscopically and partly because of its low cost [59]. The lesion size that still allows for an optimal result needs refinement as Steadman reported good results with lesions greater than 4 cm^2, while Knutsen et al. found less optimal results with lesions over 4 cm^2 as did Mithoefer et al. [60–62]. Steadman reported the advantage of the microfracture technique was that it did not cause thermal necrosis and the act of fracturing would stimulate the "healing response" cascade. While microfracture does not cause thermal necrosis, neither does drilling as recently shown by Chen [63]. In that basic science report, it also shows that drilling allows clearer channels for cell ingression and that deeper drilling is associated with better bone repair. In addition, they showed that the microfracture compacted bone around the holes and essentially sealed them off from viable bone marrow. In contrast, they demonstrated drilling cleanly removed bone from the holes to provide access channels to marrow stroma [64].

Marrow Stimulation Augmentation

To encourage the pluripotential cells to differentiate into a chondrocyte-like phenotype with three-dimensional (3D) structure, European clinicians have applied an acellular scaffold, which provides a framework for cells to organize (autologous membrane induced chondrogenesis, or AMIC). The scaffolds are variable and range from a true physical membrane to a biphasic liquid hydrogel that congeals in situ (Gelrin-C, Regentis Biomaterials, Or Akiva, Israel) to micronized acellular allograft cartilage (BioCartilage®, Arthrex, Naples, FL, USA). With each of these techniques, it may be possible to further influence the pluripotential cells with growth factors, such as reported with bone morphogenetic protein 7 (BMP-7), also known as osteogenic protein-1 [65–67]. To date, the nuances of marrow stimulation continue to be refined as, for example, Steadman initially reported a trend of possible improvement with an injection of pluripotential cells after microfracture with similar improvements of the cartilage fill by Saw [68, 69].

Cultured Chondrocyte Implantation

Peterson's original description of autologous chondrocyte implantation (ACI) is now termed "first-generation cell therapy" [70]. This is a two-stage cartilage restoration technique. At arthroscopic evaluation of the cartilage lesion, a biopsy of healthy articular cartilage is harvested from a low load location. The cartilage is then enzymatically treated to release the chondrocytes, which are subsequently expanded in culture. Various laboratories culture the chondrocytes differently, but the original technique created more than 10–12 million cells from the biopsy of approximately 200,000 chondrocytes. A watertight periosteal patch was sutured over the defect, and the cells injected under the patch. Generation 1.5, also termed ACI collagen patch or ACI-C, used the same technique, but with a biologic xenograft patch (Chondro-Gide®, Gieshlitch Pharma AG, Wolhusen, Switzerland), which decreased the incidence of periosteal hypertrophy and the need for secondary surgery to debride the overgrowth as shown by Gomoll et al. [71]. A variation of this Generation 1 uses the same patch, but Steinwachs showed excellent cell adherence and possible better dispersion for larger lesions by seeding the cells onto the patch intraoperatively instead of injecting them and thus this may be referred to as ACI-seeded or ACI-S [72]. A recent consensus report by Steinwachs attempts to standardize this technique [73]. Generation 2 has been available in Europe for several years and became available in the United States in 2017. The chondrocytes are seeded onto the patch/scaffold and have a very short culture timing before delivery. This allows minimal if any sutures and in some centers, arthroscopic implantation [74].

All ACI is not the same. There may be a lack of uniformity of the cultured chondrocytes from patient to patient and laboratory to laboratory. To quantitate the cultured chondrocytes, laboratories are currently testing cells for their ability to regain the chondrocyte phenotype and their ability to produce hyaline matrix elements (VIP Assays®) [75–77]. Ultimately, the ability to manipulate chondrocytes (e.g., hydrostatic loading as per Histogenics or growth factors as per ProChon [now merged with Histogenics]) during the culturing process may optimize the production of tissue that is most like hyaline cartilage. Currently, "Generation 3" products that are more mature at the time of delivery are undergoing investigation in the United States (NeoCart®, Histogenics, Waltham MA, USA, and Novocart3D®, Aesculap AG, Tuttlingen, Germany) noting that Novocart has been available for years in the EU.

A one-stage procedure is appealing to surgeon, patients, and payers. Based on the historical work with minced cartilage in the rabbit by Albrecht, further preclinical studies with goat and horse models showed that minced autograft cartilage could produce new cartilage fill in focal defects [78, 79]. A pilot trial was completed, which demonstrated the safety and efficacy of implanting a construct composed of a scaffold coated with minced cartilage fragments obtained arthroscopically during the same surgical setting (Cartilage Autograft Implantation System or CAIS, DePuy/Mitek, Johnson and Johnson, Inc., Raynham, MA). These promising results, published in 2011, led the FDA to approve a statistically powered randomized controlled pivotal trial to evaluate the clinical efficacy of CAIS [80] that was cancelled during recruitment because of concerns about return on investment. Another one-stage procedure which utilizes allograft cell-based tissue is RevaFlex (ISTO, St. Louis, MO, USA; formerly DeNovo ET-Engineered Tissue), a product developed by ISTO and licensed by Zimmer Biomet (Zimmer Biomet, Warsaw, IN, USA). Juvenile donor chondrocytes create robust matrix leading to the creation of a 3D disk of articular cartilage without a scaffold. A pilot study demonstrated satisfactory safety and efficacy to the point that the FDA approved a pivotal study [81], yet the pivotal study was cancelled because of slow enrollment and concerns about return on investment.

Osteochondral Autografts

Osteochondral autograft techniques create a circular socket at the chondral defect (recipient site) with a drill or circular punch. The autograft is harvested using a circular tube osteotome. Medium-sized (7–11 mm) osteochondral autograft plugs were popularized by Morgan and Bobic, whereas Hangody popularized the use of smaller plugs (mosaicplasty) [14, 15]. Several donor sites have been described including the medial and lateral trochlea proximal to the sulcus terminalis and the intercondylar notch, noting that Cole et al. demonstrated in vitro that the medial intersection of the trochlea harvest site had less stress [14, 82–84]. There are subsets of patients who experience postoperative hematoma or pain at the harvest sites in the near-term, yet the long-term sequelae related to donor site harvest remain in question. To decrease this potential morbidity, low load areas are used for the donor site, and the resultant harvest voids are often back-filled with allograft or synthetic engineered plugs.

Technique is the key for optimal success. As with OC allograft, the use of minimal force during impaction can avoid chondrocyte death, and fitting the plug to the surrounding surface can minimize alterations in contact stress [29, 85]. Filling the recipient socket entirely can avoid cyst formation. The long-term effects of peripheral chondrocyte death, lack of marginal integration, and the fibrocartilage fill of voids between the plugs remain to be determined although many case reports demonstrate positive intermediate-term outcomes [86]. Several synthetic plugs (monophasic, biphasic, and triphasic such as MaioRegen®, Fin-ceramica, Faenza, RA, Italy) are in various stages of testing to assess their ability to become an alternative to the autograft plug. These may allow the same ease of use as autograft plugs, but would avoid harvest morbidity and would allow an on-the-shelf alternative. Caution is key for these new products, especially in light of the failure of the Tru-Fit Plugs® (Smith-Nephew, London, UK).

Optimizing the Patient Joint Status for the Cartilage Restoration Construct

Minas showed the importance of a patient's preoperative outlook on life in allowing for a positive postoperative outcome [87]. For the knee, it needs to be emphasized that articular cartilage is just one part of the knee "organ" and, in fact, the only part that is aneural. How this aneural chondrosis affects the knee in a negative manner must be thoroughly investigated for opportunities to effect reversal. Not only must the cartilage construct be optimized, but also the tissues and forces acting on the construct must be optimized. Thus, the ligaments and menisci must be normalized as well as the mechanical effects of alignment in all planes. In addition, cartilage function loss may alter bone loading leading to bone marrow lesions (microscopic stress fractures) highlighted on T2 fat-suppressed MRI. Likewise, the chondral degradation can lead to alterations in the knee (specifically, the synovium) creating a shift toward inflammation and catabolism. Can these perturbations be optimized preoperatively or simultaneously? All of these factors must be taken into account when planning surgery, which is currently based on the relatively short history of knee cartilage restoration.

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