Journal of Clinical Orthopaedics and Trauma 61 (2025) 102875

Contents lists available at ScienceDirect

Journal of Clinical Orthopaedics and Trauma

journal homepage: www.elsevier.com/locate/jcot

Articular cartilage reconstruction: Review of concepts, techniques, complications, risk factors, and Bail out/salvage strategies☆

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A B S T R A C T

Chondral lesions are difficult and challenging depending on their size, location, and chronicity. In cartilage reconstruction, our aim is to employ techniques to help save the joint, regenerate lost or diseased cartilage, and hopefully prevent or delay the progression of osteoarthritis and the need for arthroplasty. As patient and lesion characteristics differ from case to case, there is no single surgical strategy ideal to treat all chondral lesions. With the advancement of our knowledge and comprehensive research efforts, marrow-stimulating techniques like microfracture and microdrilling, as well as cartilage regeneration methods such as autologous chondrocyte implantation, autologous matrix-induced chondrogenesis, and the application of hyaluronic acid-based scaffolds with MSCs, have become fundamental approaches in confronting this growing challenge. Emphasizing the importance of patient selection is vital, given that compliance with rehabilitation and return-to-play protocols, along with adherence to established timelines, is essential. Furthermore, it is necessary to select patients who are free from biomechanical malalignment and do not present with concomitant meniscal or ligamentous issues that must be addressed prior to surgery. However, despite all our attempts to ensure the best outcomes for our patients, complications are sometimes unavoidable. Thus, being able to recognize possible complications, utilize strategies to prevent these complications, and knowing how to manage complications when encountered are important for any orthopaedic surgeon.

1. Introduction

Hyaline cartilage facilitates smooth and pain-free movement of the joint, functioning as a shock absorber that dissipates and distributes forces. However, high rate forces and excessive mechanical loading can lead to subchondral bone and cartilage injury. It is this articular cartilage damage that may cause pain, decreased range of motion, and affect joint function. All these factors pose significant challenges in clinician decision making. These lesions have been seen in as high as 66 % of arthroscopies[1] and have potential to advance to more extensive and higher grade forms of the disease, ultimately leading to the development of osteoarthritis. It is the avascular nature, low cellularity, and minimal chondrocyte migration and proliferation that makes articular cartilage particularly vulnerable to injury and progression due to its limited intrinsic healing ability. These factors make restoration of a functional articular surface particularly difficult.

There are various surgical techniques available for the repair and restoration of articular cartilage, but the outcomes may not always meet expectations. In current literature, there are few publications specifically discussing complications, strategies for their prevention, and salvage techniques when they arise. Our goal is to briefly review the osteochondral unit, various cartilage reconstruction techniques, common complications encountered, and risk factors to watch out for.

2. The osteochondral unit

The osteochondral unit consists of subchondral bone and the overlying articular cartilage.[2] Articular cartilage serves a dual purpose: it absorbs mechanical stress and facilitates the lubrication of the joint surface. This functionality is attributed to the distinctive architecture of articular cartilage, which is characterized by a limited population of chondrocytes and an extracellular matrix (ECM) rich in collagens and proteoglycans. Cartilage is avascular, aneural, and alymphatic, with only diffusion through the matrix as a source of nutrition. Chondrocytes represent merely 2 % of the overall volume of articular cartilage, with mature chondrocytes playing a crucial role in metabolic processes, including the synthesis and breakdown of proteoglycans and collagens. The metabolism of chondrocytes is modulated by both systemic and local factors. Inflammation and mechanical stress can disrupt the equilibrium between synthesis and degradation, leading to cartilage degeneration.[2]

Subchondral bone consists of two primary components: the subchondral spongiosa and the subchondral bone plate. The subchondral bone plate has numerous small openings that allow blood vessels

☆ The authors have received no financial support for the research conducted.

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https://doi.org/10.1016/j.jcot.2024.102875
Received 28 October 2024; Received in revised form 10 December 2024; Accepted 16 December 2024
Available online 17 December 2024
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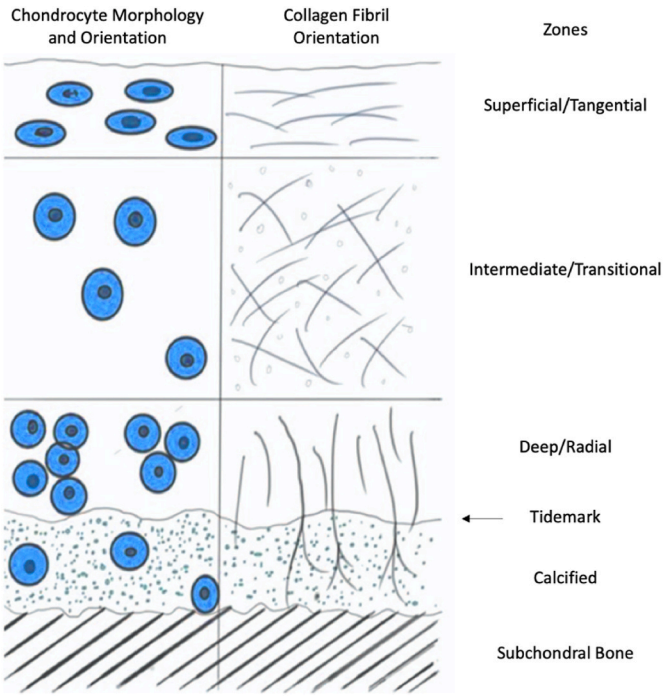


Fig. 1. Zones of articular cartilage showing chondrocyte and collagen density and orientation.



Fig. 2. Arthroscopic microfracture used to create holes into the subchondral plate penetrating only enough to observe fat droplets ensuring formation of marrow-rich fibrin clot.

originating from the subchondral spongiosa to traverse the calcified layer. These blood vessels are essential for supplying nutrients to the chondrocytes located within the calcified layer. A critical role of the subchondral bone is its ability to absorb mechanical loads in conjunction with the articular cartilage. Its structural composition is more adept at load absorption compared to the articular cartilage itself. The osteochondral unit, characterized by its multilayered architecture, facilitates the transmission and distribution of forces necessary for the mechanical adaptation of the joint.

Articular cartilage is composed of four zones: a superficial/tangential zone, an intermediate/transitional zone, a deep/radial zone, and a calcified zone (Fig. 1).

The superficial zone is characterized by the presence of "lamina splendens," a structure composed of collagen fibers that align parallel to the surface of the joint. Lubricin, a glycoprotein that is crucial for preserving lubrication, is located here. In the deeper section of the superficial zone, referred to as the tangential zone, the chondrocytes exhibit a flattened morphology, the matrix and collagen fibers are condensed and remain oriented parallel to the joint surface, and there is a reduced concentration of proteoglycans. In this layer, there is the highest concentration of collagen and the lowest concentration of proteoglycans. This is the only zone in which articular cartilage progenitor cells are located.

In the intermediate/transitional zone, matrix fibers exhibit a reticulated structure and adopt a predominantly vertical orientation. The chondrocytes in this region are characterized by their large, rounded morphology. The deep/radial zone represents the main part of the articular cartilage. This is the thickest layer with rounded, high-density chondrocytes and has an abundant proteoglycan layer.

The boundary separating the deep/radial zone from the calcified zone is referred to as the tidemark. This separation differentiates the true articular cartilage from the underlying deep cartilage, which is a remnant of cartilage that expanded and contributed to enchondral bone ossification during childhood growth. The articular cartilage is linked to the subchondral bone through the calcified cartilage, with this interface identified as the cement line. Notably, the cement line is characterized by the absence of crossing collagen fibrils, rendering it the most vulnerable area within the osteochondral unit. The presence of calcified cartilage facilitates ongoing remodeling, thereby playing a significant role in the natural repair processes at the cartilage base.

3. Articular cartilage reconstruction techniques

As adult articular cartilage has a very limited ability to repair itself, articular cartilage lesions that exceed 9 mm in diameter are typically biomechanically unstable and are prone to progress to joint degeneration. There are many factors to consider when determining which is the best technique to employ in the management of chondral lesions such as, chronicity of the lesion, history of other associated soft tissue injuries, desired activity level, level of osteoarthritis at the time of surgery, status of the meniscus, pain and mobility, as well as specific lesion characteristics (anatomic location, size, depth, subchondral bone involvement).[3] Cartilage debridement (shaving or chondroplasty) may provide temporary symptom relief with the goal of removing loose chondral fragments and creating a smooth articular surface with stable margins. However, the limited ability of peripheral chondrocytes to regenerate the defect leads to the filling of the lesion with fibrocartilage, which is high in type I collagen and possesses inferior mechanical properties.[3] In an attempt to restore organized hyaline cartilage, rather than mechanically inferior fibrocartilage, many different surgical techniques have been developed, including microfracture, autologous membrane induced chondrogenesis (AMIC), autologous chondrocyte implantation (ACI), hyaluronic acid-based scaffolds combined with MSCs (HA-B-MAC), osteochondral autograft transfer (OATS), mosaicplasty, and osteochondral allograft transplantation (OCA).

4. Microfracture and marrow stimulation techniques

Marrow stimulation has come a long way from the initially proposed technique pioneered by Pridie in 1959 using subchondral drilling.[4] Steadman et al. further developed the now-familiar “microfracture” technique in the 1990s.[5] Marrow-stimulating techniques such as microfracture and microdrilling, utilize the creation of holes into the underlying subchondral plate (Fig. 2), elucidating subchondral bleeding

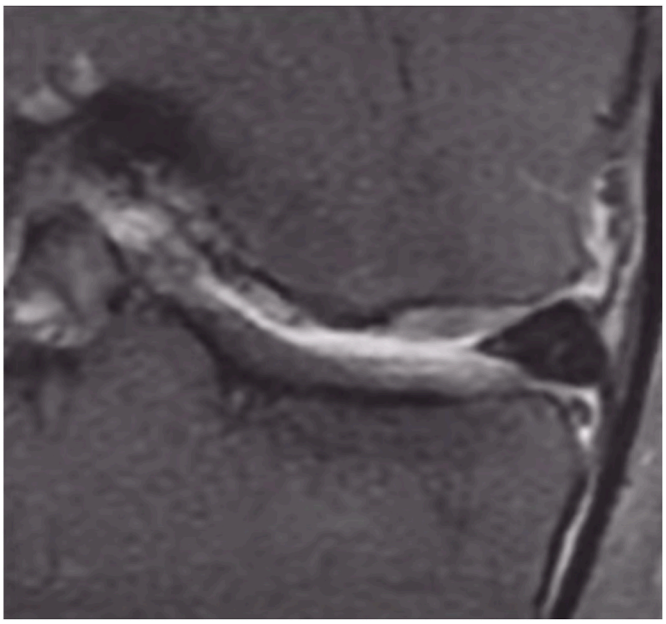


Fig. 3. MRI showing overgrowth of subchondral bone compared to native bone following microfracture.

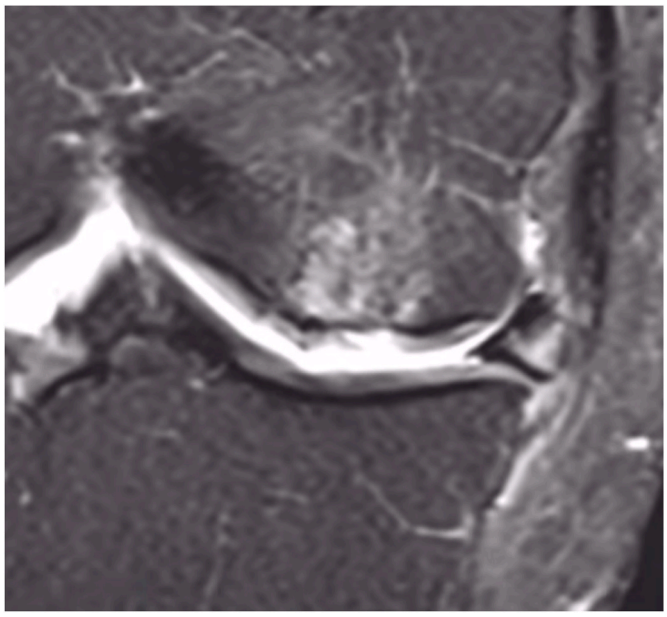


Fig. 4. MRI showing fibrocartilage deterioration and subchondral edema at 10 years post-microfracture.

and an influx of marrow products. This creates a marrow-rich fibrin clot, rich in mesenchymal stem cells (also known as medicinal signaling cells, "MSCs") and growth factors, in the area of the cartilage defect. This clot eventually remodels into fibrocartilage rather than normal hyaline articular cartilage. Mature fibrocartilage is mainly composed of type I collagen with scarce amounts of type II collagen. Regardless, microfracture has proven to be less complicated, quicker, and more cost-effective compared to other cartilage reconstruction techniques.[6,7]

Positive factors with typically better results and common indications for microfracture include smaller full-thickness chondral lesions less than 4 cm^2, BMI of less than 30 kg/m^2, and failure of non-operative treatment. Relative contraindications may include patients over the age of 40 years old, inability to create a sufficient and stable cartilage rim, defects larger than 4 cm^2, bipolar "kissing" lesions, and BMI of greater than 30 kg/m^2. While axial malalignment, partial thickness defects, meniscal deficiency, ligament instability, and uncooperative patients with rehabilitation protocols are absolute contraindications.[6–9]

Steadman recommended microfracture into the subchondral bone after arthroscopic debridement, in which he and other authors have demonstrated functional, clinical, and radiologic improvement in long-term follow-ups.[10,11] However, there are concerns about the durability of the fibrocartilage produced, the lack of hyaline repair tissue, and the variability of defect filling as a result of marrow-stimulating techniques.[6,12,13]

5. Microfracture and marrow stimulation technique complications

Perioperative complications in relation to microfracture procedures are relatively rare,[5,10–12] however, common complications encountered in relation to defect healing can include bone overgrowth, fibrocartilage deterioration, and poor defect filling.

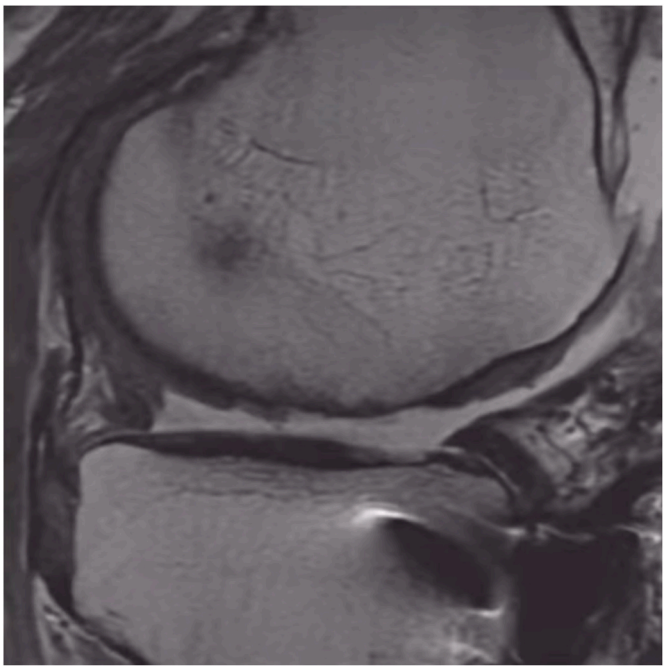
5.1. Bone overgrowth

Bone overgrowth (Fig. 3), also referred to as osseous overgrowth, intralesional osteophytes, or subchondral plate elevation, has been reported as high as 62 % in cohort studies.[14] The exact mechanism of the cause of bone overgrowth after microfracture is not fully understood; however, many theorize that it is a consequence from the release of pluripotent MSCs from the subchondral bone that has the capacity for osteo- and chondrogenesis. MSCs released from marrow, along with increased mechanical loading, promote a suitable environment for potentially unchecked osteogenesis.[13]

Mithoefer et al. showed that most bone overgrowth after microfracture occurred between 6 and 12 months postoperatively. It is also theorized that bone overgrowth may result in thinning of the overlying fibrocartilage layer, cause changes in cartilage biomechanics, and may lead to alteration in joint loading in weight-bearing areas. It was demonstrated that the clinical failure rate was higher in patients with bone overgrowth, and these patients with bone overgrowth were 10 times more likely to have a failed microfracture surgery. In fact, more than 90 % of patients who had failed microfracture surgery had bone overgrowth. There was an increased incidence of bone overgrowth in patients with higher BMI and in lesions located on the lateral femoral condyle, which may support theories relating the stimulatory effect of increased load on the incidence of bone overgrowth. There was no correlation between the diameter of holes made or penetration area with bone overgrowth; however, over-aggressive deep removal/debridement of the calcified cartilage layer resulting in punctate bleeding was shown to be a positive risk factor.[14]

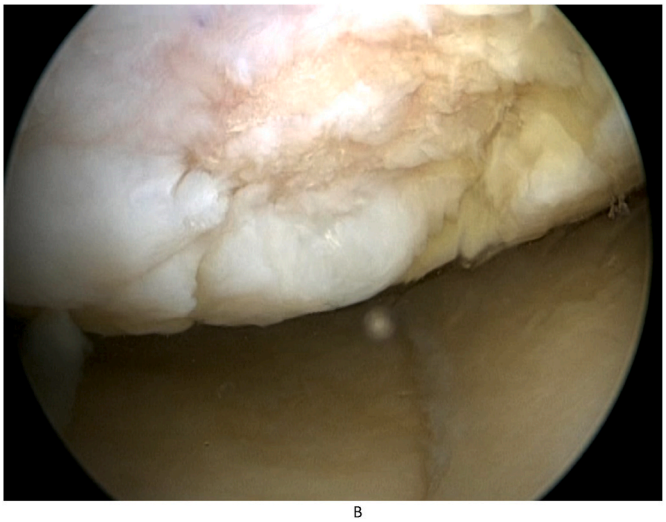
5.2. Fibrocartilage deterioration

Deterioration of the newly regenerated cartilage is also a very common and observed complication of microfracture (Fig. 4). This is mainly due to the fact that the composition of this new cartilage is mainly fibrocartilage comprised predominantly of type I collagen, which is less durable and resistant to forces across the joint compared to native hyaline cartilage primarily composed of type II collagen. Many studies have shown favorable short-term results, demonstrating 67 %–80 % having good to excellent results, as well as many athletes returning to preinjury level. However, these short-term improvements were not maintained, and there was a demonstrable decline in sport activity amongst athletes as high as 80 % at mid-to long-term follow-ups. This decline was most pronounced in those with multiple or larger lesions.[6,10–12] This deterioration can also be observed on MRI as early as 18 months postoperatively.[13] To improve the quality and type of regenerated cartilage as well as long-term durability, many augmentation strategies to microfracture have been investigated, such as the use of



A

Fig. 5A. MRI showing poor cartilage fill at 5 years post-microfracture.



B

Fig. 5B. Poor defect filling and fibrocartilage deterioration seen 1 year post-microfracture in a high level contact sport athlete.

scaffolds, additional chondrocytes, bone marrow, growth factors, cytokines, and hyaluronic acid.[15,16]

5.3. Poor defect filling

As microfracture relies on the formation of a marrow-rich fibrin clot to maximally fill the chondral defect, there are times when the resultant clot only fills a portion of the lesion or may fully cover the defect but not be completely adherent. Submaximal defect filling (Fig. 5A and B) may result in decreased functional results as well as affect regenerated cartilage stability.[6,7] Appropriate but not too aggressive depth of penetration into the subchondral bone, proper debridement and lesion bed preparation, and creation of stable cartilage borders are all steps that may be done to increase the chances of maximal filling. Mithoefer et al.[14] demonstrated that results of complete cartilage fill varied from 18 % to 95 %. Complete peripheral integration was also seen to be very low at 4 %–8 %. Many different strategies to improve clot stability have been investigated through augments such as utilizing cytokines, various growth factors, hyaluronic acid, and chitosan, showing promising results.

Author's Tips and Tricks to Avoid Complications and Salvage Treatment after Microfracture
We personally suggest treatment with microfracture only in smaller isolated condylar lesions (less than 2 cm^2) in biomechanically normal aligned knees in young patients. We recommend against treating patellar lesions and large multiple lesions with marrow stimulation techniques alone. Debridement must be meticulous and accurate, as it is vital to remove the calcified layer while respecting and maintaining the underlying subchondral bone. The use of precise instruments to create small holes is essential.
Salvage procedures include debridement and shaving in cases of bone overgrowth, while ACI, HA-BMAC, and OATS can be used for cases of poor defect fill and fibrocartilage deterioration. We typically reserve the use of OCA as a last resort for non-healing defects after a failed salvage procedure.

6. Improving microfracture

As microfracture grew in popularity with annual growth of 3%–5% from 2003 to 2024, there were concerns with the durability of the resultant fibrocartilage and the longevity of clinical improvement in long-term follow-ups.[6,7] Many suspected that the resultant fibrocartilage, which is less durable and hyaline cartilage lacking, was due to instability of the resultant fibrin clot formed after microfracture.[6] In an effort to improve microfracture, prevent leakage of MSCs, and stabilize the marrow-rich fibrin clot from shrinkage and detachment, many different scaffolds were introduced, such as the collagen-based membrane, Chondrogide® (Geistlich Pharma, Switzerland), chitosan-based scaffold, BST-CarGel® (Smith and Nephew, Watford, England), and hyaluronic acid-based membrane, Hyalofast® (Anika Therapeutics Inc., Bedford, MA, USA). These scaffolds and membranes were combined with microfracture and were termed autologous membrane-induced chondrogenesis (AMIC) (Fig. 6).

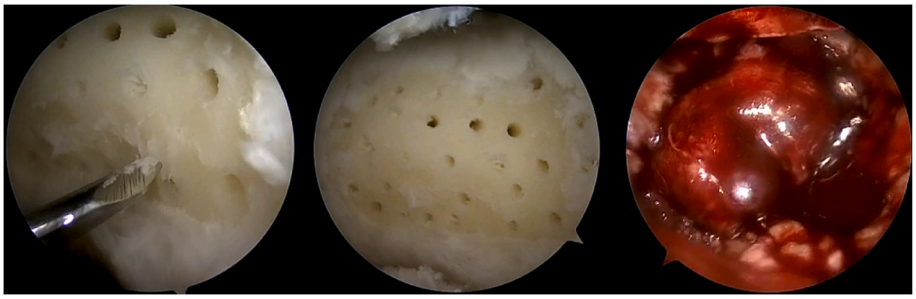


Fig. 6. Autologous membrane induced chondrogenesis (AMIC) done on a femoral condyle. Following microfracture, scaffolds are secured over the defect area in a dry knee allowing a marrow-rich fibrin clot to form in and around the scaffold.

AMIC draws from the concept of marrow stimulation and its regenerative potential utilizing MSCs derived from penetration into subchondral bone, forming a marrow-rich fibrin clot. Similar to scaffolds used in autologous chondrocyte implantation (ACI) techniques, type I and III collagen matrices are used to guard and stabilize the marrow-rich fibrin clot and provide an environment ideal for cell adhesion, growth, and chondrocyte differentiation. The main advantage of this technique is that it is based off of the marrow stimulation and harnessing MSCs in the subchondral bone, circumventing the need of having a donor site and the subsequent donor site morbidity, as well as allowing a single-staged procedure without the need of harvesting chondral tissue, culturing, and expanding them in a laboratory seen in ACI. This reduces total operation time and makes cartilage reconstruction more cost-effective with similar outcomes compared to other techniques, most especially ACI.[17] It has also been shown that AMIC can also be combined with other sources of MSCs, such as bone marrow aspirate concentrate and adipose tissue.[18,19]

With concerns of damaging subchondral bone, the main connecting line of nutrients and cells needed for cartilage regeneration, subchondral needling procedures, such as Nanofracture® (Arthrosurface, MA, USA), were developed to minimize damage to the subchondral plate while maximizing MSC extraction and recruitment to the focal defect. This was done by using a needle (approximately 1 mm), which was of significantly smaller diameter than drill bits, chondropicks, and awls, and allowed deeper penetration into the subchondral bone. The use of needling led to improvement in the overall quality of the regenerated tissue and prevented bone compaction seen with traditional microfracture awls. However, it was shown that there were no significant differences in clinical and functional outcomes between nanofracture and microfracture.[20]

7. Autologous chondrocyte implantation (ACI)

One of the caveats of microfracture is that the restored cartilage is mainly composed of fibrocartilage rather than native hyaline articular cartilage. As an attempt to restore more native-like hyaline cartilage in chondral lesion treatments, autologous chondrocyte implantation (ACI) techniques were developed.

Pioneered by Dr. Lars Peterson in 1987, the first generation of ACI was developed and the first pilot study was published in 1994.[21] The first generation of ACI involved a two-staged procedure wherein the first stage, cartilage and chondrocytes were harvested from healthy cartilage in minor or non-load-bearing areas and later cultured and expanded in a laboratory. The second stage involved re-implanting the expanded autologous chondrocytes under an autologous periosteal patch, typically harvested from the proximal tibia, which was secured over the chondral lesion. The use of an autologous periosteal patch necessitated additional surgical morbidity, or rather, donor site pain and healing.

There were many disadvantages to using this technique, such as the intricacy and invasiveness of the transplantation procedure, the heterogeneous quality of the periosteum harvested, as well as the need for careful and complete suturing of the periosteal patch at the area of the prepared lesion. Along with the difficulties of performing these procedures, there was a high incidence of postoperative complications. Periosteal overgrowth and hypertrophy were later established as common postoperative complications.[22] Other complications for first-generation ACI techniques include leakage of chondrocytes from the transplanted site, decreased productivity and regeneration of the matrix secondary to the monolayer nature of the culture, and uneven distribution of chondrocytes on the periosteal patch. These complications can ultimately lead to deficient fill of regenerated cartilage, insufficient peripheral integration, and delamination.

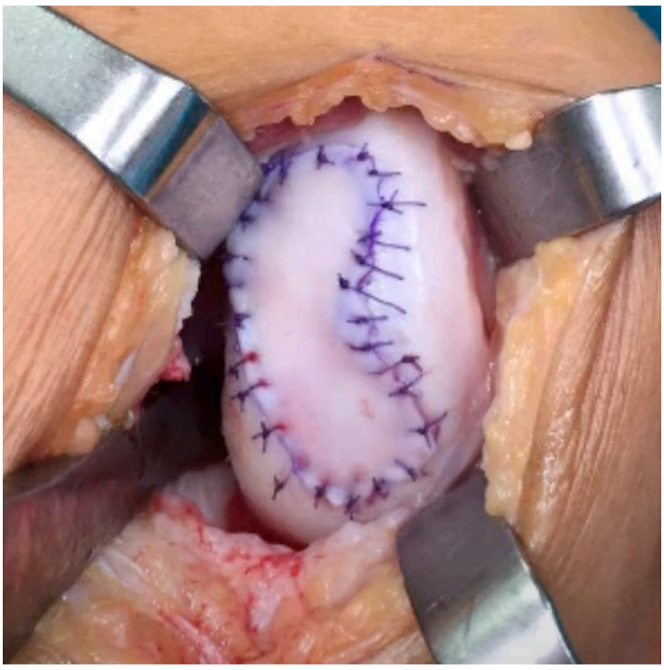


Fig. 7. ACI technique using a collagen-based patch with chondrocytes implanted under the membrane scaffold and secured over the defect.

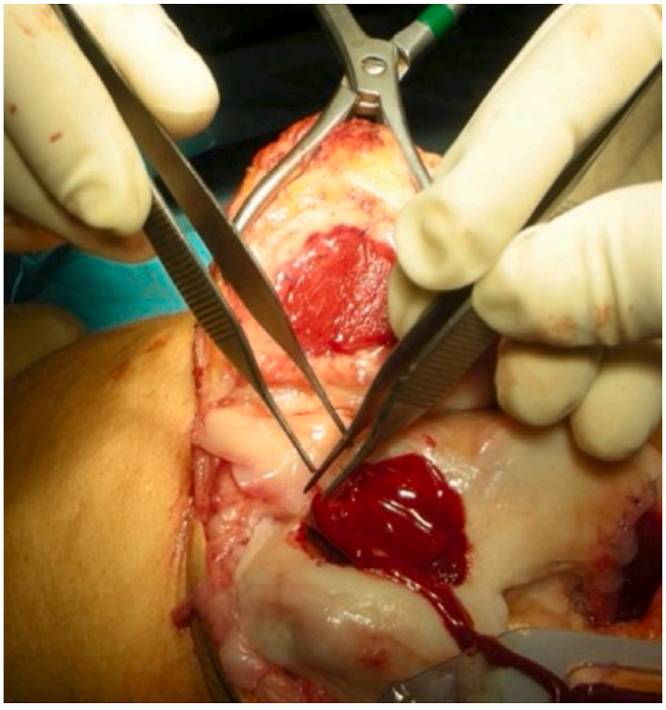


Fig. 8. HA-BMAC used to salvage ACI graft delamination secondary to insufficient peripheral integration.

8. Abandoning periosteal patches – next generation ACI techniques

Moving our discussion into the new techniques developed after the use of periosteal patches, there has been much confusion in the past with regards to the "generation" nomenclature and classification of these techniques. This confusion typically arises with respect to when and where the seeding of the newly expanded chondrocytes is incorporated

into a newly utilized membrane and scaffold. Therefore, we will not use the terms "second-" and "third generation" to avoid any further confusion and simply refer to these procedures as "next-generation ACI techniques," which are typically two-staged procedures that utilize membranes and cultured/expanded chondrocytes.

The next-generation ACI techniques were developed to solve common issues seen by the use of periosteal patches. As periosteum is a live and viable type of tissue, there were many occurrences of periosteal hypertrophy, which caused mechanical symptoms, eventually needing revision surgery. In response to this, different types of membranes and scaffolds were developed (Fig. 7). Many various types of scaffolds were used, such as protein-based polymers (ie: collagen, fibrin, gelatine), carbohydrate polymers (ie: hyaluronic acid, agarose, chitosan, alginate), artificial polymers (ie: Teflon, dacron, hydroxyapatite), and a combination of the aforementioned. Membrane and scaffold technology progressed from simply spreading a monolayer distribution of cells on a membrane to the use of 3-dimensional scaffolds, allowing a more robust 3D distribution of chondrocytes[23] (Fig. 8). Products such as BioSeed®-C, Hyalograft C®, CaReS®, NOVOCART 3D®, Atelocollagen-associated ACI, MACI® (Genzyme), and alike have been shown to reduce the chances of adverse effects and complications of graft delamination, hypertrophy, etc..[22,24–26]

Membrane scaffolds were not the only aspect improved upon in the next-generation ACI techniques. Chondrocyte cell therapy and processing also improved. Allowing the development of techniques such as characterized chondrocyte implantation (CCI). Here, chondrocytes are expanded with a particular marker profile predictive of forming hyaline-like cartilage in a consistent and reproducible manner. Through optimizing cell expansion procedures and selecting chondrocytes with this particular marker profile, phenotypic characteristics and biologic activities toward chondrogenesis were enhanced.

These next-generation techniques still involved two stages. The first stage still involved harvesting cartilage from minor or non-weightbearing areas and then sending these chondral fragments to a laboratory where chondrocytes are cultured and expanded. These newly expanded chondrocytes were then processed and sent back to the orthopaedic surgeon for implanting under a membrane, or additional steps in the laboratory were taken, and through complimentary tissue engineering, these chondrocytes were processed and seeded onto a three-dimensional membrane. These processes helped promote chondrocyte attachment, increase in vitro chondrocyte proliferation, and improve expression and maintenance of the cell-differentiated cartilage phenotype.[27]

The use of membrane implants allowed for faster and easier implantation, with no donor site morbidity seen with the use of periosteal patches, and also opened the possibility for the use of arthroscopy instead of an open or mini-open exposure during the implantation stage. Many of these techniques also involved utilizing fibrin glue for fixation, circumventing the need for time-consuming circumferential suturing. The use of these next-generation ACI techniques helped overcome complications associated with the use of periosteal patches, such as graft hypertrophy, the need for suturing, monolayer distribution of chondrocytes, as well as poor access to lesions necessitating open or mini-open exposures.[28] Kon and Gobbi et al. demonstrated that the use of next-generation ACI techniques, such as those utilizing hyaluronic-based membranes seeded with chondrocytes, Hyalograft C®, not only had improved clinical and functional outcomes in the long term but also had a similar return to sport with improved durability compared to other cartilage reconstruction techniques.[29,30]

9. From two-stage to single-stage ACI – ACI done in a single setting

Due to the need for at least two separate surgeries, the need for outside laboratory culturing and expansion of chondrocytes, extended wait times, and increased costs for the entire treatment, a newer generation of chondrocyte therapies involving only a single-staged procedure was developed. We will term this group of procedures "single-staged ACI techniques." These single-staged ACI techniques involve chondral defect preparation followed by the use of minced allogenic or autologous cartilage harvested in the same setting without culturing and expansion. These techniques may or may not use scaffolds and are commonly combined with other biologic materials (ie: PRP, MSCs, BMAC, etc.) prior to implantation into the prepared defect (Fig. 9). Early developments of this concept were first described in 1983 and later elaborated by Cole et al.[31] and their use of the cartilage autograft implantation system (CAIS), where autologous hyaline cartilage is arthroscopically harvested and mechanically minced, affixed on a synthetic scaffold without previous culturing or expansion, and implanted directly onto the lesion in a single-staged procedure. This technique was successful in forming more hyaline-like cartilage with improved clinical outcomes. Variations of the minced cartilage one-stage technique include IMPACT (Instant MSC Product accompanying Autologous Chondron Transplantation) and Autocart®.

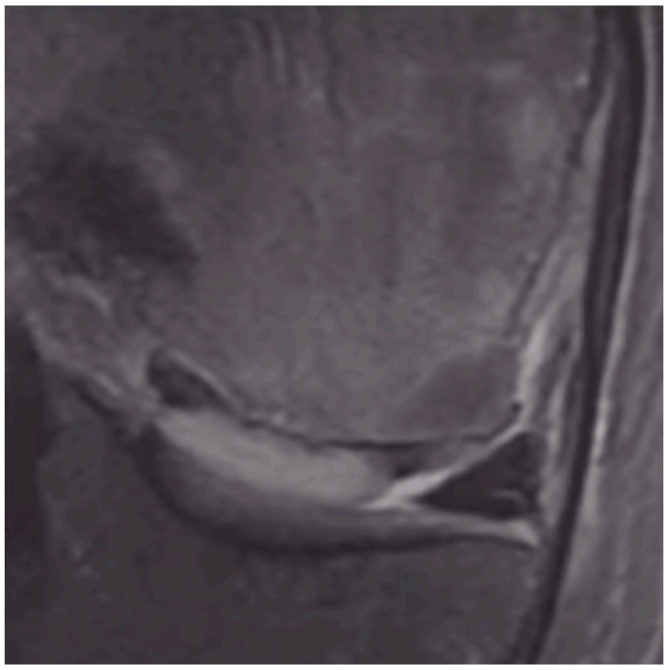


Fig. 9. MRI showing graft hypertrophy after ACI. Regenerated cartilage exceeds space of native defect protruding beyond initial borders.

10. Other single-stage scaffold-based cartilage repair techniques

Other one-stage techniques, such as those involving scaffolds combined with MSCs derived from various sources (ie: bone marrow aspirate, adipose tissue) along with the separate development of synthetic bioengineered acellular scaffolds (ie: MaioRegen, Agili-C), are related to but have distinct differences from ACI. These techniques do not directly utilize autologous or allogenic chondrocytes, but rather, through the use of trophic signaling seen with MSCs or through bioengineered scaffolds, they induce and enhance chondrogenesis. Synthetic bioengineered acellular scaffolds were demonstrated to have improved clinical results with low complication and failure rates.[32]

A notable single-stage cartilage repair technique was introduced by Gobbi et al., In 2004, Gobbi et al. were the first to present their idea for the use of collagen-based or hyaluronic acid-based matrices combined with bone marrow aspirate concentrate (BMAC) used in a single-stage cartilage repair procedure. After long-term follow-ups, they demonstrated significantly improved functional, clinical, and pain scores in the long-term follow-up with successful outcomes in patients older than 45

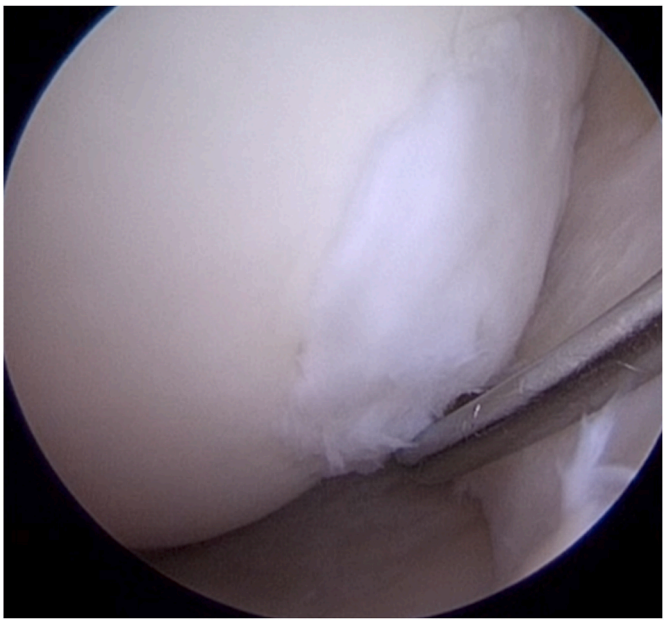
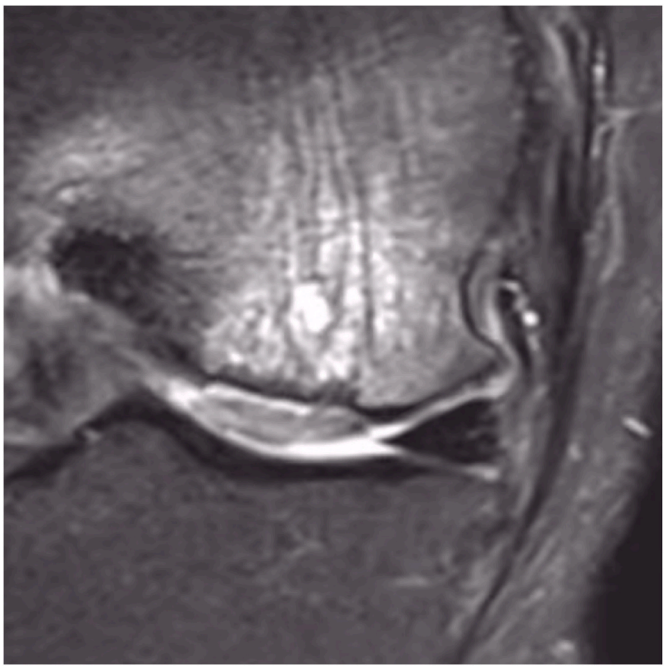
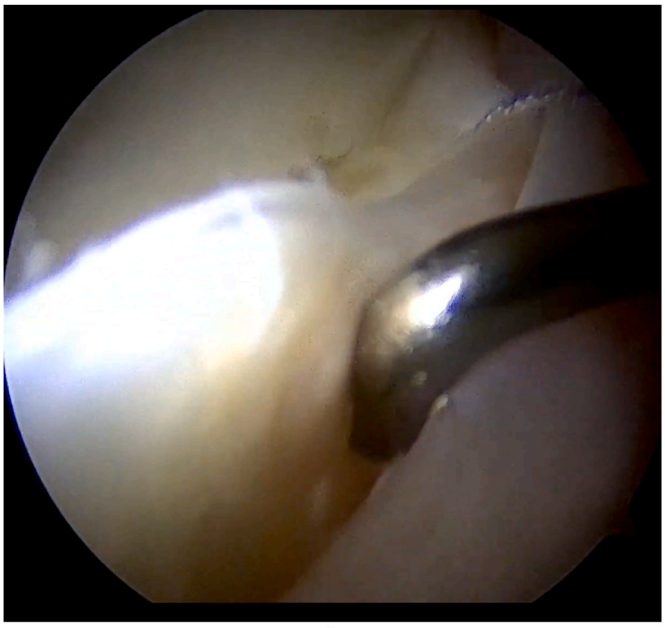


Fig. 10. Graft hypertrophy seen during arthroscopy undergoing arthroscopic debridement and debulking.



A

Fig. 11A. MRI showing delamination of graft after next generation scaffold-based ACI. A linear hyperintensity between subchondral bone and cartilage indicates graft delamination.



B

Fig. 11B. Arthroscopy shows delamination of cartilage from underlying subchondral bone.

years of age and in lesions up to 20 cm^2. With the concept of using HA-BMAC as a way to regenerate cartilage, they introduced the idea of "biologic arthroplasty." However, it was noted that despite having successful subjective outcomes, there were less successful objective outcomes in patients older than 45 years, indicating that there may be greater benefit in using this treatment in younger populations as first-line treatment. In long-term prospective comparison studies, HA-BMAC showed significantly better and longer-lasting results when compared to microfracture.[15] HA-BMAC has also been proven to be a versatile procedure that can be done open or under dry arthroscopy and is recognized to be a successful primary cartilage regeneration technique or even as a salvage procedure (Fig. 8) for previously failed cartilage repair or reconstruction techniques, demonstrating comparable outcomes to other well-established procedures.[16,17,19,26,33,34]

Typical indications for ACI, AMIC, and other scaffold-based procedures include symptomatic, younger patients (14–50 years old, depending on their physiological fitness) who have failed conservative treatment, mid-to large-sized, full-thickness focal chondral lesions (typically $\geq$1.5 cm^2), ICRS grade 3–4, and in a mechanically normal or corrected joint. Relative contraindications include patients with inflammatory or autoimmune conditions, obesity, abnormal biomechanics, smokers, and those with large or degenerative lesions.[22]

Despite having relatively favorable survivorship and outcomes, complications still exist. These complications include graft hypertrophy, mobilization of the scaffold and delamination, insufficient integration of newly regenerated cartilage to the native cartilage borders, and deficiency in regenerated cartilage.

11. ACI, AMIC, and other scaffold-based procedure complications

11.1. Graft hypertrophy

Graft hypertrophy is recognized as the most common complication arising from ACI techniques, with incidence rates reported as high as 36 %.[22,23] Clinically, graft hypertrophy often manifests as a persistence or recurrence of pain or a decline in knee function and range of motion within the first postoperative year. This condition is particularly common among patients who have undergone ACI techniques utilizing a periosteal flap (Fig. 9). This could be due to the presence of fibrocytes and metaplastic periosteal remnants found in the most superficial layer of regenerated tissue. These periosteal cells have the ability to differentiate into chondrocytes to form fibrocartilage. Growth factors, more specifically vascular endothelial growth factor (VEGF), may play a role in these hypertrophic changes and enchondral ossification seen at the base of the regenerated tissue. No study has investigated this process, but preparing the periosteal batch to be as thin as possible may reduce factors that can contribute to graft hypertrophy. With regards to which areas are most prone to graft hypertrophy, the patellar region has been

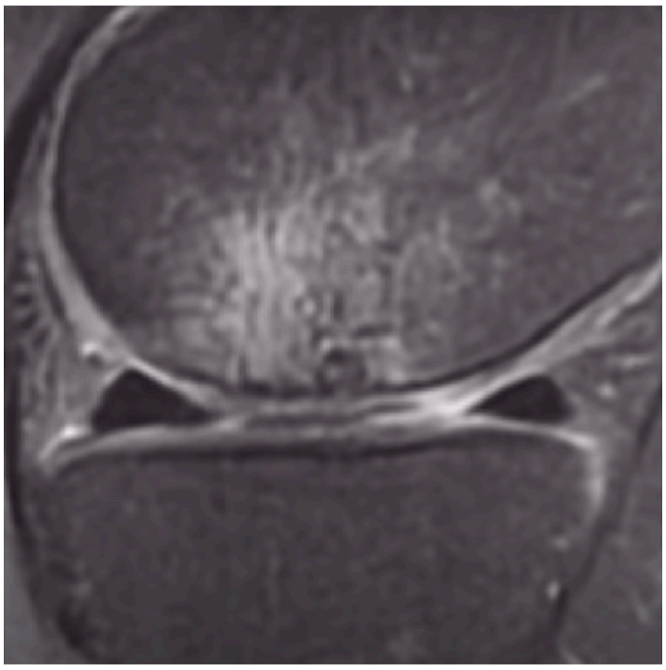


Fig. 12. MRI showing insufficient peripheral integration after ACI. Fissuring and hyperintensity between native cartilage and newly regenerated cartilage seen at the anterior border.

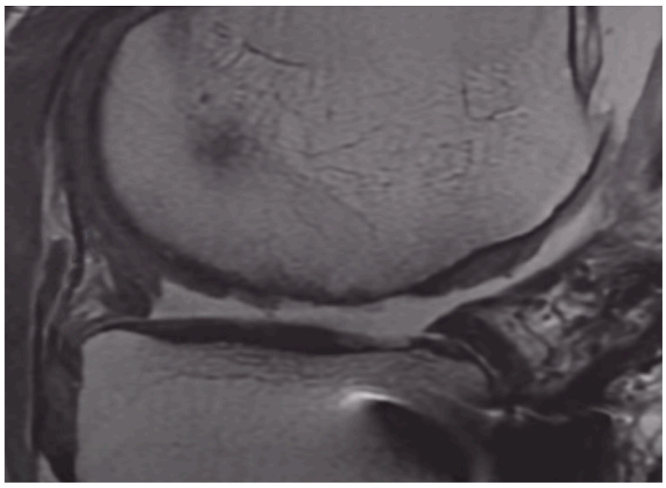
shown to be the most frequent site, followed by the medial and lateral femoral condyles.[23]

Not all cases of graft hypertrophy require surgical intervention. As described by Kreuz et al., grade 1 or 2 hypertrophy may present with no or minimal symptoms, and only 50 % of grade 3 hypertrophies underwent revision surgery. In patients with grade 4 hypertrophy, 100 % required revision. Interesting enough, no further hypertrophic changes were seen after 36 months, and in some there was a decrease in hypertrophy grade over time. This could be the result of tissue remodeling due to compression during movement and weight bearing.[22] The decision to pursue revision surgery, which generally involves arthroscopic shaving or partial resection of the hypertrophied graft (Fig. 10), is contingent upon the degree of clinical symptoms present, the degree of hypertrophy observed via MRI, and the possibility of tissue remodeling with time.

11.2. Delamination

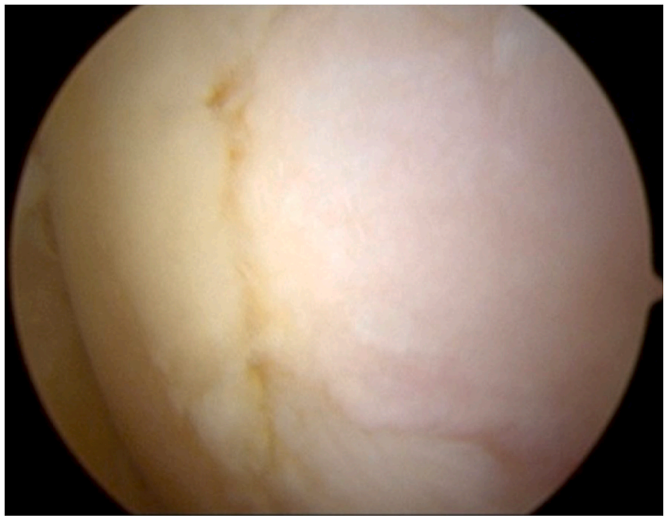
Delamination is a notable complication associated with ACI, defined as the separation of the regenerated cartilage from the underlying subchondral bone at the level of the tidemark (Fig. 11A and B). This condition arises due to shearing forces that cause the cartilage layer to slide over the subchondral bone before the two layers can properly fuse.[35] Such events are often the result of noncompliance with rehabilitation protocols or the premature resumption of weight-bearing activities, as most delamination cases are seen during the first postoperative year. However, there have been documented cases of delamination secondary to trauma years after the primary surgery, which can be evidence of incomplete graft healing at the level of the cartilage and subchondral bone interface, despite seemingly fully integrated grafts on MRI or second-look arthroscopy.[35] Intraoperatively, delamination is more prevalent in larger or uncontained defects.

Management of delamination involves the complete removal of the delaminated areas of cartilage down to a stable base, followed by further treatment options, typically determined by the size of the remaining defect and the area in which the chondral defect is located, such as microfracture/microdrilling and refixation of delaminated areas with



A

Fig. 13A. MRI showing poor and deficient fill of regenerated cartilage after ACI.



B

Fig. 13B. Insufficient peripheral integration and incomplete fill of the cartilage defect seen on arthroscopy 5 years post-ACI.

sutures or fibrin glue for the smaller lesions in the femoral condyle and repeat ACI treatments, HA-BMAC, osteochondral autologous transfer, or osteochondral allografts for larger lesions.

11.3. Insufficient peripheral integration

Insufficient peripheral fusion is characterized by the inability of the regenerative cartilage to integrate effectively with the adjacent healthy cartilage (Fig. 12). Niemeyer et al.[24] revealed an incidence rate of 23.1 % for insufficient fusions. There were no instances of insufficient peripheral integration in those treated with first-generation ACI. However, in those treated with the next-generation scaffold-based ACI, there were rates as high as 4.9 %. In the same study, insufficient peripheral fusion was most prevalent in the medial femoral condyle (5.8 %), with the patella having the lowest prevalence (0.8 %), which was theorized that shear forces, seen higher in the patella, may provide stimuli for integration and hypertrophy.

As insufficient peripheral integration may be a sign of graft delamination, it is important to confirm the stability and successful integration of these grafts arthroscopically and investigate signs seen in MRI.



Fig. 14. Single osteochondral plug transplanted arthroscopically during OATS procedure.

Treatment is done in the same manner as discussed when encountering delamination.

11.4. Deficient fill of regenerated cartilage

Deficient fill of regenerated cartilage is a complication signifying a failure of the graft to regenerate in the defect adequately (Fig. 13A and B). Niemeyer et al.[24] observed this phenomenon in 21.2 % of cases through MRI and seen in 17.3 % of cases intraoperatively. The complication was more frequently seen in the ACI involving periosteal patches and groups who had membranes pre-seeded with chondrocytes, with incidences of 3.8 % and 3.7 %, respectively. ACI groups who underwent techniques involving membrane scaffolds with chondrocytes implanted underneath at the time of surgery had the lowest incidence at 1.9 %. The areas that have deficient fill of regenerated cartilage were observed as soft, mechanically unstable, or less durable regenerated tissue.

Deficient fill was also associated with older populations, which could be due to chondrocyte senescence, resulting in the reduction of chondrocyte regenerative capacity. As chondrocytes get older, there is a decline in mitochondrial function, a decrease in responsiveness to anabolic mechanical stimuli and to growth factors, and a decrease in synthetic and mitotic activity. The decreased regenerative capacity of chondrocytes and the higher incidence of complications or failure in older groups undergoing ACI can help reiterate the importance of proper patient screening and choosing the appropriate candidates for these procedures.

The strategy for addressing insufficient cartilage regeneration through revision surgery is typically influenced by the size of the defect, where larger defects may require mosaicplasty, repeat ACI, HA-BMAC, or the use of osteochondral allografts, while smaller defects can typically be treated with marrow stimulation techniques or osteochondral autograft transplantation.

Author's Tips and Tricks to Avoid Complications and Salvage Treatment after ACI

- First-generation ACI has been utilized for many years in the USA, while in Europe, we moved on quickly to next-generation scaffold-based and single-stage techniques in order to avoid the need for complex two-staged procedures and the cost of cell cultivation.
- In order to avoid possible leakage of the cartilage suspension, careful and thorough suturing of the periosteal membrane to the surrounding cartilage is imperative.
- In cases of graft hypertrophy, precise and comprehensive debridement is typically sufficient. If delamination or deficient fill is encountered, a revision surgery involving MACI, HA-BMAC, OATS, or OCA can be performed. In cases of insufficient peripheral integration, we typically try a trial of orthobiologic treatments utilizing PRP or MSCs (BMAC or microfragmented adipose tissue). If there is no improvement after biologic treatments, we treat these lesions as delamination.

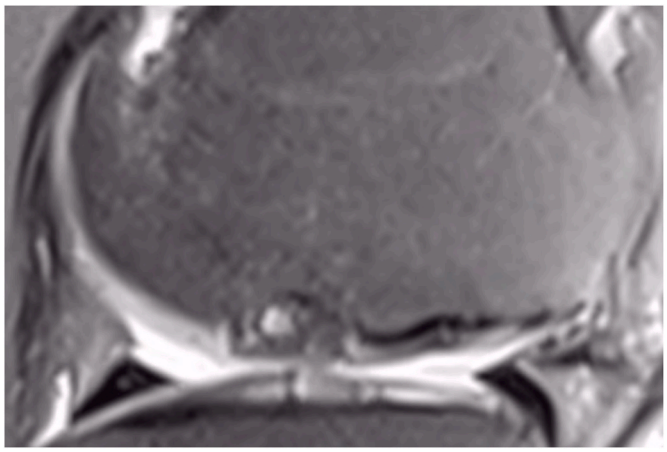


Fig. 15. MRI showing suboptimal graft placement after OATS with the graft protruding compared to the surrounding bone. This can increase contact pressures within the joint and lead to subchondral changes and thinning of the transplanted cartilage.

12. Osteochondral autograft transplantation (OATS) and mosaicplasty

Osteochondral autograft transplantation (OATS) is a single-staged procedure in which a single osteochondral plug (Fig. 14) or set of multiple plugs is harvested from non-weight-bearing areas and used to fill in chondral defects. The use of multiple plugs is typically termed "mosaicplasty." When using a single plug, it is important to find a donor surface that is similar to the contour of the recipient site. Incongruency can lead to abnormal pressure on loading sites, which can ultimately lead to pain or graft failure. Moreover, in mosaicplasty, the application of multiple plugs results typically in even more incongruency in the recipient area. The use of osteochondral plugs bypasses the problem of fibrocartilage repair products and allows direct transfer and restoration of the hyaline cartilage at the level of the defect. Because there is restoration of viable and native hyaline cartilage to the area, these procedures can be used in higher-demand patients with greater durability and improved functional and clinical outcomes.[36]

Good predictors for favorable outcomes include single lesions surrounded by normal cartilage, higher baseline Lysholm scores, normal patellofemoral joint tracking, younger age, smaller defects, and acute lesions. Indications for OATS or mosaicplasty are typically younger patients in good physical condition and for focal, full-thickness, chondral or osteochondral defects typically between 1.0 and 4.0 cm^2. Relative contraindications include lesions >4 cm^2 (ie: 10 mm $\times$ 40 mm), patients older than 60 years old, uncorrected asymmetric biomechanically malaligned joints, uncorrected ligamentous injury, uncontrolled diabetes, inflammatory or crystalline arthritis, and patients unable to comply with postoperative restrictions.[37]

Complications and limitations with OATS and mosaicplasty typically relate to the technical precision needed to prevent donor-recipient site mismatch, the need to properly shape and sculpt grafts to provide a congruent surface after transplantation, and all while preventing chondrocyte damage or graft fracture upon implantation. Common complications associated with OATS and mosaicplasty include donor-recipient site incongruity, donor site morbidity, and chondrocyte injury and graft fracture upon plug transfer.

13. Osteochondral autograft transplantation (OATS) and mosaicplasty complications

13.1. Donor-recipient graft incongruity

Incongruity between the donor and recipient sites (Fig. 15) can lead to various complications and possible failure. It is essential to harvest donor tissue from regions characterized by low- or non-weight-bearing stresses, as well as from areas that have similar characteristics in contour, morphology of the recipient site, and thickness of the cartilage. It is emphasized that a perfect plug congruity in terms of orientation, tilt, and height during harvesting and implantation is required to achieve ideal healing. However, despite how meticulous and careful a surgery can be performed and in choosing an appropriate donor site, incongruity of graft plugs cannot always be avoided. Incongruity of grafted plugs just 0.5 mm–1 mm proud or above the surrounding surface or those who sunk lower, below the surrounding surface, can lead to significantly increased contact pressures within the joint. Malreduced or incongruent grafts with the native chondral are associated with elevated rates of necrosis, resorption, and, ultimately, worse clinical outcomes.[38]

The risk for incongruity and gapping between plugs becomes more pronounced with the application of multiple grafts during mosaicplasty, leading not only to a loss of congruity but also to the formation of fibrocartilaginous tissue in the interstitial spaces. Consequently, it is advised to limit the number of plugs used in osteochondral autograft transplantation (OAT) to two or three. Furthermore, it is critical to ensure that the depth of the recipient cavity is appropriately matched and completely filled by the graft. An inadequately seated graft may compromise stability, as it will depend solely on circumferential frictional forces, which could eventually result in subsidence. The presence of multiple plugs in mosaicplasty is likely to further diminish stability due to the gaps that reduce friction between the plugs.

Ultimately, donor-recipient incongruence should be avoided; be it protuberance or sinking, it appears that proud graft may be more problematic. One strategy to avoid proud graft is through resection of the plug surface to achieve higher levels of congruity.[38] However, resection does not come without its own consequences. As you resect the surface of the graft, the superficial and upper middle layers are sacrificed. These layers are vital for resisting compressive, tensile, and shearing forces, as well as for secreting lubricin and other proteins from chondrocytes to minimize joint friction. It is advised to limit resection to no more than 1 mm as the matrix can remain intact and spared in most cases.

Another strategy may be in the selection of graft plug sizes. Larger plugs may lead to decreased mean total contact area and increased contact zone mean pressures compared to surrounding native cartilage; however, peripheral cell death and improved viability in the center of plugs may be factors that should be considered. As some advocate for larger plugs due to this fact, larger plugs may be associated with increased incongruence.[38] A balance between the improved viability of larger plugs and the improved congruity of smaller plugs should be considered and weighed upon the individual characteristics of the patient and lesions encountered.

13.2. Donor site morbidity

Another common complication of OATS is the donor site morbidity caused by harvesting the autograft plugs from the medial or lateral trochlea or from the intercondylar notch. Donor site morbidity has been reported with an incidence as high as 92 %, but with a pooled average of 5.9 % with patella-femoral disturbances and crepitation as the most common complaints.[39] Even though these plugs are harvested from non- or minimal-weight-bearing areas, these donor sites may present with persistent pain or mechanical irritation. Mechanical irritation from donor sites may be due to the resultant healing after harvesting graft plugs. These areas may become excessively filled with hypertrophic fibrocartilage, which can cause pain secondary to mechanical irritation or locking.

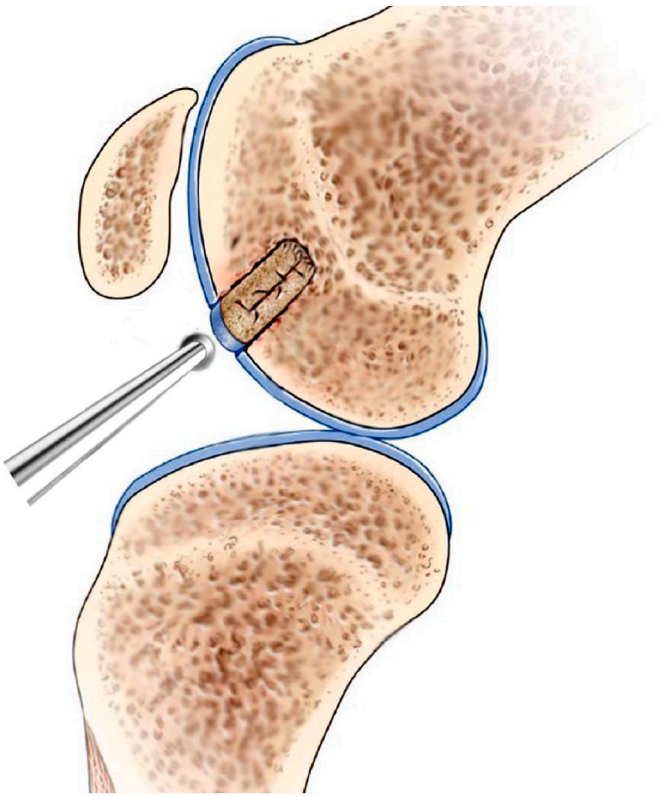


Fig. 16. Aggressive or oblique impaction may cause graft fracture. Use of lighter, more frequent blows may decrease incidence of graft fracture upon implantation.

Strategies to decrease donor site morbidity have been developed, such as using multiple smaller grafts in mosaicplasty to reduce donor-site morbidity, enhance graft incorporation, and minimize incongruity. However, we have had good success with the use of larger grafts despite the heightened risk of donor site morbidity. Other strategies include the use of osteochondral allograft plugs, demineralized bone matrix (DMB), or synthetic bone plugs to backfill donor sites to prevent any maltracking issues or fibrocartilage hypertrophy commonly seen when donor sites are left alone or treated with autologous bone graft. Moreover, the practice of maintaining adequate spacing (more than 2 mm) between donor harvest sites, to minimize the risk of fragmentation or creating plug convergence, and employing proper and meticulous harvesting techniques can help minimize morbidity.

13.3. Chondrocyte injury and graft fracture

Intraoperative complications such as graft fracture and chondral injury can significantly compromise surgical outcomes. As early as the harvesting phase, graft fracture can occur. This has been observed in poor surgical technique in handling and using the osteochondral harvester.

A recommended technique in using the donor harvester is to gently impact a sharp harvester perpendicular and flush to the articular cartilage. The perpendicular orientation ensures the integrity of the donor plug, maintaining the desired surface morphology, as well as ensuring no oblique orientation at the recipient site after implantation, which may result in stepping or protrusion. It is wise to refrain from using a dull harvester, as this may cause crushing injury to the chondrocytes or underlying subchondral bone, resulting in fragmented, fractured, or morselized bone on the periphery of the plug instead of creating a

cleanly cut, well-harvested, stable plug of good integrity. The donor harvester should be impacted to a depth of 12–15 mm as it is vital to harvest a graft plug of at least 10 mm. This ensures that there is enough subchondral bone to support the plug upon implantation. Once the harvester has reached the desired depth, the harvester should not be toggled or rocked back and forth, as this may cause fracture/fragmentation or incongruity of the graft. The harvester should be turned at least 180° to ensure a clean cut and proper disengagement of the graft from the surrounding cartilage and subchondral bone.

During the implantation phase, many graft fractures or fragmentations occur during graft insertion using a tamp or mallet (Fig. 16). If possible, insertion of the graft should be done using simple finger pressure, especially in cases done with an arthrotomy. However, as these cases are frequently done under arthroscopy, this may not be possible. It is frowned upon to use a mallet directly onto the graft during implantation, as this may lead to higher rates of graft fracture and chondrocyte injury. The use of an oversized tamp larger than the graft plug can help ensure proper and straight insertion of the plug. This can also help distribute impact forces evenly and reduce the incidence of graft fracture or chondrocyte injury. Gentle and multiple taps to impact the graft into the recipient socket should be practiced instead of techniques using fewer hits with impact of greater force. It is, in fact, the mean impact force during impaction of the graft that is a positive predictor of chondrocyte death in OATS and mosaicplasty, with no evidence showing the number of hits or impacts required to place the graft having any correlation to chondrocyte death. We recommend using one's finger or hand to insert a graft plug, but when this is not possible, a series of lighter blows at a greater number, using a padded and oversized tamp with a very small and light mallet, is used when impacting grafts into their recipient site.

Author's Tips and Tricks to Avoid Complications and Salvage Treatment after OATS and Mosaicplasty

When considering OATS and mosaicplasty, one must be very meticulous and precise in their surgical technique. The use of new instruments helps facilitate proper and optimal preparation of the recipient site and the plug itself. Careful, organized, and systematic approaches are vital, as many steps are absolutely crucial in order to harvest good quality grafts with minimal donor site morbidity and to implant and position these grafts into the recipient site, creating a congruent joint with no protrusion or depression. We do not recommend the use of many small plugs and have had better results using a large single plug whenever possible. We also recommend not damaging the patellofemoral joint surfaces when determining harvest sites and obtaining grafts.

For salvage procedures, graft incongruity may be addressed depending on the size of the incongruity. For smaller lesions, debridement and shaving may be sufficient; however, larger lesions may need revision with a new graft. Revision of fractured grafts is most important when the grafts are unstable within their sockets. For cases with the absence of multi-compartment arthritis, revision with a new graft may be enough. However, if failure of the OATS or mosaicplasty has been long-standing, there may be progression into multi-compartmental arthritis, which may necessitate total arthroplasty. In cases where revision with a new graft is not possible in the absence of multi-compartment arthritis, partial or unicondylar arthroplasty may be considered.

14. Osteochondral allograft (OCA)

Osteochondral allograft (OCA) transplantation is a single-staged procedure that uses full-thickness, viable hyaline cartilage along with the underlying subchondral bone from a cadaver or donor. The benefit of allografts is that this avoids donor site morbidity, the potential to better match the contour of the native recipient surface, as well as allow resurfacing of large defects. Other than osteochondral autograft transplantation (OATS), this is the only other method that results in regeneration of hyaline cartilage with viable chondrocytes. Limitations for OCA include cost, risk of graft rejection, graft availability, and risk for disease transmission.[37] Clinical results have shown excellent functional and clinical outcomes, a high rate of return to sport, and high graft survivorship in the short and long term.[40]

Indications for OCA transplantation include patients with avascular necrosis, large osteochondritis dissecans, traumatic chondral defects, chondral defects secondary to

intraarticular fracture, and salvage surgery for previously failed cartilage repair or reconstruction. Relative contraindications include small lesions less than 1 cm^2 (ie: 10 mm × 10 mm), patients older than 60 years old, BMI greater than 35 kg/m^2, uncorrected asymmetric biomechanical malalignment, uncorrected ligamentous injury, uncontrolled diabetes, history of inflammatory or crystalline arthritis, history of infection, and patients unable to comply with postoperative protocols and restrictions.[37]

Complications can be similar to those of OATS without the donor site morbidity, such as premature loosening secondary to donor-recipient graft mismatch or inadequate fixation, graft overload typically secondary to biomechanical malalignment or incongruity, fracture of allograft secondary to trauma or implantation technique, and graft non-union.

15. Osteochondral allograft (OCA) complications

15.1. Premature loosening

Premature loosening of an osteochondral allograft may result from mismatch or incongruity between the harvested graft and the prepared recipient socket. Accurate sizing of the donor-recipient site is essential, and the morphology of the recipient site as well as the allograft used must be taken into account. It is generally recommended that the graft be press-fit into the recipient socket to ensure congruence of the graft with the adjacent native cartilage and subchondral bone, achieving a secure fit. When a sufficient press-fit is achieved, the graft should maintain stability without the need for additional fixation. However, another cause for loosening may be due to insufficient fixation when press-fitting does not achieve secure fixation.

There may be times when allografts achieve sufficient press-fit and are initially stable within the socket; however, the graft does not match the recipient joint surface topography, resulting in incongruity and protrusion. This can lead to excessive forces on the edges of the graft, which may result in graft toggling and loosening. Proper allograft and recipient site preparation is essential to ensure a secure and congruent allograft transplantation.

Another frequent cause of graft instability is the disruption of the circumferential integrity of the recipient site, known as blowout, which leads to the loss of hoop stresses and diminishes the structural support of the recipient site. This can be due to poor recipient harvester or reaming technique, such as toggling or rocking back and forth when cutting and removing bone to create the socket, or overaggressive and non-perpendicular strikes to the harvester or reaming, which may disturb the integrity of the surrounding walls. To mitigate this risk, it is essential to ensure that the approach chosen allows full exposure and access to the area of the defect, allowing perpendicular entry to the lesion. It is important to utilize a cannulated sizing guide to preserve 1–2 mm of native cartilage and subchondral bone around the periphery and maintain a perpendicular alignment of the initial guide pin and cannulated reamer/harvester relative to the cartilage surface during placement.

There are times when a curette is needed to create clear, smooth, and stable edges of the defect in both the area of the peripheral cartilage and the underlying subchondral bone socket. It is important to not be too aggressive and excavate beyond the dimensions of the allograft implant to ensure a secure press-fit implantation as well as maintain bone-to-bone contact healing. Should a blowout occur or if there are concerns regarding the graft's stability, the application of nonabsorbable headless compression screws, absorbable pins/screws, or fibrin glue may enhance fixation until the graft is fully incorporated.

The use of multiple allografts for exceptionally large or multiple lesions has been shown to have inferior results compared to single-graft transplantations, with reoperation rates and failure rates as high as



Fig. 17. Protrusion and incongruity of autologous plug or allograft may cause graft overload which can lead to eventual failure.

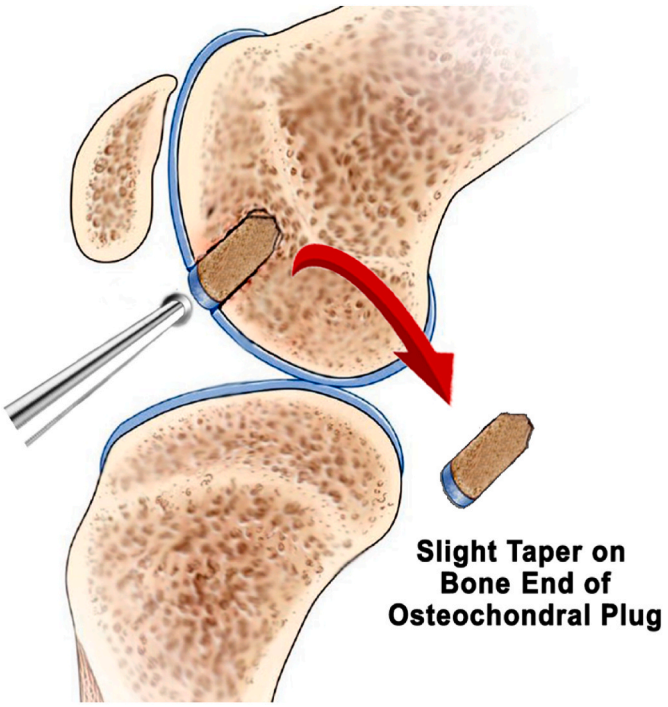


Fig. 18. Tapering graft edges may allow easier insertion of allograft plugs, avoiding the need for forceful implantation which may lead to graft fracture.

44 % and 33 %, respectively.[41] These constructs may lead to articular incongruity and cobblestoning as a result of fibrocartilage filling in gaps between the grafts. For instances where multiple allografts are needed, the use of graft-fixating devices should be used to minimize the risk of loosening.

15.2. Graft overload/incongruity

Graft overload may lead to failure as a result of malalignment of the joint biomechanically or due to incongruity of the donor-recipient interface. Compartment overload secondary to varus or valgus malalignment has been shown to overload grafts, which may ultimately lead to premature graft failure. Unloading and decreasing forces across the joint, on the other hand, has been shown to improve cartilage regeneration. Proper workup and evaluation of the patient's biomechanical alignment prior to surgery may be of great value for proper prognostication and treatment planning. Corrective osteotomies or other unloading/alignment procedures may be warranted in the same setting or prior to cartilage restoration.

An additional contributor to graft overload is graft prominence (Fig. 17). As discussed previously, congruity of the donor graft and recipient site is vital to ensure ideal outcomes. During instances where the graft may sit proud compared to the surrounding native cartilage, decreasing graft protrusion through resection of the graft height and borders may decrease stress across the graft-recipient site interface.[38] Another strategy to prevent articular surface mismatch or graft prominence lies in choosing an anatomic location of the donor that matches the same location as the recipient's chondral lesion and site for implantation. If there is still a mismatch between the same anatomic location of the donor and the recipient, there may be a different area that more closely matches the recipient's chondral morphology.

In terms of surgical technique, ensuring proper orientation of the graft upon implantation is also a step that cannot be overlooked. By making a mark on both the graft and the matching recipient site and aligning the two marks upon implantation, it may help ensure a properly oriented graft. Furthermore, the insertion of the initial guide pin and the cannulated reamer or recipient site harvester and the reaming/harvesting direction must be performed perpendicularly to the articular surface. Lastly, evaluating the congruency of the implanted graft with the native cartilage after implantation can be accomplished by



Fig. 19. At 2 year post-OCA there is slight subsidence of the osteochondral allografts and little integration of graft's subchondral bone to surrounding native bone. This is demonstrated by the persistence of the hypointense line at graft-host interface indicating graft non-union.

observing the recipient site from a perpendicular perspective.

15.3. Allograft fracture

Allograft fracture is another common complication encountered when performing osteochondral allograft (OCA) procedures. Similarly to OATS, it is more common for the graft to sustain damage during intraoperative implantation. Tapering the graft edges (Fig. 18) prior to insertion or slightly dilating the edges of the recipient site can help ensure easier initial insertion of the allograft into the prepared recipient site. The use of digital pressure, when possible, instead of the use of a mallet and tamp to press-fit the graft, can also improve chondrocyte viability. When digital pressure for graft insertion is not possible, it is important to remember that it is the mean impact force during impaction of the graft that is a positive predictor of chondrocyte death rather than the number of hits. Additionally, the use of frozen or fresh-frozen allografts should be avoided, when possible, as they are more susceptible to fissuring or delamination due to chondrocyte death and damage to the extracellular matrix incurred during the freezing process. The use of fresh allograft, whenever possible, can help minimize the risk for graft fracture.

15.4. Graft non-union

Osteochondral allografts can have mean graft survival rates as high as 86.7 %, 78.7 %, 72.8 %, and 67.5 % at 5, 10, 15, and 20 years, respectively.[42] However, when it comes to imperfect graft integration, particularly in the form of subchondral collapse or graft nonunion, these are significant concerns following OCA. Graft non-union usually presents early with persistent pain or discomfort, joint effusion, and mechanical symptoms. Non-union can also be observed in serial radiographs or MRI with the persistence of the graft-host interface (Fig. 19) with no signs of integration or healing. Other signs of non-union are osteophytes, sclerosis, subchondral cyst formation, and narrowing or obliteration of joint space. Other factors can lead to graft failure and non-union. Patients older than 30 years have a 3.5 times higher risk than those younger than 30 years. While having previous surgeries performed on the same knee can also increase graft failure by 2.5 times.[40]

Various strategies have been attempted to enhance the incorporation and healing of the graft with the surrounding native bone, such as combining OCA with marrow-stimulating techniques or utilizing biologics like bone marrow aspirate and platelet rich plasma to promote osseous ingrowth. Additionally, addressing any existing subchondral cysts prior to the placement of the new graft is crucial in mitigating the risk of graft collapse or subsidence.

Bony incorporation of the allograft usually occurs through a long and extensive process of creeping substitution in which cells remodel and repopulate the subchondral bone. It is advisable to prevent return to sport or high-impact activities for as long as one year to minimize graft subsidence, collapse, or failure.

Author's Tips and Tricks to Avoid Complications and Salvage Treatment after Microfracture

Complications in OCA are very similar to those encountered with OATS and mosaicplasty. In cases of salvage procedures for OCA, it is vital to identify the reason for failure, and corrective steps should be done during or before revision. Use of biologics (PRP, BMAC, etc.) may be an option. We recommend complete revision of the entire osteochondral graft site with a repeat OCA using fresh allographs along with additional management to the surrounding cartilage and subchondral bone, as progression or damage may have been incurred since the primary surgery. If failure was seen in the patella, patellofemoral arthroplasty may be an option. If failure was seen in femoral condyles, unicompartmental arthroplasty may also be an additional option. However, if there is progression into diffuse or multi-compartment arthritis, partial or total knee arthroplasties are suggested.

16. Orthiobiologics in cartilage regeneration

In the current era, marked by significant advancements in physiological and pathological insights as well as technological progress in orthobiologics, we see the rise of platelet-rich plasma (PRP), hyaluronic acid (HA), and mesenchymal stem cells (MSCs), now recognized as "medicinal signaling cells." These modalities have become essential components in the treatment repertoire for various musculoskeletal conditions, particularly in cases of chondral damage and arthritis. Their relative simplicity in terms of production, preparation, storage, and administration has facilitated their use not only for primary lesion treatment but also as enhancements in various cartilage reconstruction strategies and in addressing complications.

Platelet-rich plasma (PRP) has emerged as a prominent therapeutic option in orthopaedics. Among the various ortho-biologics utilized in orthopaedic settings, PRP stands out as the most widely employed, particularly in the treatment of joint diseases, as well as lesions affecting cartilage, tendons, muscles, ligaments, and menisci. PRP is defined as the plasma component derived from centrifuged autologous blood, characterized by a platelet concentration that exceeds the baseline level prior to centrifugation. The α-granules within platelets contain a variety of cytokines and growth factors, including epidermal growth factor, vascular endothelial growth factor (VEGF), endothelial cell growth factor, transforming growth factor–β (TGFβ), platelet-derived growth factor (PDGF), insulin-like growth factor (IGF-I, IGF-II), and fibroblast growth factor (FGF). These components play a crucial role in promoting tissue repair through mechanisms such as angiogenesis, neovascularization, enhanced blood supply, cell proliferation, chemotaxis, and differentiation. By isolating and concentrating these vital cytokines and growth factors, the healing process can be significantly improved when applied to injury sites, especially in chondral defects and osteoarthritis.[43]

Hyaluronic acid serves as a vital component of synovial fluid and the cartilage matrix, functioning as a glycosaminoglycan. The administration of exogenous hyaluronic acid aims to replenish the osteoarthritic synovial fluid with a higher concentration of hyaluronic acid, thereby enhancing the viscoelastic properties of the joint and improving its capacity for shock absorption and lubrication. Beyond its mechanical attributes, HA also induces pharmacological modifications. The primary mediators of HA's protective effects are the CD44 receptors. When HA molecules bind to these receptors, there is a notable inhibition of interleukin-1 beta (IL-1β) expression, which subsequently leads to a decrease in the production of matrix metalloproteinases (MMPs) 1, 2, 3, 9, and 13, thus hindering the activity of catabolic enzymes. Additionally, the interaction of exogenous HA with CD44 receptors can activate intracellular pathways that facilitate proliferation, differentiation, migration, and the breakdown of endogenous HA. The affinity of HA for CD44 receptors is a key factor driving its biological effects within the body.[44]

The strategic combination of PRP and hyaluronic acid aims to merge the therapeutic effects of both agents, with the goal of maximizing and extending their efficacy in pain relief and functional improvement. PRP, in fact, does not adversely affect the mechanical, viscous, or elastic properties of hyaluronic acid. Instead, HA functions as a bioactive scaffold, facilitating the attachment of platelets and the gradual release of growth factors.[44]

Medicinal signaling cells (MSCs), commonly derived from bone marrow aspirate (BMA and BMAC) and microfragmented adipose tissue, serve primarily as vital trophic mediators, rather than as progenitor cells, marking a significant development in the realm of regenerative medicine. MSCs have an extensive role in shaping the local cellular environment through the release of bioactive molecules. This expanded insight highlights the paracrine activities of MSCs, which include immune modulation, anti-inflammatory effects, facilitation of angiogenesis, and the activation of local repair processes, thereby emphasizing their therapeutic potential that goes beyond mere differentiation.

Recognizing MSCs as trophic mediators accentuates their ability to cultivate an optimal microenvironment for healing and regeneration, thus establishing their importance in addressing a variety of musculoskeletal disorders. The advantages of microfragmented adipose tissue as a source of MSCs are underscored by its ease of collection, minimal invasiveness, and substantial cell yield. The integration of bone marrow aspirate and adipose-derived MSCs, either as a standalone treatment or in combination with other cartilage repair strategies like debridement, microfracture, and biologic scaffolds, can effectively improve functional performance, clinical results, and pain management.[45]

17. General risk factors that affect cartilage reconstruction outcomes

There are many various patient factors that may increase the incidence of complications or failure, such as age, smoking, diabetes, and obesity. Biomechanical factors are also very important, especially when related to forces across the joint, which are typically exacerbated by joint malalignment, meniscus injury, ligament instability, and patellar maltracking.

17.1. Patient age

Age can generally be a risk factor for diffuse degenerative arthritis; however, in terms of focal chondral defects, it is the reduction in the functional capacity of chondrocytes that may be of greatest importance. Chondrocyte senescence can lead to declining mitochondrial function, decreased proliferative potential, decreased collagen deposition, decreased responsiveness to anabolic mechanical stimuli and to growth factors, and decreased synthetic and mitotic activity. Because of the increased number of complications and failures in older patients undergoing cartilage reconstruction techniques, many guidelines have suggested reserving these procedures for younger populations; however, HA-BMAC techniques have been effective in populations older than 45 years of age.[6–9,12,16,22,37]

17.2. Smoking

Smoking not only is a risk factor for various cancers, cardiovascular, and respiratory diseases, but has also been shown to affect orthopaedic and musculoskeletal conditions. Osteoarthritis, degenerative disc disease, tendon and ligament health, fracture and wound healing, as well as postoperative outcomes have all been known to have worse outcomes, particularly in smokers. These deleterious factors can be associated with the many different gases and chemicals released from cigarette smoke. Nicotine can directly affect physiologic healing through increased platelet aggregation, decreased prostacyclin levels, and decreased function of fibroblasts, macrophages, and red blood cells.[46]

17.3. Diabetes mellitus

It has been well established that diabetes mellitus has been a common enemy for orthopaedic surgeons and clinicians in terms of wound and fracture healing. These outcomes are typically consequences related to changes in the microvascular environment secondary to deficient angiogenic processes and changes to pericyte function. We have also encountered diabetes mellitus as a risk factor that predisposes patients to musculoskeletal diseases and worsens postoperative outcomes. These poor outcomes have caused some apprehension in performing cartilage reconstruction techniques in these populations.[37]

17.4. Obesity

Obesity (BMI $\geq$30 kg/m^2) is a risk factor for osteoarthritis incidence and progression as well as cartilage turnover due to increased joint reaction forces across the joint, the base of defects, and the cartilage rim, which may lead to decreased containment in focal lesions. Consequently, any newly regenerated cartilage of obese patients may be highly vulnerable to breakdown and failure. Studies have demonstrated worse functional outcomes, decreased activities of daily living scores, and decreased cartilage defect fill after microfracture in patients with BMI $\geq$30 kg/m^2.[47]

17.5. Joint malalignment

Varus and valgus malalignment can cause excessive loading and strain on articular cartilage in the medial and lateral compartments, respectively. These increased loads can eventually result in cartilage changes such as degenerative osteoarthritis or in the form of focal chondral lesions.[16] In relation to cartilage reconstruction outcomes, malalignment and excessive loading on a single compartment may lead to breakdown of regenerated cartilage and eventual treatment failure. For this reason, alignment correction procedures such as osteotomies to correct the biomechanical axis to a normal alignment or to simply unload an injured compartment are imperative prior to any cartilage procedure.

17.6. Joint instability secondary to meniscal or ligamentous injury

Previous injuries to joint stability, such as meniscal or ligamentous injuries, may greatly affect the reaction forces across a joint upon weight-bearing or movement. It has been well established that there are increased joint stresses in meniscus-deficient knees secondary to untreated injury or previous meniscectomy, which is a positive risk factor for degenerative joint disease. In patients with simple, easily repairable, or very small meniscus injuries, outcomes of cartilage repair may not be affected significantly if repair or a minor meniscectomy is done. However, if there are extensive, complex, unrepairable, or large meniscal lesions, concomitant meniscal and cartilage management may not be of benefit and may be a harbinger of worse outcomes in the future. In these cases, there may be indications favoring arthroplasty over cartilage preservation procedures.

Ligament injuries may be a source or exacerbating factor in chondral lesions. Medial collateral or lateral collateral ligament injury and instability may cause valgus or varus forces across the knee, increasing loading forces on a single compartment. Anterior cruciate ligament injury may also lead to cartilage damage due to the translational and rotational instability of the knee.

17.7. Patellar maltracking and instability

Patellar maltracking or instability is often related to abnormal and increased patellofemoral joint forces. Maltracking, especially lateral tracking of the patella on the trochlea as a result of laxity or injury to the supporting structures of the patella, can lead to cartilage damage on both the patella and trochlea. When encountering these patients, it may be wise to address the instability and maltracking problem first, prior to performing any cartilage repair procedures. By correcting patellofemoral instability, the abnormal loads that originally caused cartilage degeneration, pain, or other symptoms may be eliminated, and patients may find relief. It is after correction and the persistence of mechanical pain that cartilage repair procedures should be considered.

Not only do patient-modifiable factors affect outcomes, but characteristics of the focal defect(s) themselves may play an important role in the decision making on what type of procedure to do and if cartilage reconstruction is possible.

17.8. Defect size

The size of the focal defect may be one of the most important factors in determining what type of management is warranted. In cases of smaller lesions ($<$2 cm^2), marrow-stimulating techniques may be

enough to return the patient to their premorbid state with little to no complication or failures. However, in larger lesions, defect size may determine how high of a success rate is associated with each of the other cartilage regeneration techniques available or if the lesion is not salvageable and an arthroplasty is necessary. Typically, smaller lesions can contain and protect the base of the defect from load during weightbearing as the cartilage rim is still able to make contact with the cartilage of the opposing bone in the joint. These lesions may be without symptoms and slowly progress. While larger lesions, on the other hand, may not be able to prevent collision of the opposing surface onto the exposed bone and thinned-out cartilage. Lack of containment can increase the progression of the focal lesion size as the cartilage on the peripheral borders is subjected to increased loads. Subchondral changes can also occur as the exposed bone devoid of overlying cartilage is directly subjected to joint forces.

17.9. Defect location

The location of focal cartilage lesions is another important factor that may be a key factor in determining the success rates of cartilage regeneration techniques. Focal lesions are most commonly found in the femoral condyles and trochlea, while lesions on the patella are encountered less frequently. There has been great success in treating condylar lesions with high rates of improved outcomes and high satisfaction; however, successful outcomes from treatment of the patellofemoral joint using various cartilage techniques have been more difficult to achieve.[7,40] Lesions on the patella and those involving the patellofemoral joint are challenging to treat, as these surfaces are subject to high joint reaction forces and high joint movement, which may exacerbate symptoms and joint changes associated with patellar maltracking, instability, and overload. The complex joint topography and shape, composed mainly of the patellar medial, lateral, and odd facets, patellar ridge, and femoral trochlea, also make cartilage repair problematic. The combination of these factors can hinder the differentiation of chondrocytes and regeneration of fibro- or hyaline cartilage. Frequently, patellofemoral lesions secondary to patellar maltracking may require other procedures such as tibial tubercle anteromedialization (Elmslie--Trillat-Fulkerson techniques).

17.10. Single vs. multiple defects

It is thought that single articular defects are commonly a result of trauma, while multiple defects are typically a consequence of degenerative pathologies or repetitive minor trauma. When there are bipolar lesions, or "kissing lesions," lesions that are on the opposing cartilage adjacent to a chondral defect, there is increased compressive strain on the cartilage of the lesion and peripheral borders, which can lead to increased cartilage abrasions, fragmentation, and fissuring. This is one of the factors that has led to inferior functional and clinical outcomes in many different cartilage regeneration procedures.[48] Cartilage regeneration techniques have been shown to improve functional and clinical outcomes in patients with single and multiple defects, kissing or located in different areas; however, in the multiple lesion subgroups, improvement was not as significant compared to those with single lesions. Treatment failures also occur at a higher rate in populations with multiple lesions.[48]

17.11. Defect chronicity

The chronicity of chondral lesions can affect outcomes of cartilage regeneration techniques. Delay of surgical treatment from the onset of symptoms can be a factor that may affect the overall amount and quality of regenerated cartilage. This may be due to a delay in the referral health care system or apprehension of patients to undergo surgery, often opting to delay and maximize conservative management. It has been shown that a shorter time from symptom onset to treatment afforded patients improved clinical and functional outcomes.[49] The mechanism behind this phenomenon could be dependent on subchondral progenitor cells and their ability to generate a repair response, similar to endochondral ossification. This emphasizes the importance of maintaining healthy and viable subchondral bone to ensure a favorable environment for cartilage regeneration. With more chronic lesions, damage may not simply be limited to the overlying cartilage but may also cause injury and degeneration to the underlying subchondral bone. This can be an explanation for improved outcomes of cartilage regeneration in acute over chronic defects.[49]

17.12. Subchondral bone status

The subchondral bone cannot be ignored or overlooked when dealing with chondral lesions. Subchondral bone commonly refers to the osseous layer below hyaline cartilage and the cement line, typically divided into two parts – the subchondral bone plate (SBP) and subchondral bone trabeculae (SBT). In the SBP, many vessels and nerve fibers are present, while the SBT is an area where cancellous bony components undergo continuous remodeling. It is this subchondral bone that provides mechanical and nutritional support for cartilage health and regeneration. The cartilage layer has been shown to penetrate the underlying calcified layer through channels and extend into the subchondral bone plate, demonstrating direct communication between chondrocytes, osteoclasts, and osteocytes. These cell interactions, coupled with MSCs found in the underlying bone, promote matrix production and chondrocyte proliferation via trophic mechanisms.

In chondral repair, the subchondral bone should be assessed for extensive injury or degenerative changes. Without support from a viable subchondral bed, cartilage repair efforts have very high chances for failure. Due to the importance of the subchondral bone, when performing various cartilage regeneration techniques, especially during preparation of the lesion bed, debridement must be done in a very careful manner, only to remove the calcified layer while respecting and maintaining the underlying subchondral bone. Even though marrow-stimulating techniques may not be considered a "bridge-burning" technique that may prevent the possibility of performing other cartilage repair procedures at a later time, there may be concerns about the quality of regenerated tissue as well as clinical and functional outcomes in those who had marrow-stimulating techniques done prior compared to those with "virgin" lesions.

18. When all Else Fails … arthroplasty May be the last Resort

As we know, arthroplasty in the young and active with cartilage injuries and defects has a high risk for implant wear-related complications and the need for multiple revision surgeries over time. To avoid these complications, cartilage restoration techniques have been developed and have shown to be successful in preventing or delaying the need for joint replacement. As discussed in this chapter, there are times when, despite the best effort by the surgeon to achieve the best symptom-free, function-restoring outcomes, complications, failures, or the sometimes-unavoidable progression of cartilage degeneration and osteoarthritis may occur.

During these times, arthroplasty (total, partial, or unicompartmental) may be the last pain-relieving solution. Performing cartilage reconstruction prior to any arthroplasty procedure does not burn any bridges in terms of the possibility of arthroplasty in the future. Arthroplasty outcomes following prior knee surgeries, including cartilage restorative procedures, have shown to improve clinical and functional outcomes when comparing pre-arthroplasty and post-arthroplasty states. However, when comparing patients with prior knee surgery to controls of those who had not undergone prior procedures, outcomes are not as robust or substantial.[50] The reason why there are inferior outcomes in those with previous knee surgeries still has not been explained. The explanation may lie in differences in patients who undergo natural

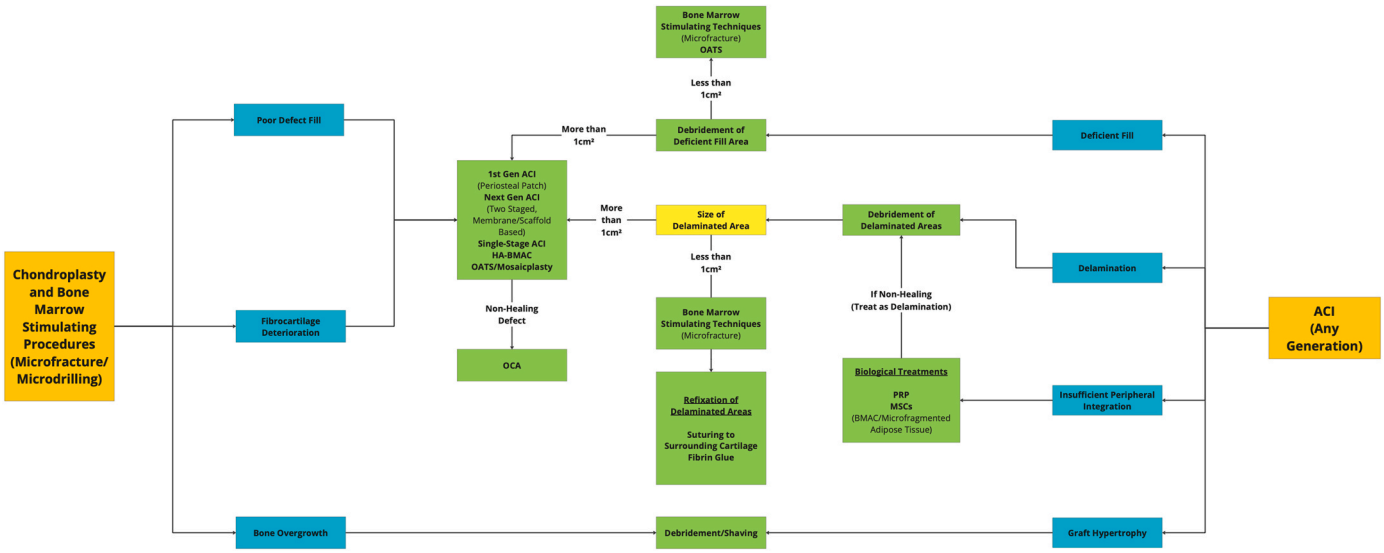


Fig. 20. Gobbi-Acosta Algorithm on managing complications encountered after Chondroplasty, Bone Marrow Stimulating Procedures, and ACI.

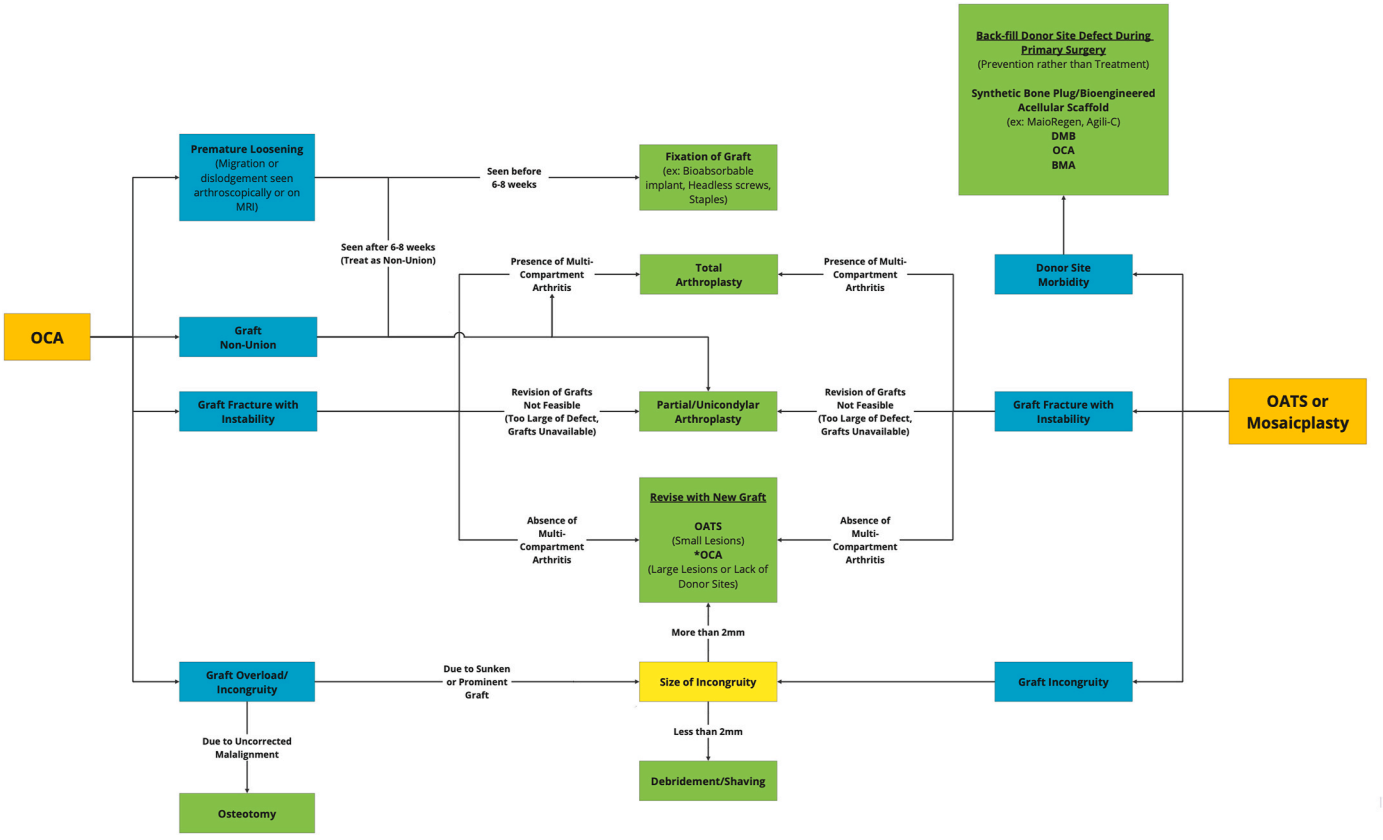


Fig. 21. Gobbi-Acosta Algorithm on managing complications encountered after OATS, Mosaicplasty, and OCA.
*In cases of OCA graft non-union in the absence of multi-compartment arthritis, we suggest revising with a new allograft over the use of an autograft.

cartilage degeneration versus those who have cartilage lesions secondary to trauma, instability, and malalignment. Another explanation may be related to possible subchondral bone changes after cartilage procedures.

19. Gobbi-Acosta Algorithm for managing cartilage reconstruction complications

To provide a straightforward approach to addressing common complications in cartilage reconstruction, we propose the use of these algorithms. They are intended to establish a cohesive framework that synthesizes the various reconstruction techniques that have been examined. We believe that these algorithms will support effective

decision-making and surgical planning in the context of salvaging unsuccessful cartilage reconstruction (Figs. 20 and 21).

20. Conclusion

Chondral lesions are sometimes difficult and challenging depending on size, location, and chronicity. In cartilage reconstruction, our aim is to employ techniques to help save the joint, regenerate the lost or diseased cartilage, and hopefully prevent or delay the progression of osteoarthritis and the need for arthroplasty. As patient and lesion characteristics differ from case to case, there is no single surgical strategy to treat all chondral lesions. With our growing knowledge and extensive research, marrow-stimulating procedures like microfracture and microdrilling, as well as techniques that aim to regenerate hyaline cartilage like autologous chondrocyte implantation, autologous matrix-induced chondrogenesis, hyaluronic acid-based scaffolds combined with MSCs, osteochondral autograft transplantation/mosaicplasty, and osteochondral allograft transplantation have become our workhorses in tackling this ever-growing problem. The importance of patient selection cannot be stressed enough, as compliance with rehabilitation and return-to-play protocols and timelines is essential, as well as finding patients who have no biomechanical malalignment or concomitant meniscal or ligamentous issues that need to be managed prior to surgery. However, despite all our attempts to ensure the best outcomes for our patients, complications are sometimes unavoidable. Thus, being able to recognize possible complications, utilize strategies to prevent these complications, as well as knowing how to manage complications when encountered, is important for any orthopaedic surgeon.

Patient consent

As this is a narrative review discussing historical, current, and future perspectives regarding cartilage reconstruction and the complications, no informed consent is needed to perform this study.

Ethical clearance

This study adheres to the ethical considerations and ethical principles set out in relevant guidelines, including the Declaration of Helsinki, WHO guidelines, International Conference on Harmonization-Good Clinical Practice, and National Ethics Guidelines for Health Research.

Author's statements

The article involves findings and conclusions derived by the authors with no knowledge or involvement in the study design, funding, execution, or manuscript preparation by any other entity or party.

Source of funding

No outside funders had any role in study design, data collection and analysis, the decision to publish, or preparation of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

The authors would like to thank Vijay Kumar Jain as well as the other editors and anonymous reviewers for their comments, insightful suggestions, and careful reading of the manuscript.

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