4 "A Unifying Theory" Treatment Algorithm for Cartilage Defects

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Introduction

Articular cartilage defects are encountered in approximately 60 % of all knee arthroscopies [1–3]. While the majority of defects are clinically silent, those that are symptomatic may cause pain and disability approaching that seen in patients awaiting knee replacement for advanced osteoarthritis [4]. The spectrum of cartilage disease ranges from small unipolar focal defects in otherwise healthy joints to large bipolar defects and even to generalized chondropenia that some consider the beginning of osteoarthritis. Appropriate treatment of cartilage defects therefore requires knowledge of chondral pathology as well as intricate knowledge of all available cartilage repair techniques and their limitations. Furthermore, while many cartilage defects have an identifiable etiology, for example, acute trauma from patellar dislocation, or repetitive overload after prior meniscectomy, the majority do not. As Engen pointed out, the majority of articular cartilage lesions presenting to a cartilage specialist are not the straightforward lesions of randomized controlled trials, but rather have comorbidities, which include malalignment and meniscal and ligamentous deficiency [5]. Unless corrected, these factors will likely compromise the outcome of any cartilage repair procedure. Therefore, successful biologic joint reconstruction requires treatment of all comorbidities as well as the cartilage defect in a concurrent or staged fashion. Furthermore it is critical to match and assess the treatment approach to the specific demands of the patient. In some cases unrealistic demands may have to be pointed out carefully in order to avoid disappointing results after treatment. This chapter will detail the work-up of cartilage defects, discuss patient- and defect-specific factors that influence treatment decisions, and illustrate different approaches based upon lesion and patient characteristics.

Epidemiology of Cartilage Defects

Articular cartilage damage is common, being encountered in more than half of knee arthroscopies [1–3]. It exhibits a wide spectrum of severity and etiology, such as acute traumatic injuries; chronic degenerative microtrauma; developmental defects, for example, osteochondritis dissecans (OCD); or acquired metabolic factors such as avascular necrosis (AVN). However, given the

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comparatively low rate of cartilage procedures, the majority of cartilage defects are either asymptomatic or a problem that surgeons choose not to treat. The natural history of cartilage defects remains controversial: some suggest that the mere presence of a lesion does not seem to lead to an increase in OA rate over time [6], while others have demonstrated that once a cartilage lesion is detected, there is more rapid cartilage loss on MRI [7–9], progression of radiographic OA [10], and lower functional outcome scores [11]. Although OCD lesions are a distinct entity, removal of a loose OCD fragment without additional treatment of the lesion effectively creates a cartilage defect. While Shelbourne reported that in the intermediate term, results are good with fragment removal, he was not able to identify which patients were going to develop joint space narrowing [11] at a later stage. Long-term follow-up studies have demonstrated the development of radiographic OA in approximately 80% of patients after 10 years [12–14].

Overall, cartilage defects are most commonly located in the femoral condyles (43–58 %), followed by the patella (11–36 %) and the trochlea (6–16 %) [1–3]. When classic osteoarthritis is excluded, the majority of defects are focal chondral defects (68 %), 3 % are OCD lesions, and 29 % were classified as degenerative defects [15]. Almost 90 % of defects are smaller than 4 cm^2 [1].

Diagnosis of Cartilage Defects

Patients with symptomatic cartilage defects typically present with activity-related joint pain and swelling. Larger lesions can also cause catching or locking. Defects on the femoral condyles result in pain at or close to the joint line with impact activities such as running or descending stairs. Patellofemoral defects present with anterior knee pain during stair-climbing, squatting, prolonged sitting in a flexed position, or getting up from a chair. Unfortunately, none of these complaints are pathognomonic for cartilage defects and frequently occur with meniscal tears, muscle/soft tissue imbalance, and patellofemoral imbalance regardless whether the patient has intact cartilage, a focal chondral defect, or osteoarthritis. The mechanism and extent of prior injuries and previous surgery influence the diagnosis and should be explored. Reading previous operative reports can provide important clues; however, they unfortunately rarely document cartilage pathology in a systematic manner using either common grading systems and/or recording measurements made with an intraarticular ruler.

Physical Findings

Articular cartilage defects do not exhibit specific physical exam findings that would clearly distinguish them from meniscal tears at the tibiofemoral articulation or anterior knee pain at the patellofemoral compartment. As an added complexity, there is no agreement as to when the gray area of advanced chondrosis should be termed early osteoarthritis. The examination begins with visual inspection, which includes functional assessment of the musculature, alignment, and gait. Any significant findings can point the examiner toward further underlying pathologies that may have a significant impact on the chosen treatment options, for example, malalignment or ligament insufficiency. The soft tissues are inspected for muscle atrophy and preexisting incisions that might dictate or preclude certain surgical approaches. Patients typically present with varying degrees of swelling and joint effusion. Range of motion is usually preserved unless more advanced changes or displaced osteochondral fragments are present. Mechanical symptoms such as catching or clicking on range-of-motion examination and patellar manipulation are nonspecific but can be associated with larger defects, particularly in the patellofemoral joint. After knee specific factors are identified, functional impairments are assessed by completing a full knee, limb, and patient evaluation.

Imaging

Cartilage imaging is discussed in detail in Chap. 3; a brief summary is as follows.

Standard radiographs do not directly depict chondral damage, unless associated with bone loss

or joint space narrowing. The main role of radiographs in the context of cartilage repair is therefore the assessment of associated malalignment as well as to rule out more advanced degenerative joint disease that would preclude cartilage repair. A standard knee series should be obtained, including weight-bearing anteroposterior views in full extension and posterior-anterior views in flexion (Rosenberg) [16], as close to true lateral as possible, and patellofemoral low flexion angle views such as merchant views, as well as a double-leg stance weight-bearing and full-length hip-to-ankle alignment radiograph. Sizing radiographs with specific radiopaque sphere (magnification) markers are required to calculate joint space, as well as meniscal or osteochondral allograft transplant size.

High-resolution (1.5 T and greater) MRI with specific cartilage-sensitive sequences is the gold standard to evaluate cartilage defects [17].

CT arthrography is often used for the evaluation of cartilage defects associated with abnormalities in the subchondral bone, such as OCD lesions, collapsed AVN, or subchondral cysts and sclerotic subchondral bone after prior marrow stimulation—or when hardware distorts the MRI images. Trochlear dysplasia, patellar subluxation and tilt, as well as the tibial-tubercle to trochlear groove/posterior cruciate ligament (TT-TG and TT-PCL) distances can be assessed through cross-sectional imaging modalities such as MRI and CT.

Indications and Contraindications for Cartilage Repair

Most cartilage defects are asymptomatic. As a result, careful assessment of the patient and joint are crucial to correctly identify the cartilage defect as the source of pain. Depending on patient age, symptom level, and defect characteristics, a conservative treatment program in conjunction with activity modification and weight normalization is the first line of treatment. "Older" patients who are eligible for arthroplasty as an alternative to cartilage restoration may benefit from a trial of injection therapy with steroids and/or viscosupplementation and an unloader brace if malaligned. While it is difficult to justify an invasive procedure in relatively well-functioning individuals, the benefit of conservative treatment for very young patients with large defects that can be expected to progress is controversial. If all factors seem to line up such as in the patient with focal unicompartmental pain that corresponds to an MRI cartilage lesion and a subadjacent MRI bone marrow focal lesion, it is very likely that treatment is indicated with a high likelihood of success. However, even in this patient, extensive counseling about the relatively long recovery period after cartilage repair is particularly important to avoid unrealistic expectations and disappointment.

Patients who smoke, are obese (BMI > 35), and have inflammatory conditions or unreasonable expectations are not good candidates and in general are advised not to have cartilage repair surgery [18]. In regard to expectations, patients generally should experience significant symptoms during activities of daily living, rather than just during specific activities, in particular athletics. The exception to this would be a young patient with a large defect that has considerable potential for further degeneration, who can be considered for cartilage repair even in the absence of severe symptoms [19, 20]. Advanced chondral changes (> 50 % joint space narrowing) are considered a contraindication to cartilage repair in most situations. Exceptions may be the very young patients that have intolerable symptoms and no other options in which case a cartilage repair procedure may be offered as a salvage procedure to buy time.

Factors Affecting the Treatment Algorithm (Table 4.1)

Table 4.1 Overview of comorbidities

The patient	Systemic illnesses (inflammation) Mental outlook (depression/unrealistic expectations) Obesity Genetic predisposition to OA
The limb	Limb muscular debilitation (core to floor) Scar (skin, capsular, flexion/extension contractures) Malalignment Coronal plane (varus/valgus) Axial plane (femoral anteversion/tibial torsion) Sagittal plane (tibial slope/recurvatum)
The knee	Meniscal deficiency Ligamentous deficiency

Patient-Specific Factors Influencing Treatment Decisions

Multiple factors have been identified that influence outcomes after cartilage repair, some due to certain characteristics of the patient, such as patient age, weight, smoking status, low scores in health-related qualify of life as measured by WOMAC scores, chronic unrelated pain, or high likelihood of pain catastrophizing [21, 22]. Like other surgical interventions, a happy preoperative patient has a higher probability of being happy postoperatively than a preoperatively unhappy patient. This is particularly true for pain and is the reason why in most randomized clinical trials for cartilage products, pain scores between 3 and 7 on the visual analog scale (VAS), or 30 to ~70 on the knee osteoarthritis outcomes score subscale for pain(KOOS-pain) are usually required for eligibility. Patients with much less pain and patients with chronically higher pain assessments are less than ideal candidates with regard to postoperative satisfaction and overall success.

Generally speaking, age has a negative correlation with outcomes, but it appears to affect marrow stimulation techniques more so than other procedures: many studies have investigated patient age in subanalyses of outcomes after microfracture. Patients older than 30–40 years did significantly worse than younger patients in most studies [23–28]. A similar correlation was found with OAT [25]. The literature is more controversial for autologous chondrocyte implantation (ACI), where some studies have demonstrated age correlation [29], while others did not [30, 31]. Basic science studies, however, suggest that chondrocytes from older donors (> 40 years of age) have lower proteoglycan and collagen production [32]. Little is known about age effects in osteochondral allograft transplantation, since donor age is generally quite young (< 30–40 years) and only macroscopically intact specimens are processed. Regarding the effect of recipient age, the older patients can be expected to have a higher percentage of degenerative, rather than acute traumatic, lesions; the latter has demonstrated better outcomes for most types of cartilage repair [29, 31, 33]. Most studies evaluating the influence of weight on outcomes have demonstrated a negative correlation, starting with BMI (body mass index) of greater than 25–30 kg/m^2. On the other hand, some authors have found little consequences of a BMI even up to 35 in patients undergoing cell-based cartilage procedures [34, 35]; a comparable BMI seems to adversely affect the results of patients undergoing microfracture treatment [26, 27]. Nicotine use after ACI is strongly associated with a higher rate of graft failure and lower functional outcomes [18]. Similar to most surgical interventions, worker's compensation patients typically have inferior clinical outcomes [36, 37].

Defect-Specific Factors Influencing Treatment Decisions

Certain characteristics of the cartilage defect have been found to influence the outcomes, such as depth, size, location, chronicity, and associated bony abnormalities. Defect depth and size are more often described by the use of the modified Outerbridge classification, rather than the traditional Outerbridge (developed to describe patellar lesions and combined both depth and area), or the more internationally accepted International Cartilage Repair Society (ICRS) classifications (Table 4.2, Fig. 4.1). For accurate communication, the defect size should also be measured in two planes—surface area and depth. When applied to osteochondral defects, the overall lesion depth (bone and cartilage) is reported with the bony portion of the defect measured from the adjacent subchondral bone, as the independent depth of bone involvement is important.

Tibiofemoral Compartment

Defect size greatly influences the choice of cartilage repair procedure for a defect in the tibiofemoral compartment. Microfracture and osteochondral autograft transfer (OAT) have demonstrated good and excellent results in 60–80 % of patients for femoral condyle lesions less than 2–4 cm^2 [25, 27, 33, 38–41]. These

Table 4.2 Classification of cartilage defects

Grade of lesion	Outerbridge classification	ICRS classification (with subclassifications)
Grade 0	Normal cartilage	Normal cartilage
Grade 1	Cartilage with softening and swelling	(a) Softening or fibrillations
		(b) Superficial fissuring
Grade 2	Partial-thickness defect with fissures on the surface that do not reach subchondral bone or exceed 1.5 cm in diameter	Less than one-half cartilage depth
Grade 3	Fissuring to the level of subchondral bone in an area with a diameter more than 1.5 cm	More than one-half cartilage depth and
		(a) not to the calcified layer
		(b) to the calcified layer
		(c) to the subchondral bone
		(d) blisters
Grade 4	Exposed subchondral bone	Osteochondral lesion violating the subchondral plate

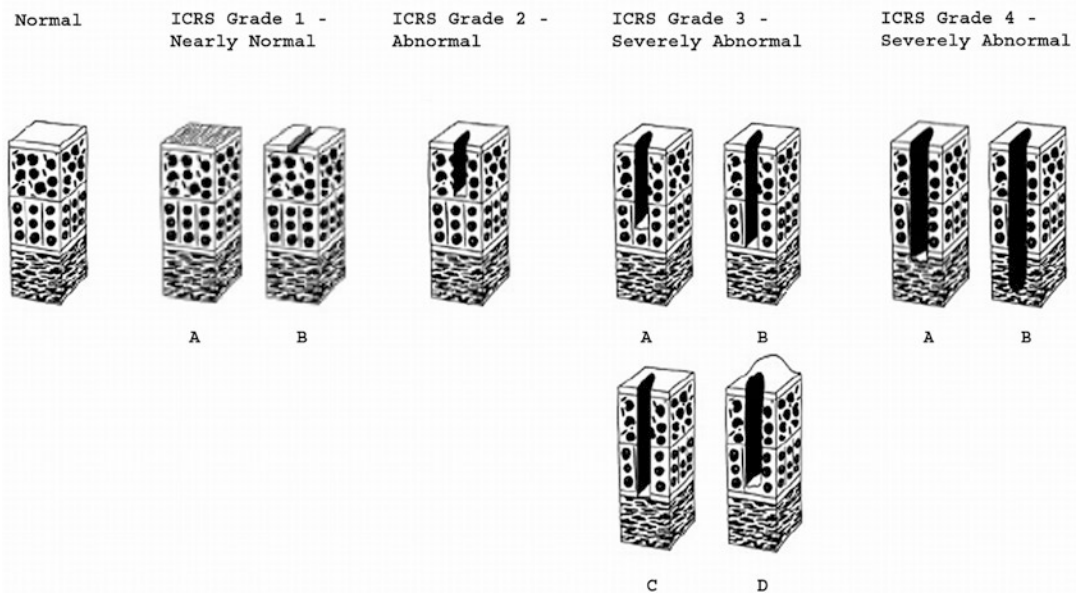

Fig. 4.1 Illustration of the International Cartilage Restoration Society (ICRS) classification system

techniques are reported to be less effective in larger lesions: a randomized controlled trial (RCT) of microfracture versus ACI reported overall similar result outcomes [24]. However, with subset analysis, larger defects (4 cm^2) treated with microfracture did significantly worse, while ACI showed no correlation with size. Another RCT specifically compared defects larger than 4 cm^2, concluding that ACI had better outcomes than microfracture in these large lesions [42]. ACI also demonstrated better histological outcomes than microfracture in smaller defects (average, 2.6 cm^2) although overall clinical outcomes were not substantially different [43, 44]. Osteochondral allograft transplantation has demonstrated comparable efficacy to ACI in the femoral condyles, with long-term outcomes reported as more than 95 % survival at 5 years, which steadily decreases to 65 % at 15 years [45]. Its main advantages lie in the transplantation of mature hyaline cartilage, without the need for tissue maturation, as well as it being a true osteochondral treatment, with restoration of both articular surface and subchondral bone.

Given the decreased efficacy of the less invasive procedures (marrow stimulation and OAT), larger defects therefore appear as the primary indication for ACI and osteochondral allografts, which have produced good and excellent results in over 70 % of patients in this smaller size range [29, 46–55].

Patellofemoral Compartment

All cartilage repair procedures have demonstrated worse outcomes in the patellofemoral (PF) joint, which is multifactorial: complex anatomy, unique biomechanics, profound muscle weakness and imbalance, as well as less familiarity with treatment applications in this compartment by some surgeons. Furthermore one has to take into account that many patients with patellofemoral defects have a long-standing history of patellofemoral instability that can lead to profound anxiety and apprehension, which needs to be overcome postoperatively and often puts these patients at a disadvantage from the outset. As cartilage repair techniques appear more sensitive to location than others, there is a growing consensus that microfracture should be used cautiously in the patellofemoral compartment. Kreuz found declining clinical scores 18–36 months after microfracture in the PF compartment [56]. The outcomes of OAT in the PF compartment are inconsistent: one group reported only minimally reduced outcomes compared with the femoral condyle [40]; others found almost universal failure of OAT in the patella [47], while another report showed good results in the patella [57]. The use of osteochondral allografts in the PF compartment results in 60 % good and excellent outcomes with monopolar grafts surviving better than bipolar grafts [58]. While the initial report on ACI in the PF compartment reported good or excellent results in only two of seven patients (28 %) [48], with better understanding and optimization of PF biomechanics, PF ACI has shown successful outcomes in over 80 % of patients [59–62]. Even when patellar ACI was an off-label indication, it was the procedure of choice in the patellofemoral compartment when bone was not compromised. Now that Matrix ACI (MACI) is approved in the USA for all compartments of the knee, availability should increase.

Articular Comorbidities Influencing Treatment Decisions

Several chapters are dedicated to the topic of articular comorbidities in greater detail. However, the recognition and correction of malalignment, maltracking, and meniscal and ligamentous deficiency is of utmost importance for the success of any cartilage repair procedure.

Treatment Recommendations

Treatment of Small Femoral Condyle Defects (< 2–4 cm²)

Microfracture and OAT represent the primary treatment options for smaller defects on the femoral condyles. While microfracture results in the formation of a fibrocartilaginous repair tissue, which is mechanically inferior to hyaline cartilage, it appears adequate to fill smaller defects. OAT transfers high-quality, mature hyaline cartilage into the defect but remains limited by donor-site availability. While the size of the maximal donor site with OAT is controversial, the harvest of 1–2 10mm diameter grafts appears safe and provides sufficient material to fill a lesion of 1–2 cm^2 size. The decision between the two procedures is based on surgeon preference and familiarity with the techniques, patient demand (impact activity as well as time to return to full function), and associated bone loss. Higher-demand patients, such as athletes, have shown better functional outcomes and histology as well as return to play with OAT when compared with microfracture (93 % vs. 52 %, respectively) [25], yet Steadman reported good outcomes in professional athletes, specifically skiers, in a case series [63]. However, in light of the majority of literature, it is suggested that OAT should be considered for lesions in high-demand athletes that are amenable to treatment with one or two plugs and

for osteochondral defects; microfracture may be better suited for defects with little or no bone loss in lower-demand patients recognizing the unique applications within the occupational demands of the professional athlete.

Particulated cartilage allograft (DeNovo NT, Zimmer, Warsaw) has emerged as a new treatment alternative for chondral defects in this size range. Clinical data regarding its clinical efficacy are limited but appear promising [64–66].

Treatment of large Femoral Condyle Defects (> 2–4 cm^2)

No RCT have compared the outcomes of ACI and osteochondral allograft for the treatment of larger defects. The decision between these two procedures is guided primarily by the condition of the subchondral bone and secondarily by the number and location of defects. Generally speaking, ACI is a surface procedure that requires intact subchondral bone as a foundation, while osteochondral allograft transplantation replaces the entire osteochondral unit. When ACI fails, a surface defect remains much like the initial lesion. Allografts tend to fail in the subchondral bone more so than in the cartilage, thereby often resulting in an osteochondral defect. In light of this, focal defects limited to the articular cartilage itself are the main indication for ACI. True osteochondral deficiencies, or cartilage defects with associated subchondral bone abnormalities, such as extensive bone marrow edema, subchondral cysts, or intralesional osteophytes, should be considered for allograft transplantation to replace the entire affected osteochondral unit. If allografts are not available, a technique known as "sandwich" ACI can be employed; sandwich ACI involves concurrent subchondral bone grafting that is sealed with a collagen membrane to restore the subchondral bone plate, and in the same sitting, a traditional ACI or MACI is performed overtop of the bone grafted area [67].

Location of the defect is a secondary factor to consider: defects in the femoral condyles are treated as mentioned in the preceding paragraph. Occasionally, however, patients present with multiple defects, for example, an osteochondral defect in the medial femoral condyle and a cartilage defect in the patella. Even though an allograft would be preferable for the osteochondral defect, overall, ACI might be considered, since it allows treatment of the femoral condyle (through sandwich ACI) as well as the patellar lesion, which would be more difficult with an allograft. Furthermore, there is concern that the more OC allograft tissue transplanted, the higher a likelihood for a humoral immune response to surface antigens. There is some evidence that it is antigenic load that may play a role in the success and failure of bulk osteochondral allografts [68].

While most cartilage repair procedures have less optimal outcomes reported when used in the PF compartment than in the femoral condyle, ACI appears to be relatively unaffected by location. Very small defects, especially when in the trochlea, could be considered for microfracture or OAT, and extensive lesions may be best managed with OC allograft. Correction of PF mechanics, contact area, and stability are especially critical, and further information can be found in Chap. 7.

Treatment of OCD Lesions

Symptomatic unstable osteochondritis dissecans (OCD) lesions should be repaired with arthroscopic or open reduction and internal fixation (A/ORIF) whenever possible [69] since it appears to result in better outcomes than cartilage repair, specifically when compared with osteochondral allograft transplantation [70]. Ideally, compression screws should be utilized; metal and resorbable devices are available and have specific advantages and disadvantages. Metal implants ideally should be removed after bony healing and before return to full activities. Resorbable devices remain for years and do have the potential to damage the opposing articular surface if they become proud to the surface. In addition, they can result in the formation of large cysts. Both types of screws should be seated well under the articular surface to avoid damage to the opposing surface.

Fragment removal alone without repair can provide excellent short-term symptomatic improvement and is a reasonable option for the treatment of very small defects or the management of in-season athletes. Long-term follow-up studies of isolated debridement have demonstrated the development of radiographic osteoarthritis in up to 80 % of patients within 10 years, especially in lesions larger than 2 cm^2 [12–14]. There are several cartilage repair options after fragment removal. In an RCT comparing OAT with microfracture revealed a better outcome with OAT at 4 years (83 % vs. 63 %, respectively) [71]. ACI is associated with over 80 % success [72, 73], and osteochondral allograft transplantation is successful in approximately 70 % [50].

Revision of Failed Cartilage Repair

Revision of failed cartilage repair is usually reserved from the restorative technology approaches such as ACI or osteochondral allograft, depending on the condition of the subchondral bone. If the bone is intact, surface treatment with ACI is reasonable. However, in the presence of significant subchondral edema, large subchondral cysts, or intralesional osteophytes, replacement of the entire osteochondral unit through osteochondral allograft transplantation should be considered, although a sandwich technique of concurrent bone grafting and ACI is an alternative. Repeat treatment with the same procedure should be considered only if a reason for failure can be identified and is unrelated to the procedure itself, or not likely to recur, for example, traumatic delamination of an ACI graft or subchondral collapse of an osteochondral allograft.

Conclusion

Choosing the correct cartilage repair procedure is influenced by numerous factors. After correction of comorbidities, small defects of the femoral condyles can be treated efficiently with marrow stimulation or OAT, while larger defects should be considered for ACI and osteochondral allograft transplantation (Table 4.3). Patellofemoral defects require unique consideration, and it is

Table 4.3 Treatment algorithm

Small defects (< 2–4 cm^2)		Large defects (> 2–4 cm^2)	
Osteochondral autograft	Microfracture	ACI	Osteochondral allograft
Preferred for small defects than can be covered with 1–2 plugs. Can be used for osteochondral defects	Preferred for acute, well-shouldered defects on the femoral condyles	Preferred for patellofemoral and bipolar defects. Better with intact subchondral bone (OCD lesions are acceptable)	Preferred for uncontained defects and those with abnormal subchondral bone on the femoral condyles
Advantages			
Mature hyaline cartilage	No donor-site morbidity	No size limitation	No size limitation
Primary bone healing	Arthroscopic procedure	Hyaline-like cartilage	Hyaline cartilage
Quicker recovery and return-to-play (RTP) than microfracture			Simpler rehab
Disadvantages			
Technically difficult (mini-open)	Complex rehab (CPM and TDWB 6–8 weeks)	Arthrotomy	Arthrotomy
Donor-site morbidity with multiple plugs	Prolonged RTP 6–9 months	High re-op rate	Limited graft availability
		Very complex rehab (CPM + TDWB 6–8 weeks)	Disease transmission
		Prolonged RTP 12–18 months	Cytotoxic anti-bodies
		High cost	Fails through bone
			Prolonged RTP 9–12 months
			High cost

TDWB touchdown weight bear, *CPM* continuous passive motion

important to optimize all comorbidities concomitant with the cartilage repair.

References

1. Hjelle K, Solheim E, Strand T, Muri R, Brittberg M. Articular cartilage defects in 1,000 knee arthroscopies. Arthroscopy. 2002;18(7):730–4.
2. Widuchowski W, Lukasik P, Kwiatkowski G, et al. Isolated full thickness chondral injuries. Prevalance and outcome of treatment. A retrospective study of 5233 knee arthroscopies. Acta Chir Orthop Traumatol Cech. 2008;75(5):382–6.
3. Curl WW, Krome J, Gordon ES, Rushing J, Smith BP, Poehling GG. Cartilage injuries: a review of 31,516 knee arthroscopies. Arthroscopy. 1997;13(4):456–60.
4. Heir S, Nerhus TK, Rotterud JH, et al. Focal cartilage defects in the knee impair quality of life as much as severe osteoarthritis: a comparison of knee injury and osteoarthritis outcome score in 4 patient categories scheduled for knee surgery. Am J Sports Med. 2010;38(2):231–7. Epub 2009 Dec 30
5. Engen CN, Engebretsen L, Årøen A. Knee Cartilage Defect Patients Enrolled in Randomized Controlled Trials Are Not Representative of Patients in Orthopedic Practice. Cartilage. 2010;1(4):312–9. https://doi.org/10.1177/1947603510373917. PubMed PMID: 26069562; PubMed Central PMCID: PMC4297053
6. Widuchowski W, Widuchowski J, Faltus R, et al. Long-term clinical and radiological assessment of untreated severe cartilage damage in the knee: a natural history study. Scand J Med Sci Sports. 2011;21(1):106–10.
7. Cicuttini F, Ding C, Wluka A, Davis S, Ebeling PR, Jones G. Association of cartilage defects with loss of knee cartilage in healthy, middle-age adults: a prospective study. Arthritis Rheum. 2005;52(7):2033–9.
8. Davies-Tuck ML, Wluka AE, Wang Y, et al. The natural history of cartilage defects in people with knee osteoarthritis. Osteoarthritis Cartilage. 2008;16(3):337–42.
9. Ding C, Cicuttini F, Scott F, Boon C, Jones G. Association of prevalent and incident knee cartilage defects with loss of tibial and patellar cartilage: a longitudinal study. Arthritis Rheum. 2005;52(12):3918–27.
10. Messner K, Maletius W. The long-term prognosis for severe damage to weight-bearing cartilage in the knee: a 14-year clinical and radiographic follow-up in 28 young athletes. Acta Orthop Scand. 1996;67(2):165–8.
11. Shelbourne KD, Jari S, Gray T. Outcome of untreated traumatic articular cartilage defects of the knee: a natural history study. J Bone Joint Surg Am. 2003;85(Suppl 2):8–16.
12. Murray JR, Chitnavis J, Dixon P, et al. Osteochondritis dissecans of the knee; long-term clinical outcome following arthroscopic debridement. The Knee. 2007;14(2):94–8.
13. Aglietti P, Ciardullo A, Giron F, Ponteggia F. Results of arthroscopic excision of the fragment in the treatment of osteochondritis dissecans of the knee. Arthroscopy. 2001;17(7):741–6.
14. Wright RW, McLean M, Matava MJ, Shively RA. Osteochondritis dissecans of the knee: long-term results of excision of the fragment. Clin Orthop Relat Res. Jul. 2004;424:239–43.
15. Widuchowski W, Widuchowski J, Trzaska T. Articular cartilage defects: study of 25,124 knee arthroscopies. Knee. 2007;14(3):177–82.
16. Rosenberg TD, Paulos LE, Parker RD, Coward DB, Scott SM. The forty-five-degree posteroanterior flexion weight-bearing radiograph of the knee. J Bone Joint surg Am. 1988;70(10):1479–83.
17. Potter HG. Chong le R. Magnetic resonance imaging assessment of chondral lesions and repair. J Bone Joint Surg Am. 2009;91(Suppl 1):126–31.
18. Jaiswal PK, Macmull S, Bentley G, Carrington RW, Skinner JA, Briggs TW. Does smoking influence outcome after autologous chondrocyte implantation?: a case-controlled study. J Bone Joint Surg Br. 2009;91(12):1575–8.
19. Micheli L, Curtis C, Shervin N. Articular cartilage repair in the adolescent athlete: is autologous chondrocyte implantation the answer? Clin J Sport Med. 2006;16(6):465–70.
20. Micheli LJ, Moseley JB, Anderson AF, et al. Articular cartilage defects of the distal femur in children and adolescents: treatment with autologous chondrocyte implantation. J Pediatr Orthop. Jul-Aug. 2006;26(4):455–60.
21. Núñez M1, Núñez E, del Val JL, Ortega R, Segur JM, Hernández MV, Lozano L, Sastre S, Maculé F. Health-related quality of life in patients with osteoarthritis after total knee replacement: factors influencing outcomes at 36 months of follow-up. Osteoarthritis Cartilage. 2007;15(9):1001–7.
22. Riddle DL, Wade JB, Jiranek WA, Kong X. Preoperative pain catastrophizing predicts pain outcome after knee arthroplasty. Clin Orthop Relat Res. 2010;468(3):798–806.
23. Kreuz PC, Erggelet C, Steinwachs MR, et al. Is microfracture of chondral defects in the knee associated with different results in patients aged 40 years or younger? Arthroscopy. 2006;22(11):1180–6.
24. Knutsen G, Engebretsen L, Ludvigsen TC, et al. Autologous chondrocyte implantation compared with microfracture in the knee. A randomized trial. J Bone Joint Surg Am. 2004;86-A(3):455–64.
25. Gudas R, Kalesinskas RJ, Kimtys V, et al. A prospective randomized clinical study of mosaic osteochondral autologous transplantation versus microfracture for the treatment of osteochondral defects in the knee joint in young athletes. Arthroscopy. 2005;21(9):1066–75.
26. Asik M, Ciftci F, Sen C, Erdil M, Atalar A. The microfracture technique for the treatment of full-thickness articular cartilage lesions of the knee: midterm results. Arthroscopy. 2008;24(11):1214–20.

27. Mithoefer K, Williams RJ 3rd, Warren RF, et al. The microfracture technique for the treatment of articular cartilage lesions in the knee. A prospective cohort study. J Bone Joint Surg Am. Sep;87(9):1911–20.
28. Mithoefer K, McAdams T, Williams RJ, Kreuz PC, Mandelbaum BR. Clinical efficacy of the microfracture technique for articular cartilage repair in the knee: an evidence-based systematic analysis. Am J Sports Med. 2009;37(10):2053–63.
29. Bartlett W, Skinner JA, Gooding CR, et al. Autologous chondrocyte implantation versus matrix-induced autologous chondrocyte implantation for osteochondral defects of the knee: a prospective, randomised study. J Bone Joint Surg Br. 2005;87(5):640–5.
30. Rosenberger RE, Gomoll AH, Bryant T, Minas T. Repair of large chondral defects of the knee with autologous chondrocyte implantation in patients 45 years or older. Am J Sports Med. 2008;36(12):2336–44.
31. Vanlauwe J, Saris DB, Victor J, Almqvist KF, Bellemans J, Luyten FP. Five-year outcome of characterized chondrocyte implantation versus microfracture for symptomatic cartilage defects of the knee: early treatment matters. Am J Sports Med. 2011;39(12):2566–74.
32. Adkisson HDt, Martin JA, Amendola RL, et al. The potential of human allogeneic juvenile chondrocytes for restoration of articular cartilage. Am J Sports Med. 2010;38(7):1324–33.
33. Mithoefer K, Williams RJ 3rd, Warren RF, Wickiewicz TL, Marx RG. High-impact athletics after knee articular cartilage repair: a prospective evaluation of the microfracture technique. Am J Sports Med. 2006;34(9):1413–8.
34. Zaslav K, Cole B, Brewster R, et al. A prospective study of autologous chondrocyte implantation in patients with failed prior treatment for articular cartilage defect of the knee: results of the Study of the Treatment of Articular Repair (STAR) clinical trial. Am J Sports Med. 2009;37(1):42–55.
35. Rue JP, Yanke AB, Busam ML, McNickle AG, Cole BJ. Prospective evaluation of concurrent meniscus transplantation and articular cartilage repair: minimum 2-year follow-up. Am J Sports Med. 2008;36(9):1770–8.
36. McNickle AG, Provencher MT, Cole BJ. Overview of existing cartilage repair technology. Sports Med Arthrosc. 2008;16(4):196–201.
37. Minas T, Gomoll AH, Solhpour S, Rosenberger R, Probst C, Bryant T. Autologous chondrocyte implantation for joint preservation in patients with early osteoarthritis. Clin Orthop Relat Res. 2010;468(1):147–57.
38. Kon E, Gobbi A, Filardo G, Delcogliano M, Zaffagnini S, Marcacci M. Arthroscopic second-generation autologous chondrocyte implantation compared with microfracture for chondral lesions of the knee: prospective nonrandomized study at 5 years. Am J Sports Med. 2009;37(1):33–41.
39. Steadman JR, Briggs KK, Rodrigo JJ, Kocher MS, Gill TJ, Rodkey WG. Outcomes of microfracture for traumatic chondral defects of the knee: average 11-year follow-up. Arthroscopy. 2003;19(5):477–84.
40. Hangody L, Fules P. Autologous osteochondral mosaicplasty for the treatment of full-thickness defects of weight-bearing joints: ten years of experimental and clinical experience. J Bone Joint Surg Am. 2003;85-A(Suppl 2):25–32.
41. Hangody L, Kish G, Karpati Z, Szerb I, Udvarhelyi I. Arthroscopic autogenous osteochondral mosaicplasty for the treatment of femoral condylar articular defects. A preliminary report. Knee Surg Sports Traumatol Arthrosc. 1997;5(4):262–7.
42. Basad E, Ishaque B, Bachmann G, Sturz H, Steinmeyer J. Matrix-induced autologous chondrocyte implantation versus microfracture in the treatment of cartilage defects of the knee: a 2-year randomised study. Knee Surg Sports Traumatol Arthrosc. 2010;18(2010):519–27.
43. Saris DB, Vanlauwe J, Victor J, et al. Treatment of symptomatic cartilage defects of the knee: characterized chondrocyte implantation results in better clinical outcome at 36 months in a randomized trial compared to microfracture. Am J Sports Med. 2009;37(Suppl 1):10S–9S.
44. Saris DB, Vanlauwe J, Victor J, et al. Characterized chondrocyte implantation results in better structural repair when treating symptomatic cartilage defects of the knee in a randomized controlled trial versus microfracture. Am J Sports Med. 2008;36(2):235–46.
45. Gross AE, Shasha N, Aubin P. Long-term followup of the use of fresh osteochondral allografts for posttraumatic knee defects. Clin Orthop Relat Res. 2005;435:79–87.
46. Behrens P, Bitter T, Kurz B, Russlies M. Matrix-associated autologous chondrocyte transplantation/implantation (MACT/MACI)-5-year follow-up. The Knee. 2006;13(3):194–202.
47. Bentley G, Biant LC, Carrington RW, et al. A prospective, randomised comparison of autologous chondrocyte implantation versus mosaicplasty for osteochondral defects in the knee. J Bone Joint Surg Br. 2003;85(2):223–30.
48. Brittberg M, Lindahl A, Nilsson A, Ohlsson C, Isaksson O, Peterson L. Treatment of deep cartilage defects in the knee with autologous chondrocyte transplantation. N Engl J Med. 1994;331(14):889–95.
49. Peterson L, Minas T, Brittberg M, Nilsson A, Sjogren-Jansson E, Lindahl A. Two- to 9-year outcome after autologous chondrocyte transplantation of the knee. Clin Orthop Relat Res. 2000;374:212–34.
50. Emmerson BC, Gortz S, Jamali AA, Chung C, Amiel D, Bugbee WD. Fresh osteochondral allografting in the treatment of osteochondritis dissecans of the femoral condyle. Am J Sports Med. 2007;35(6):907–14.

51. Shasha N, Aubin PP, Cheah HK, Davis AM, Agnidis Z, Gross AE. Long-term clinical experience with fresh osteochondral allografts for articular knee defects in high demand patients. Cell Tissue Bank. 2002;3(3):175–82.
52. Aubin PP, Cheah HK, Davis AM, Gross AE. Long-term followup of fresh femoral osteochondral allografts for posttraumatic knee defects. Clin Orthop Relat Res. 2001;(391 Suppl):318–27.
53. Gortz S, Bugbee WD. Allografts in articular cartilage repair. J Bone Joint Surg Am. 2006;88(6):1374–84.
54. LaPrade RF, Botker J, Herzog M, Agel J. Refrigerated osteoarticular allografts to treat articular cartilage defects of the femoral condyles. A prospective outcomes study. J Bone Joint Surg Am. 2009;91(4):805–11.
55. McCulloch PC, Kang RW, Sobhy MH, Hayden JK, Cole BJ. Prospective evaluation of prolonged fresh osteochondral allograft transplantation of the femoral condyle: minimum 2-year follow-up. Am J Sports Med. 2007;35(3):411–20.
56. Kreuz PC, Steinwachs MR, Erggelet C, et al. Results after microfracture of full-thickness chondral defects in different compartments in the knee. Osteoarthritis Cartilage. 2006;14(11):1119–25.
57. Astur DC, Arliani GG, Binz M, Astur N, Kaleka CC, Amaro JT, Pochini A, Cohen M. Autologous osteochondral transplantation for treating patellar chondral injuries: evaluation, treatment, and outcomes of a two-year follow-up study. J Bone Joint Surg Am. 2014;96(10):816–23.
58. Jamali AA, Emmerson BC, Chung C, Convery FR, Bugbee WD. Fresh osteochondral allografts: results in the patellofemoral joint. Clin Orthop Relat Res. 2005;437:176–85.
59. Farr J. Autologous chondrocyte implantation improves patellofemoral cartilage treatment outcomes. Clin Orthop Relat Res. 2007;463:187–94.
60. Henderson IJ, Lavigne P. Periosteal autologous chondrocyte implantation for patellar chondral defect in patients with normal and abnormal patellar tracking. The Knee. 2006;13(4):274–9.
61. Minas T, Bryant T. The role of autologous chondrocyte implantation in the patellofemoral joint. Clin Orthop Relat Res. Jul. 2005;436:30–9.
62. Pascual-Garrido C, Slabaugh MA, L'Heureux DR, Friel NA, Cole BJ. Recommendations and treatment outcomes for patellofemoral articular cartilage defects with autologous chondrocyte implantation: prospective evaluation at average 4-year follow-up. Am J Sports Med. 2009;37(Suppl 1):33S–41S.
63. Blevins FT, Steadman JR, Rodrigo JJ, Silliman J. Treatment of articular cartilage defects in athletes: an analysis of functional outcome and lesion appearance. Orthopedics. 1998;21(7):761–7. (discussion 767–8)
64. Bonner KF, Daner W, Yao JQ. 2-year postoperative evaluation of a patient with a symptomatic full-thickness patellar cartilage defect repaired with particulated juvenile cartilage tissue. J Knee Surg. 2010;23(2):109–14.
65. Hatic SO 2nd, Berlet GC. Particulated juvenile articular cartilage graft (DeNovo NT Graft) for treatment of osteochondral lesions of the talus. Foot Ankle Spec. 2010;3(6):361–4.
66. Farr J, Yao JK. Chondral defect repair with particulated juvenile cartilage allograft. Cartilage. 2011;2:346–53.
67. Bartlett W, Gooding CR, Carrington RW, Skinner JA, Briggs TW, Bentley G. Autologous chondrocyte implantation at the knee using a bilayer collagen membrane with bone graft. A preliminary report. J Bone Joint Surg Br. 2005;87(3):330–2.
68. Hunt HE, Sadr K, Deyoung AJ, Gortz S, Bugbee WD. The role of immunologic response in fresh osteochondral allografting of the knee. Am J Sports Med. 2014;42(4):886–91. https://doi.org/10.1177/0363546513518733. Epub 2014 Feb 4. PubMed PMID: 24496509
69. Gomoll AH, Flik KR, Hayden JK, Cole BJ, Bush-Joseph CA, Bach BR Jr. Internal fixation of unstable Cahill Type-2 C osteochondritis dissecans lesions of the knee in adolescent patients. Orthopedics. 2007;30(6):487–490.
70. Pascual-Garrido C, Friel NA, Kirk SS, et al. Midterm results of surgical treatment for adult osteochondritis dissecans of the knee. Am J Sports Med. 2009;37(Suppl 1):125S–30S.
71. Gudas R, Simonaityte R, Cekanauskas E, Tamosiunas R. A prospective, randomized clinical study of osteochondral autologous transplantation versus microfracture for te treatment of osteochondritis dissecans in the knee joint in children. J Pediatr Orthop. 2009;29(7):741–8.
72. Krishnan SP, Skinner JA, Carrington RW, Flanagan AM, Briggs TW, Bentley G. Collagen-covered autologous chondrocyte implantation for osteochondritis dissecans of the knee: two- to seven-year results. J Bone Joint Surg Br. 2006;88(2):203–5.
73. Peterson L, Minas T, Brittberg M, Lindahl A. Treatment of osteochondritis dissecans of the knee with autologous chondrocyte transplantation: results at two to ten years. J Bone Joint Surg Am. 2003;85-A(Suppl 2):17–24.