3 Treatment Algorithm for Articular Cartilage Repair of the Knee: Towards Patient Profiling Using Evidence-Based Tools

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Abbreviations

ACI Autologous chondrocyte implantation
AMZ Anteromedialization
MF Microfracture
OA Osteoarthritis
OAT Osteochondral autologous transplantation

3.1 Introduction

The management of patients with articular cartilage defects continues to pose significant challenges to orthopedic surgeons worldwide. The evolution in diagnostic and treatment modalities or "technovolution" [15, 50] in cartilage repair of the last decade as well as the increase in physical demands has rapidly increased the number of patients seeking a solution for their cartilage defect. The challenge for physicians lies in the decision-making process where timing and selection of the procedure are of paramount importance. Current cartilage repair techniques include

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nonoperative strategies; debridement; marrow stimulation methods such as microfracture (MF), drilling, and abrasion; and transplantation methods such as autologous chondrocyte implantation (ACI) and osteochondral autologous or allograft transplantation [6]. In clinical practice, these techniques are selected based on algorithms that are derived from previous (randomized controlled) trials and long-term cohort studies. However, strong (comparative) evidence to support one single algorithm is lacking [9, 19, 34]. Furthermore, there is a variance in treatment selection between different expert centers based on healthcare availability and surgeon preference. Taking this into account, it is difficult for the surgeon to make an evidence-based decision for the individual patient. This chapter seeks to explore the current evidence for treatment selection and provides tools for daily clinical practice as well as an updated comprehensive evidence-based treatment algorithm.

3.2 General Indications and Contraindications for Cartilage Repair

When assessing a patient suspected of having a cartilage defect, identifying concomitant knee (ligament) injuries is crucial as subsequent treatment of these injuries may provide symptom relief and improve the joint homeostasis [67]. Furthermore, symptoms following knee injury may not be related to the cartilage defect. Nonoperative treatment including physiotherapy and anti-inflammatory medication (NSAIDS) along with (sports) activity and dietary modification can be considered as primary treatment options, especially for smaller defects with normal joint function and limited physical demands [75]. However patients are frequently referred to specialized centers with long-standing complaints, and symptom to treatment delay is known to negatively influence treatment outcome [16, 45, 56, 76]. In fact, the average patient suitable for cartilage repair had 2.1 prior treatments which again are potential impediments for clinical outcome [21, 36, 64]. Therefore, careful interpretation of a patient's history and early and accurate diagnostics are needed before determining the treatment modality of choice. Furthermore, body mass index, mechanical alignment, occupation, sports participation, responsiveness, and rehabilitation are important factors to take into consideration in the decision-making process [14]. Patients with degenerative joints, particularly older patients, can be treated with steroid injections, viscosupplementation, and physiotherapy. Of these, patients with a desire to maintain certain (sport) activities can be counselled in terms of expectations to decide whether or not a salvage procedure and subsequent rehabilitation program is viable. In general, surgery should be reserved for patients with grade III to IV full-thickness cartilage defects where conservative treatment has failed or has a limited probability of success. In these, timing of surgery should be considered an important parameter. Obesity, smoking, and meniscal and/or ligamentous injury are relative contraindications, although strong supporting evidence is lacking [25].

3.3 Indicators for Treatment

3.3.1 Defect Size

Once an (osteo)chondral defect has been identified, the current literature suggests (postdebridement) defect size to be an important indicator for treatment selection. In randomized controlled trials comparing autologous transplantations with MF, both Knutsen et al. and Gudas et al. found inferior clinical outcome after MF for defects larger than 4 and 2 cm^2, respectively [29, 39]. This was corroborated by prospective studies of Asik et al., Mithoefer et al., and Steadman et al. who found similar size thresholds that reduced clinical outcome of MF after a mean of 2–11 years [2, 56, 72]. Fortunately, the clinical outcome after ACI or osteochondral autologous transplantation (OAT) has not been found to correspond to defect size. However, defects greater than 4 cm^2 seem to respond better to ACI than

OAT [10]. In a more recent randomized controlled trial, the histological and functional outcomes of ACI were also significantly better than those for MF in defects averaged 2.5 cm^2 [68]. Although a single size threshold is difficult to identify, the literature suggests that defects greater than 2–3 cm^2 should be treated with more complex transplantation procedures, and MF nor other treatments are useful in defects larger than 4 cm^2. Indeed, one systematic review concluded that defects larger than 2.5 cm^2 should be treated with ACI or OAT [7]. Here, again, individual decision making is considered to be important as relative defect size and depth (i.e., in comparison to the femoral condyle) and the extent to which the local homeostasis has been disturbed vary between patients [67].

3.3.2 Age

A variety of studies reported that patients under 30 years of age benefit more from cartilage repair in terms of clinical outcome when compared to older patients [2, 16, 38, 43]. Conversely, a recent randomized controlled trial in patients aged 18–50 years did not find correlation between age and clinical outcome [76]. In fact, several other studies did not find correlation between age and treatment success [17, 23, 65]. One study demonstrated low failure rates in patients 45 years and older, while another study showed no difference in clinical outcome after ACI in patients 40 years and older compared to younger patients [40, 60]. Overall, there is insufficient and inconclusive data to support age as primary indicator for treatment selection.

3.3.3 Patient Activity

Patient activity can be considered an important indicator for treatment selection in cartilage repair. A randomized controlled trial demonstrated that more active patients (as indicated by the Tegner score) achieved superior clinical results, regardless of treatment type [38]. In a 5-year follow-up study, Kon et al. found ACI to be more durable in terms of (sport related) activity compared to MF [41]. The superior histomorphometric and histologic scores found for ACI compared to MF and a higher return to sports rate further suggest ACI to be a better option for active patients [54, 68]. Interestingly, deterioration in sports activity has been observed after MF, possibly due to poor repair morphology, defect fill, and peripheral integration [54]. Nevertheless, MF has been found to be effective in different high-impact (professional) sports such as American football and soccer [56, 73].

3.4 Treatment Selection for Patients with Smaller Defects

Debridement can be considered as initial treatment for defects <2 cm^2 in less demanding patients especially for defects found incidentally during arthroscopy and in mild to moderate osteoarthritis (OA) [1, 66]. Randomized controlled trials in patients with OA have shown that arthroscopic debridement has no advantage over optimal physical and medical care [37, 58]. Although debridement of small defects can provide symptom relief in terms of pain and catching and locking, the response to treatment of these defects as well as their natural history remains unpredictable [18, 22, 71]. Both MF and OAT are generally considered good options for smaller (<2–3 cm^2) defects. OAT may be indicated in deep osteochondral defects of up to 2 cm^2. In defects 2–3 cm^2, MF or ACI is usually preferred over OAT based on the possible risk of donor-site morbidity. However, the bone portion also influences treatment choice. Although strong supporting evidence is lacking, donor-site morbidity may lead to pain, tissue deterioration, and a decline in knee function [32, 46]. In contrast, in a case series following 112 patients, Paul et al. found no influence of the size or number of donor grafts on clinical outcome [63]. Concerning smaller defects, more complex procedures such as ACI are generally reserved for high demand and revision cases as marrow-stimulating techniques seem less reliable in these instances [17, 54].

3.5 Treatment Selection for Patients with Larger Defects

For larger (>3 cm^2) defects, both ACI and allograft transplantation have shown good to excellent results. As a randomized controlled comparison between these interventions is lacking, local availability and surgeon and patient preference will still largely determine the treatment of choice. For ACI, good to excellent clinical outcome has been reported up to 20 years in 70–90 % of patients with defects >3 cm^2 [25, 65]. An advantage of allograft transplantation might be that it permits treatment of relatively large defects, particularly when there is accompanying bone loss [25]. Shasha and colleagues found an 85 % femoral condylar graft survival rate at 10 years and a 65 % graft survival rate after failed tibial plateau fractures [28, 70]. Bugbee et al. demonstrated an 86 % success rate after allograft transplantation for unipolar defects averaged 8.2 cm^2 while 54 % of bipolar defects were rated good to excellent [13]. In like manner, Beaver et al. found a higher failure rate for bipolar defects [5]. Other factors that were reported to reduce clinical outcome after allograft transplantation include primary osteoarthritis and malalignment [6]. Interestingly, Ossendorf et al. recently demonstrated good midterm results after ACI in 51 patients with large and complex articular defects [61]. In their cohort, kissing lesions had similar results as single defects indicating that ACI might be a safer treatment modality for this category. If for larger defects deeper than 8–10 mm, allograft transplantation is not feasible, the ACI sandwich technique can be a viable option. Barlett et al. used a sandwich technique with two matrix-induced ACI (MACI) membranes and a bone graft in deep osteochondral defects (mean 5.2 cm^2, range 2.2–8.0) and found good to excellent 1-year results in all eight patients treated [4].

3.6 Treatment Selection for Patients with Defects in the Patellofemoral Joint

The limited healing capacity and the frequently occurring abnormalities in the extensor mechanism make defects in the patella a considerable challenge. For these defects, MF has been found to have limited effect on clinical outcome, deteriorating after 18–36 months [44]. OAT also seems less promising for patellar defects. Although Hangody et al. reported good results in 19 of 26 patients after OAT, patellofemoral defects had significant lower improvement than femoral defects [30]. Moreover, Bentley et al. reported failure of all five patients treated with OAT, possibly due to the difference in thickness of donor and recipient cartilage which can make healing and incorporation difficult [10]. Because of the difficult local topography and the risk of donor-site morbidity, allograft patellar resurfacing is preferred over OAT in patients with severe articular cartilage disease if available. Jamali et al. found a 72 % success rate in 18 such patients (mean age 42) treated with fresh osteochondral allografts after a mean of 8 years [35]. For isolated cartilage defects in the patellofemoral joint, clinical results seem to be improving in recent years, possibly due to the increase in experience with ACI and focus on the biomechanical shearing forces of the extensor mechanism [59]. Pascual-Garrido et al. reported significant short-term improvement in patients receiving ACI for defects (mean size 4.2 cm^2) in the patellofemoral joint [62]. The 50 % of patients who received a concomitant anteromedialization (AMZ) achieved statistically higher clinical scores. However, it remains difficult to compare the treatment effect of each individual procedure and a randomized trial for ACI with or without concomitant AZM is lacking. Nevertheless, a variety of reports have demonstrated success rates of 70–90 % for ACI with or without concomitant correction of the extensor mechanism [20, 24, 27, 31, 52, 77]. Others have shown no significant difference in clinical outcome after ACI compared to other locations supporting its use as primary treatment for defects in the patellofemoral joint [17, 69].

3.7 Early Osteoarthritic Defects and Salvage Repair

Early osteoarthritic defects are increasingly being recognized in younger active patients, creating a new challenging population for the orthopedic surgeon. Compared to OA, early OA is considered more difficult to diagnose as signs and symptoms may still be limited, often becoming manifest after higher strains during sport activities [47]. As standard measures for OA include temporary symptom relief or invasive joint replacement, cartilage repair procedures are increasingly being introduced in this population [26]. Bae et al. evaluated 44 patients with an average lesion size of 3.9 cm^2 with moderate osteoarthritic changes who underwent MF [3]. After a mean of 2.3 years, significant improvement in pain and daily living was seen. In addition, using second-look arthroscopy, defect filling was confirmed. Miller et al. and Steadman et al. evaluated MF for degenerative lesions and high-impact athletics, respectively, with satisfying clinical outcome and return to high-impact sports for more than five seasons [51, 74]. However, these studies were not aimed specifically at (early) OA. Brittberg et al. used drilling and subsequent carbon fiber scaffold implantation for treatment of early osteoarthritic defects in two separate cohorts with a short-term success rate of over 80 % in terms of pain and clinical outcome [11, 17]. Minas et al. reported on a large cohort consisting of 153 patients (mean age 38 years) with early OA treated with ACI and followed for up to 11 years [53]. At 5 years, 92 % of patients were functioning well, delaying the need for joint replacement. At final follow-up, eight percent of joints were considered failures while 50–75 % experienced significant improvement. Although limited clinical data are available, OAT has been implemented in early OA. Hangody et al. used OAT in 82 professional athletes with signs of OA. In this 17-year prospective study, similar success rates were found to that of less athletic patients, although high motivation resulted in better subjective evaluation [30]. Jakob et al. found good results in ten patients with patellofemoral OA treated with OAT [33]. Concomitant procedures for patellofemoral maltracking may be an important confounder. Könst et al. used autologous bone grafting combined with gel-type ACI (GACI) to treat 9 patients with severe osteochondral defects [42]. At 1-year follow-up, statistically significant improvement was demonstrated in eight patients with only one patient needing conversion to total knee arthroplasty (TKA).

3.8 Treatment Algorithm: Summarizing the Findings from the Literature

Although there is no strong evidence supporting a single treatment algorithm, the literature does provide tools for clinical decision making. In short, early diagnostics for cartilage defects and concomitant injuries are required as a disturbed joint homeostasis and treatment delay reduce clinical outcome. Defects smaller than 2.5 cm^2 respond well to MF and OAT, the latter being indicated in deeper osteochondral defects. For larger defects (>2.5 cm^2), ACI is generally the treatment of choice. Depending on availability and experience, (fresh) osteochondral allograft transplantation or the ACI sandwich technique can be used in large osteochondral defects. Cartilage repair procedures for treatment of (early) OA are still in their early phase, and an evidence-based algorithm is difficult to construct. As such, careful treatment selection is warranted, specifically in more advanced OA and younger patients. Current evidence suggests that TKA can be delayed with cartilage repair. Furthermore, the short-term results (up to 5 years) in patients with early osteoarthritic defects are promising [48]. Figure 3.1 provides a summary of the evidence-based treatment algorithm.

3.9 Addendum: Treatment Selection for (Professional) Athletes

The high impact and torsional loads subjected to the knee joint in (professional) athletes are an important cause of cartilage injury and

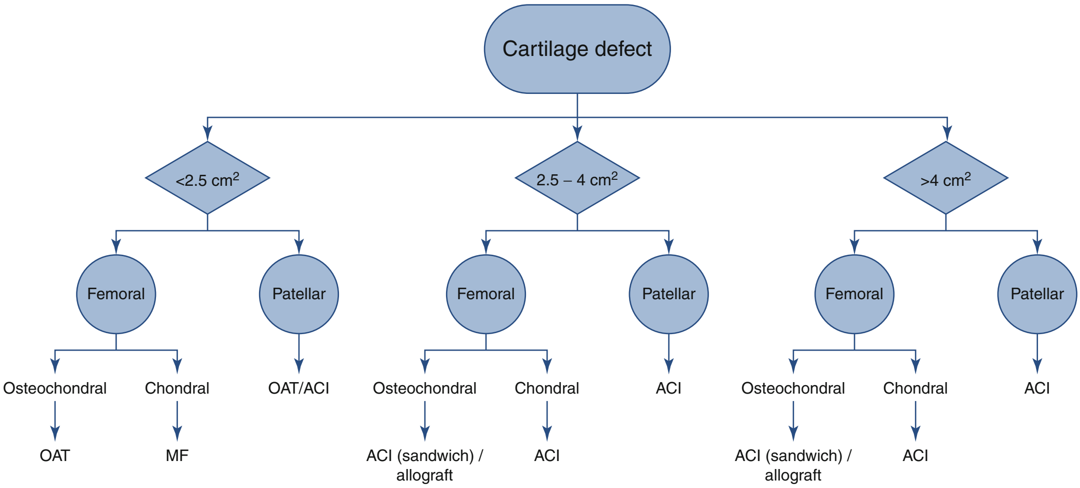

Fig. 3.1 Evidence-based treatment algorithm for articular cartilage repair of the knee

subchondral bone turnover [12]. This in turn may lead to functional disability and (early) OA during and after (professional) sports participation [55]. For professional soccer players and adolescent athletes, ACI resulted in higher functional improvement compared to MF [56, 57]. Indeed Mithoefer et al. showed a decline in sports participation after MF in 47 % of athletes while 87 % of patients treated with ACI remained at the pre-injury level [54]. OAT also showed superior clinical outcome in a randomized study among both professional and recreational athletes [29]. For defects larger than 2 cm^2, both MF and OAT showed significantly worse clinical outcome and a lower return to sports when compared to smaller defects [49, 56]. Although it seems ACI provides a more durable return to sports participation, especially in larger defects, the average time to return to sports is higher (18 months) compared to MF (8 months) and OAT (7 months). Therefore, in reviewing the literature for athletes, Bekkers et al. previously suggested to use OAT or MF as treatment of choice in defects smaller than 2 cm^2. If ACI is the treatment of choice, a surgical debridement of the traumatic defect with additional biopsy during the season and subsequent transplantation during the off-season might optimize professional sports participation [8].

Conclusion

Each patient should be assessed individually based on physical demands and expectations, concomitant injuries, previous treatments, symptom to treatment duration, as well as defect characteristics such as chronicity, location, size, and depth. Although age as such should not limit treatment selection, careful consideration in terms of patient expectations is warranted for patients older than 40 years. According to the available evidence, defect size seems to be a reliable primary indicator for treatment selection. Finally, based on this literature review, an extensive evidence-based treatment algorithm was created (Fig. 3.1).

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