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REVIEW ARTICLE

Managing Chondral Lesions: A Literature Review and Evidence-Based Clinical Guidelines

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Abstract

Background Articular cartilage lesions are becoming increasingly common. Optimum diagnosis and management of chondral defects cause a lot of dilemma. A number of surgical methods have been reported in the literature for treating focal cartilage defects. There is a lack of consensus on the most effective management strategy, with newer surgical and cell-based treatments being advocated regularly.

Study Design and Methods A clinical review is constructed by appraising the published literature about clinical evaluation and diagnostic modalities for articular cartilage defects and subsequent surgical procedures, management strategies employed for such lesions. Prominent available databases (PUBMED, EMBASE, Cochrane) were also searched for trials comparing functional outcomes following cartilage procedures. Synthesis of a practical management guideline is then attempted based on the evidence assessed.

Results Systematic examination and optimal use of diagnostic imaging are an important facet of cartilage defect management. Patient and lesion factors greatly influence the outcome of cartilage procedures and must be considered while planning management. Smaller lesions < 2 cm^2 respond well to all treatment modalities. Autologous osteochondral transplants (OATs) are effective in high activity individuals with intermediate lesions. For larger lesions > 4 cm^2, newer generation autologous chondrocyte implantation (ACI) has shown promising and durable results. Stem cells with scaffolds may provide an alternate option. Orthobiologics are a useful adjunct to the surgical procedures, but need further evaluation.

Conclusions Most treatment modalities have their role in appropriate cases and management needs to be individualized for patients. The search for the perfect cartilage restoration procedure continues.

Keywords Articular cartilage · Cartilage lesions · Arthroscopy · Microfracture · Autologous chondrocyte implantation · Mosaicplasty · Bone marrow aspirate · Orthobiologics · Stem cells · Functional outcome

Background

Articular cartilage is devoid of blood vessels which limit its capacity to heal and regenerate, particularly in full-thickness defects [1]. These defects affect the functioning of the knee and can progress to degenerative osteoarthritic changes [2]. While the exact incidence of articular cartilage defects is unknown, reports indicate that nearly 900,000 patients are affected by it annually in the US and leads to nearly 200,000 invasive interventions [3].

Another study reports that 57.3% of knees examined arthroscopically show indications of cartilage lesions [4].

The major disease load is concentrated in active adults, and thus, any debilitation leads to a significant drop in the functioning of individuals, a recent study analyzing the trends found the mean age of patients undergoing cartilage procedures to be 44 years in 2016 and a 206.4% increase in the number of procedures overall [5]. This has led to the development of various procedures, demonstrating the role of surgery in treating these defects [6]. Surgical procedures for managing cartilage defects can be categorized into three groups. Marrow stimulation technique best exemplified by microfracture is one of the most common technique used [5];

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however, the repair tissue wears quickly and results are not durable [7]. Autologous osteochondral transplant (OATS) provides hyaline cartilage replacement for chondral defects. While it is reported to be effective in treating smaller lesions (< 2–4 cm^2) [8], it is limited by donor side morbidity [9] and fibrocartilage hypertrophy/uneven surface between plugs [10].

Autologous chondrocyte implantation (ACI) is based on the principle of restoration of hyaline cartilage and thus providing durable improvements [11]. Even though it has been reported to have improved clinical outcome over long follow-up [12]; it has its own drawbacks and is constantly being evolved to provide better delivery and less invasive methods of chondrocyte implantation [2].

Currently, there is no standardized protocol for treatment of cartilage defects and considerable ambiguity persists regarding surgical management providing optimum and durable results. In theory, ACI should have an advantage with better histological quality [13]; however, the results have been mixed. A number of publications have been based on trials that have low power and inadequate follow-up [3]. Another compounding factor is the modifications in ACI techniques (periosteal flap, collagen layer, and matrix induced).

Cartilage restoration techniques have been further augmented using orthobiologics.

Orthobiologics are a very heterogenous mix of compounds and consist of but not limited to platelet-rich plasma (PRP), hyaluronic acid, mesenchymal stem cells (MSCs), adipose-derived stem cells, bone marrow aspirate concentrate (BMAC), growth factors, and cytokine modulators [14, 15]. Their role in treating cartilage defect is currently the topic of intense scrutiny in the research community.

Multiple treatment modalities and their interplay augur well for breakthroughs and improved understanding of the cartilage defects; it, however, causes considerable confabulation in the minds of the clinician looking for evidence-based answers and possibly an algorithm on managing cartilage defects in his settings. A further caveat especially in developing countries like ours is the economics and non-availability of the newer treatment options.

This review is an attempt to search the available literature on the various diagnostic tools utilized, treatment modalities, and reported outcomes, appraise it and endeavor to synthesize practical and evidence-based recommendations for management of articular cartilage defects.

Diagnosis

A precise and early diagnosis is cornerstone to optimum management of cartilage defects and ensuring good prognosis [16].

Diagnosis of articular cartilage lesions involves following three approaches:

- Clinical symptoms and examination

  Cartilage lesions of the knee, hip, or ankle often present as pain during activities, while lesions of shoulder joint can be relatively asymptomatic and are diagnosed incidentally [17].

  The signs and symptoms, none of which are specific to the lesions, include activity-related pain, often associated with swelling and progressive in nature, a decrease in the functional range of motion of the joint and mechanical symptoms like popping, locking, or catching [18, 19].

  A thorough physical examination is essential as it will elucidate tell-tale signs of joint health. Examination of the ROM of the joint is essential as lack of terminal extension in knee joint is a pointer toward OA [19] as is the loss of terminal abduction and rotations in hip and shoulder joint. The stability and alignment of the joint plays a crucial role not just in the pathogenesis but also the outcome of subsequent surgical procedures; hence, the joint must be carefully assessed for ligamentous stability, mechanical alignment, and the condition of menisci, capsule, and labrum [19, 20].
- Radiology and imaging

  Conventional radiology does not delineate cartilage lesions properly, but is essential to look for signs of OA and mechanical alignment. The imaging modality of choice is MRI, and while conventional MRI provides moderate-to-good clarity, newer image modes and programs have been developed to enhance image quality [16].

  Proton density-weighted (PD) and fast spin echo (FSE) images help better appreciate hyaline cartilage, and differentiate it from synovial fluid and underlying bone [21], as depicted in Fig. 1. They also help in quantifying the severity of lesions, as depicted in Fig. 2.

  Another development in MRI has been the use of contrasts to study glycosaminoglycan degradation products using delayed gadolinium enhanced magnetic resonance imaging of cartilage (dGEMRIC) protocols and sodium MRIs to evaluate the level of sodium in glycosaminoglycan in the cartilage tissues [22].
- Arthroscopy

  Arthroscopy allows for direct visualization of the cartilage lesions and remains, the first point of diagnosis for many lesions. However, it suffers from two disadvantages, one being the subjective nature of observations, and to counter this, a number of objective grading systems have been developed. The most widely known amongst these are Outerbridge scale [23] and the ICRS grading, as presented in Table 1.

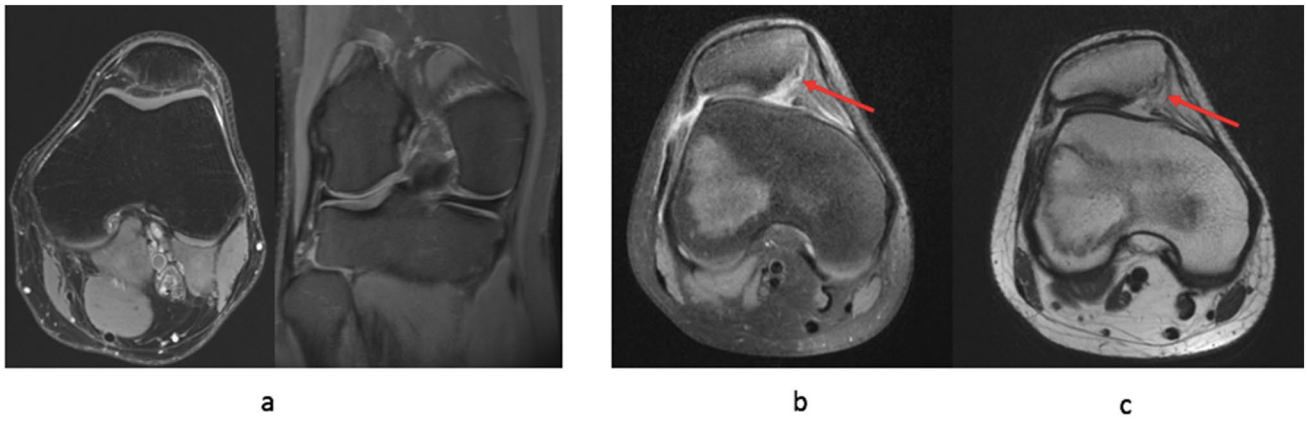

Fig. 1 Normal articular cartilage and cartilage defects on MRI

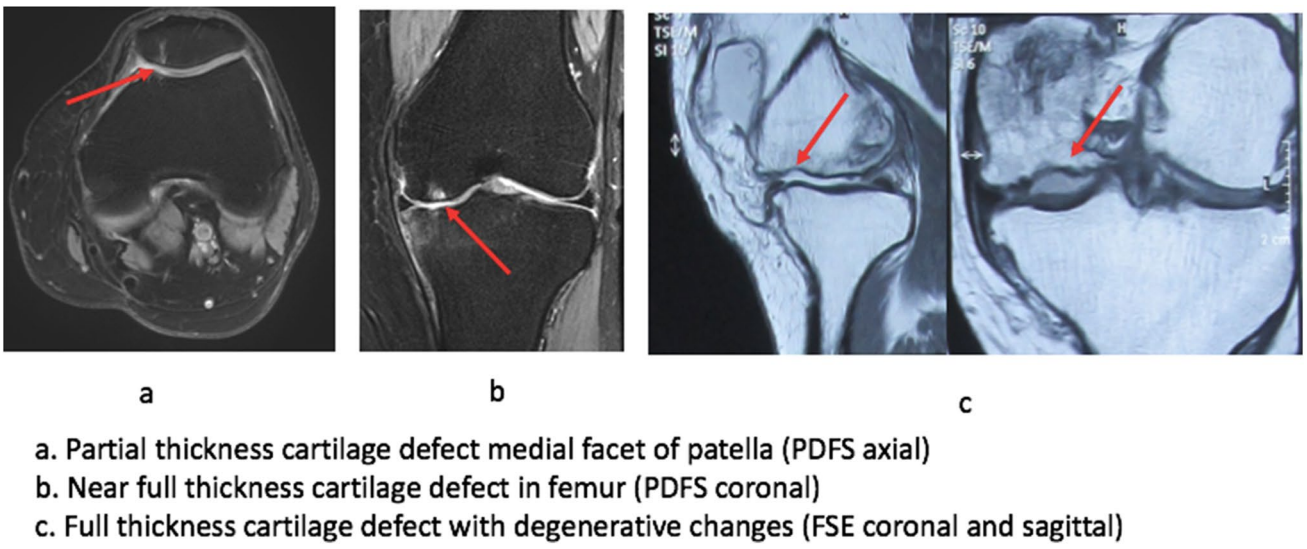

Fig. 2 Spectrum of cartilage lesions on MRI imaging

Second, only macroscopic damage can be visualized, which means that while it can be a good tool to grade and plan treatment for moderate-to-severe lesions, it is not recommended in identifying early lesions [16].

Management of Cartilage Defects

The mainstay of treatment is surgical as the literature does not provide sufficient evidence about conservative management. Conservative treatments include but are not limited to NSAIDS, physiotherapy, visco-supplementation, and steroids; these may be used prior to surgical intervention.

The surgical treatment of cartilage defects can be broadly categorized into three groups.

- Palliative

  Debridement/chondroplasty.

- Reparative

  Microfracture
  AMIC
  Microfracture + augmentation with orthobiologics.

- Restorative

Table 1 Classification and grading of chondral lesions

Outerbridge		
Grading	Depth	Size
0	Normal	
1	Softening and swelling of cartilage	
2	Partial thickness, < 50% of cartilage thickness	< 1.25 cm diameter
3	Partial thickness, > 50% of cartilage thickness	> 1.25 cm diameter
4	Full thickness down to subchondral bone	Any

ICRS cartilage injury classification	
Grade	Naming and description
0	Normal
1	Nearly normal: superficial indentations/fissures
2	Abnormal: lesions extending < 50% of cartilage thickness
3	Severely abnormal: lesions extending > 50% of cartilage thickness and up to but not through the subchondral bone
4	Severely abnormal: lesions extending through the subchondral bone

Modified from Dallich et al. [36]

OATS/mosaicplasty
Autologous chondrocyte implantation
BMAC/MSC + scaffolds.

Debridement and chondroplasty: involve smoothening of partial thickness defects and shaving off loose flaps to create stable edged lesions [24].

These procedures reduce the chances of formation of loose bodies and consequential mechanical blocks. They do not alter the natural progression of disease and are reserved for patients with advanced arthritis.

- Microfracture

  Originally described by Steadman [7], microfracture involves curetting the lesion down to subchondral bone and then making perforations into the bed of the lesions to release blood clots, as shown in Fig. 3. The blood clot induces cartilage formation in the lesion; however, the cartilage produced has been shown to be fibrocartilage in nature, and hence, this procedure is classed as a reparative procedure [25].

  Microfracture remains the most commonly performed procedure for cartilage defects worldwide. Gowd et al.

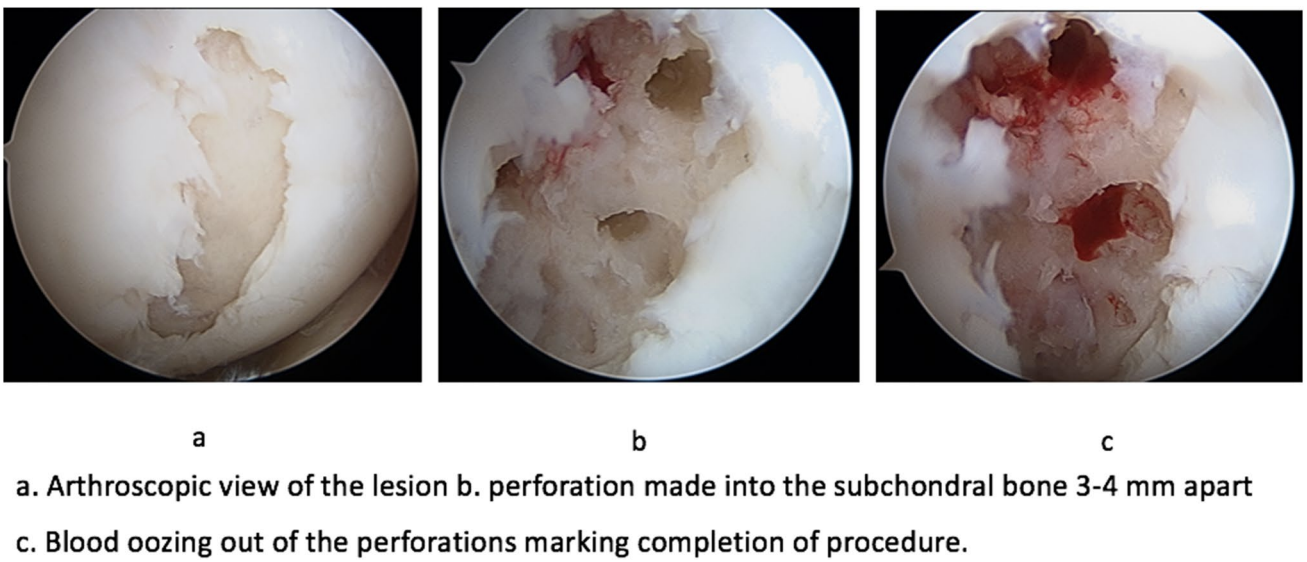

Fig. 3 Microfracture for treatment of focal chondral defects

[5] reported that microfracture accounts for nearly 1/3 of all cartilage procedures performed. This can ascribed to the fact that it is inexpensive, technically easy and minimally invasive [7].

Multiple studies have assessed outcome of microfractures in treating cartilage defects [18, 26, 27].

While the outcomes reported vary greatly, it provides significantly improved outcome in short-to-mid-term, but the benefits are not durable (i.e., beyond 5 years) [28].

Reported results have been better in patients < 40 years of age [29] and in lesions < 2.5 cm^2 and definitely inferior outcomes in lesions > 4 cm^2 [30].

Another pertinent point is inferior outcome in patients with damage to the subchondral bone and also inferior outcomes of revision cartilage restorative surgeries [5].

- AMIC

  Researchers have proposed the idea of concentrating and augmenting the growth factors/cells within the lesion leading to the development of autologous matrix induce chondrogenesis, often described as microfracture deluxe edition, and involves covering the microfracture site with collagen membrane. This is postulated to allow better outcome and durability of the results in medium lesions > 2.5 cm^2 [31].

  Investigators have reported equivalent results to ACI in small lesions 2–4 cm^2 [32].

  There is not sufficient evidence yet to recommend it above ACI or other restorative procedures, but it may be preferable to MF alone specially in moderate-sized lesions.

- OATS/mosaicplasty

  This involves debridement of defect bed and transfer of osteochondral plug from donor site to recipient bed [9].

  It has shown reproducible results in small lesions < 2–4 cm^2 [8] and is also recommended in athletes and high-demand individuals as it allows early return to activity [33]. The harvested plugs have matured native hyaline cartilage, which once incorporated can start functioning fairly quickly [18].

  The harvested plugs have both hyaline cartilage and subchondral bone making it ideal for treatment of osteochondritis dissecans lesions [9].

  Hangody et al. [9] reported good-to-excellent outcome at long-term follow-up (10 years) following OATS for knee lesions.

  However, it is technically demanding and clinical outcomes depend greatly on perpendicular and flush seating of the harvested grafts within the recipient bed [34].

  The procedure is limited by the size of lesion, and another option described for larger lesions and for revision procedures is the use of osteochondral allografts (OCA), which mitigates the donor side morbidity and provides hyaline cartilage at the defect side [35]. Success of the procedure hinges upon the viability of the chondrocytes in the allograft and freshly harvested allograft < 28 days prior to transplant have the best viability. The availability and matching of graft along with the chances of disease transmission, and failure of graft incorporation are issues which currently limit the use of this technique [36].

- Autologous chondrocyte implantation

  This entails, in the first surgery, a biopsy of healthy articular cartilage. Chondrocytes are extracted from the sample and cultured in-vitro to massively multiply the number of chondrocytes [11]. In second procedure, the defect bed is debrided, and the cultured chondrocytes are injected in and sealed with periosteal flap/collagen membranes [6].

  This is hypothesized to produce hyaline cartilage and leads to a better functional outcome and is expected to have more durability [11]. It can be used to cover relatively large defects. While the principle has remained intact, research has concentrated on ensuring effective delivery of cultured chondrocytes.

  In the first generation/conventional ACI (ACI-P), periosteal flap was sutured to cover the lesion. The shortcomings were large incision to harvest flap, technical difficulty in sealing the flap to prevent leakage and graft hypertrophy [37].

  Second generation/(ACI-C) involves the use of type I/III collagen membrane to cover the defect, and sealed using fibrin glue. Steinwachs and Kreuz [38] reported significantly improved outcomes and no graft hypertrophy.

  Matrix-induced autologous chondrocyte implantation (MACI) involves seeding of chondrocytes onto a collagen bilayer/scaffold (type I/III). The advantages of MACI are reported to be less invasive, possible arthroscopic procedure, and good stability of construct, and it has been shown to provide good outcomes [2].

  More recently systematic reviews have analyzed outcomes following ACI and suggest it as the preferable method of treating larger defects (> 4 cm^2) [39]. It is also purportedly preferable in fresh lesions and in younger patients [12].

  One distinct characteristic evident is the higher rate of failure with ACI following microfractures as against ACI as the first procedure [40]. This has been attributed to the fact that marrow stimulation can lead to degeneration of osteochondral unit [41].

  While the reported advantages have been more pronounced with the newer generation of ACI; high cost, need for second surgery, and longer recovery time means that the search for an ideal procedure continues.

- Orthobiologics

Numerous biological options have been studied to assess their roles in managing cartilage defects in the last decade. Notable amongst them are bone marrow aspirate concentrate (BMAC), platelet-rich plasma (PRP), mesenchymal stem cells (MSCs), and adipose-derived stem cells (ASCs).

BMAC: This involves harvesting and concentrating bone marrow to increase the number of MSCs in the specimen. Not only does it provide stem cells it is also a veritable kitchen sink of growth factors and cytokines notably transforming growth factor beta, VEGF, bone morphogenic protein (BMP)-2 and 7, and other chondropoietic factors [42].

Initially, BMAC was used as an adjunct, but it is being increasingly utilized with scaffolds as an alternative to ACI. Gobbi et al. [43] found significantly improved functional outcomes with BMAC supplemented collagen scaffolds in focal cartilage lesions.

A key advantage of using BMAC with scaffolds is that it is a one step process, reducing cost and treatment time and with no reported adverse effects. It makes BMAC an attractive alternative to ACI with good efficacy and safety profile [14].

PRP: Although it is beneficial for cartilage wear in OA patients, its role in cartilage lesions is mainly as an adjunct. Lack of standardized protocol makes it very difficult to compare outcomes following its application. Leukocyte poor PRP reportedly provides a favorable climate for stem cell expansion and improved cartilage growth [44]. PRP is utilized with micronized allogenic articular cartilage to augment microfractures [45].

However, currently, there is insufficient evidence to recommend its usage for cartilage defects outside of research settings.

Adipose-derived mesenchymal stem cells (ASCs): They provide an easily accessible route to harvesting stem cells; and are reported to have a higher concentration of stem cells than BMAC [46].

ASC still remains an experimental option [14] with lot of research interest.

Outcome Comparisons

We searched published literature for clinical trials comparing ACI to other cartilage repair and restoration techniques. Greater emphasis was laid on identifying studies that were comparative trials or cohorts, had a longer follow-up and larger sample size. Preference was given to recently published trials. We searched PUBMED, EMBASE and Cochrane database for clinical studies that reported functional outcomes/PROM following cartilage procedures. Table 2 outlines the characteristics, outcome measures and results of the studies utilized for outcome comparison between cartilage procedures.

- ACI v/s microfracture

  Knutsen et al. [47] compared first-generation ACI to microfracture in 80 participants and followed them over 14–15 years. They found that both group of patients improved significantly following intervention. There was no significant difference in Lysholm scores, VAS, or SF-36 reported outcomes amongst the two groups. At the last follow-up (14–15 years), there were 17 failures in the ACI group and 13 in MF group, which was not statistically significant.

  Similarly, Vanlauwe et al. [48] reported no significant difference in the outcome between ACI and MF at 5 year follow-up, measured using KOOS ($p = 0.116$).

  Kon et al. [49] studied second-generation ACI compared to MF in 80 patients and at 5 year follow-up reported significantly better IKDC scores and return to sports in ACI group. They also reported deterioration of results with MF over time.

  Recently, Brittberg et al. [50] compared MACI with MF after 5 year follow-up, and they too reported significantly better objective functional outcomes in the MACI group (KOOS, $p = 0.02$).

  Thus, the reported literature shows equivalent results with first gen-ACI and MF, but better and more durable outcomes with newer generation ACI interventions.
- ACI v/s OATS

  Horas et al. [51] evaluated 40 patients treated with OATS and ACI, and found no significant difference between PROMs at 2 years.

  In a larger study, Bentley and associates [52] followed up patients undergoing ACI/OATs for 10 years and found that significantly better maintained results in the ACI group. The Cincinnati rating scores were also significantly higher in the ACI cohort.

  These studies point toward improved outcome with ACI and OAT, but improvements were sustained better over long term with ACI.
- BMAC v/s ACI

  Gobbi and colleagues [43] compared BMAC against MACI, found no adverse events in either arm, and showed improvements in both arms with significantly improved subjective IKDC scores in BMAC group.

  In a study with minimum 10 year follow-up, Teo et al. [53] analyzed outcomes comparing BMSCs with conventional ACI and found comparable PROM scores at final follow-up.

  BMAC appears to be potential candidate for primary cartilage procedure along with newer generation ACI, but needs further evaluation in larger cohorts.

Table 2 Studies comparing outcomes following ACI and other cartilage procedures

S. no.	Author name (year of publication)	No. of subjects	Follow-up	Outcomes reported	Conclusions/recommendations
ACI v/s microfracture					
1	Knutsen et al. 2016 [47]	80 (ACI = 40, MF = 40)	180	Tegner activity levels Lysholm score Visual analogue scale (VAS) Short form-36 (SF-36)	No significant difference in two interventions using Lysholm score ($p = 0.267$), VAS ($p = 0.071$) and SF-36 ($p = 0.747$) Both groups had a median Tegner score of 4 at the last follow-up Significantly better outcome in young patients (< 30) $p = 0.013$ Association of histological quality and risk of later failure seen at 5 years was no longer significant
2	Vanlauwe et al. 2011 [48]	112 (ACI = 51, MF = 61)	60	KOOS	No significant difference
3	Kon et al. 2009 [49]	80 (CCI = 40, MF = 40)	60	Tegner activity levels IKDC scores Return to competition	IKDC: significant improvements in both groups Significantly better for ACI at 5 years TAS: degraded for MF at 5 years follow-up
4	Brittberg 2018 [50]	128, MACI = 65, MF = 63	60	KOOS SF 12 Cincinnati knee rating system	All parameters improved significantly ($p > 0.05$) over baseline for MACI and MF Significantly better KOOS for MACI group at 5 years ($p = 0.02$)
ACI v/s OATS					
1	Horas et al. 2003 [51]	40 (ACI = 20, OAT = 20)	24	Lysholm knee surgery score Meyers score Tegner activity level score	No significant difference in two interventions with Meyers score and Tegner score Significantly better Lysholm score in OAT patients ($p \leq 0.012$ at 24 months)
2	Bentley et al. 2012 [52]	100 (ACI = 58, OAT = 42)	120	Cincinnati rating Stanmore–Bentley functional rating	ACI shows significantly reduced number of failures (17% v/s 55%, log rank, $p < 0.001$) significantly better Cincinnati scores ($p = 0.02$) and non-significantly better Stanmore–Bentley functional rating ($p = 0.27$) with ACI (assessed in patients without failures)
BMAC v/s ACI					
1	Gobbi et al. 2015 [43]	37 (MACI = 19, BMAC = 18)	36	IKDC KOOS Tegner activity level	No adverse events in either group Both groups showed significant improvement from baseline ($p = 0.001$) Significantly better IKDC subjective scores for BMAC group ($p = 0.015$) MACI had better outcome in trochlear lesions than patellar lesions

Table 2 (continued)

S. no.	Author name (year of publication)	No. of subjects	Follow-up	Outcomes reported	Conclusions/recommendations
2	Teo et al. 2019 [53]	62 (ACI = 32, BMSCs = 30)	120	IKDC SF-36 Lysholm knee score Tegner activity scale	Improvement on all PROMs except mental component of SF-36 Equivalent outcomes, no significant difference between the two groups

Factors Affecting Outcome and Management Guidelines

As evident from the preceding paragraphs, there is no one size fits all procedure for cartilage defects. An attempt is now made to focus on features, which have the potential to influence treatment protocols and subsequent outcome of the cartilage reparative/restorative procedure.

The patient characteristics that influence outcomes following cartilage procedures and consequently the choice of procedure are detailed in Table 3.

Lesion characteristics play a pivotal role in the outcome of cartilage reparative/restorative procedures. The subsequent table delineates the recommendations for cartilage procedures based on lesion characteristics (Table 4).

While appraising all the evidence, it has to be borne in mind that the reported studies have a lot of heterogeneity in terms of outcome scores, defining success and treatment failure, and follow-up periods, and hence, it is difficult to pool the data to synthesize a consolidated recommendation. This in a way mirrors the actual clinical scenario wherein patient characteristics and expectations, surgeon preferences, and availability and economics of the procedure play a big part in the management decision. Nevertheless, an attempt has been made to create an evidence-based algorithm/guidance tool for managing cartilage lesions, and is presented in Fig. 4.

Summary

In general, cartilage procedures discussed have been reported to be efficacious in varying degrees across the spectrum of cartilage defects managed and management strategy needs to be customized for each patient. Newer generation ACI has shown improved mid- to long-term outcomes in properly selected patients. Stem cells with scaffolds have also shown promising early results, and further research and longer prospective trials are needed to assess their comparative efficacy. The search for the ideal cartilage restorative therapy continues, with further refinements being developed and assessed. The ever-increasing use and research into biologics and chondrogenic factors are another potential area from which newer methods of managing chondral defects may emerge.

Table 3 Patient characteristics influencing outcome of cartilage procedures

Characteristics	Preferred option	Alternative option	Remarks/reference
Age			
< 30	ACI, MF	OATS	[17, 25]
30–40	OATS	BMAC	ACI and MF are more affected by the age of the patient [18]
> 40	OATS	BMAC	However, presence of OA is a relative contraindication to OATS [36]
Demand/activity level			
Low demand	MF	OATs/ACI	
Athletes/high demand	OATS	ACI	Quicker return to activity with OATS [18, 33]
Chronicity of the disease			
Acute	ACI	IE	[2, 11]
Chronic	IE	IE	

IE insufficient evidence to recommend any specific modality over the other

Table 4 Lesion characteristics influencing outcome of cartilage procedure

Characteristics	Preferred option	Alternative option	Remarks/reference
Size			
<2 cm^2	MF	OATS	Universal good results, but MF preferred due to low cost and ease of procedure [18]
2–4 cm^2	OATS	ACI	[18]
>4 cm^2	ACI	BMAC	[39, 43]
Location of lesion			
Trochlea	All procedures	–	MACI is better in trochlear lesions, while BMAC is not influenced by location [43]
Patellar lesions	BMAC	ACI	[43] OATS has inferior outcomes and may be avoided [9]
Type of lesion			
Non-traumatic lesions (osteochondritis dissecans)	OATS	–	[9] MF should be avoided in partial thickness lesions and lesions with subchondral bone defects [36]
Previous treatment			
Microfracture	OAT	–	ACI has poorer outcomes after failed MF [40]
OAT	OAT/OCA	–	[35]

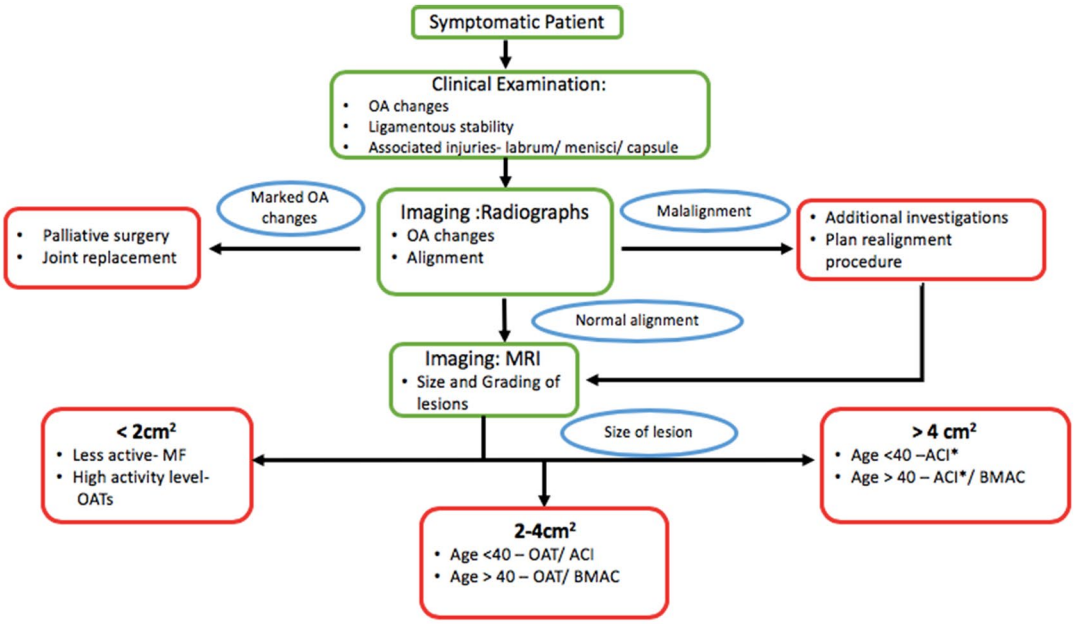

Fig. 4 Algorithm for management of full-thickness cartilage defects

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Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest. No financial aid of any nature was obtained from any source for this article.

Ethical standard statement This article does not contain any studies with human or animal subjects performed by the any of the authors.

Informed consent For this type of study, informed consent is not required.

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