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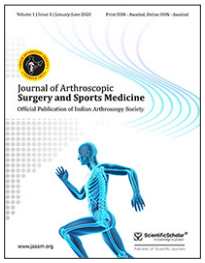

Regenerative Orthopaedics *Review Article*

Recent advances and future trends in articular cartilage repair

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ABSTRACT

Hyaline cartilage is an absolute necessity for a painless and a fully functional joint. A chondral or an osteochondral injury that doesn't heal or doesn't undergo a timely repair, eventually lead to arthritis. Many surgical options have been advocated and practiced in last three decades to treat the chondral and the osteochondral lesions. While some of the techniques are now available with the long term results, many techniques have evolved further to produce better results and lesser complications. Newer technologies have also been developed and they are looking promising. In 2020, it is timely to do a literature review of all the techniques suggested and practiced in last three decades and analyze their current status. It is also prudent to envisage, what can we expect in near future from the recent technologies on cartilage repair. The purpose of this paper is to update about the recent status of the established procedures and to review the future trends in cartilage repair.

Keywords: Cartilage repair, Microfracture, ACI, Mosaicplasty, Scaffolds

INTRODUCTION

Hyaline cartilage is an absolute characteristic of a painless joint. An untreated chondral or an osteochondral (OC) defect has a great potential to progress to a localized arthritis and then to a generalized osteoarthritis. Total knee arthroplasty is a good alternative to treat osteoarthritis in the elderly, but not in the young. For the younger generation, a long-lasting joint preserving treatment that can provide hyaline repair is a necessity now. However, we must answer how, when and with what; to meet this necessity.[1]

Past three decades have seen a plethora of surgical options to treat the cartilage defects.[2] Many techniques came and vanished, while many techniques stood the test of time and evolved further. A few techniques could produce a hyaline (like) cartilage but the hyaline cartilage produced was nowhere near to a pristine hyaline cartilage. New ideas must pour-in and should get enough considerations by the scientific community, as we are far away from reaching the gold standard in cartilage repair.[1] It is quite timely to analyze the present position of cartilage repair in 2020, and to analyze what the future holds. Past 5 years of literature would provide an insight into the long-term results of many procedures that were started around the beginning of the 21st century and would also provide an insight into the upcoming technologies that might hold a promising future. The purpose of this paper is to update about the recent status of the established procedures and to review the future trends in cartilage repair.

METHODS

As the cartilage repair is a very wide and diverse topic, a systematic review of such a broad topic is beyond the purpose and expectation of this review. Rather, important studies in the past 5 years were scanned to understand the current concepts behind each cartilage repair procedure and to create a summary of the future expectations from the various cartilage repair surgeries. A literature review was done on PubMed utilizing terms "Cartilage Repair Knee" with filters as English literature, 5 years, and humans. A total of 788 studies were filtered that were further scanned to meet the purpose of our study. The cross references relevant to the purpose were also looked into, so as to trace the important mile stones papers of the past 10 years. Finally, a total of 86 studies were found relevant and were reviewed.

RATIONALE BEHIND CARTILAGE REPAIR SURGERIES

Before reviewing the various techniques, it is quite important to understand a rationale behind performing the cartilage repair surgeries. The important questions are still the same as they were two decades ago, "Is it worth performing cartilage repair surgeries?" or "Do these technologies help in delaying osteoarthritis?" The current review of various techniques and studies revealed encouraging results. Jungmann *et al*.[3] (2019) did a prognostic Level II study comparing the progression of osteoarthritis in 16 patients treated with cartilage repair surgery for the focal chondral defects (osteochondral autograft transplant system [OATS] $n = 12$; membrane based autologous chondrocyte implantation [MACI], $n = 4$) with similar non-operated 16 subjects from osteoarthritis initiative study group having identical cartilage defects. The chondral defects in both the groups were equally distributed at the femoral condyles ($n = 8$) and the patella ($n = 8$) and the mean defect size was 1.4 cm^2 (SD ± 1.3) and 1.3 cm^2 (SD ± 1.2) for the control and the cartilage repair groups, respectively. Morphological knee abnormalities were assessed using whole organ MRI score (WORMS) and magnetic resonance observation of cartilage repair tissue (MOCART) scores on a baseline MRI and a follow-up MRI at the mean duration 5.7 ± 2.3 years. The total WORMS score and cartilage defect scores were significantly more severe in the non-operated individuals ($P < 0.05$). In the non-operated subjects, T2 values also increased continuously from a baseline to 8 years follow-up ($P = 0.001$). The authors concluded that the cartilage repair surgery cases showed less progression of the degenerative MRI changes at 6 years follow-up compared to a similar control cohort.

CARTILAGE REPAIR TECHNIQUES

Microfracture (MF)

MF is being considered as the gold standard and the first-line treatment for the cartilage repair by some.[4,5] Belk and McCarty[6] (2020) in their editorial commentary stated ease, low cost, and short-term good outcomes as the reasons behind the preferences for the MF procedure. Multiple studies have shown that the outcomes of MF worsen after 5 years postoperatively, particularly for the larger lesions. Kim *et al*.[7] (2019) reviewed the long-term results of MF in the middle aged (mean age 51.3 ± 4.7 years) Asian patients. Seventy-one patient aged between 40 and 60 years underwent MF for localized chondral defect and followed for a mean 7.2 ± 2.6 years (range, 1.0–17.4 years). Most patients showed a 50% of the defect filling on MRI at 2 years, however the clinical scores that improved at 1 year reached the pre-operative levels at 10 years. There was also evidence of a radiological progression of the osteoarthritis at 5 years. Goyal *et al*.[8] in Level II systematic review of literature showed a better short-term results of MF for the treatment of small lesions in younger patients with low post-operative demands. They concluded that the results of MF tend to fail beyond 5 years regardless of the lesion size.

Based on the review of many recent studies, MF cannot be recommended as the first line of treatment or the gold standard but can certainly be recommended as the baseline treatment for certain limited indications such as small size defects in young and low post-operative demand patients. The results of MF will have a high tendency to deteriorate beyond 5 years or in larger lesions, mainly attributed to the poor mechanical qualities of the fibrocartilaginous repair [Figure 1] and a subchondral (SC) bone overgrowth.[9] To expand the usage of MF beyond the small lesions or in high demand patients, the post-MF repair environment must be optimized using augmented procedures like using scaffolds. The future of MF lies in the incorporation of the biological scaffolds that can improve chondrogenic differentiation and a proliferation of the cells for a better quality cartilage repair tissue.[10,11] Some of the extensively used products such as autologous matrix-induced chondrogenesis (AMIC) and CarGel are discussed in the later sections of this review.

Osteochondral cylinder transfer technique

OC cylinder transfer technique (OCT) is the transferring of the cylindrical OC autografts from the less weight bearing area of the femur to the chondral defect in the weight bearing area of the femur. The procedure is technically highly demanding and has donor site limitations.[12] Originally described by Hangody and Kárpáti[13] (1994), there are

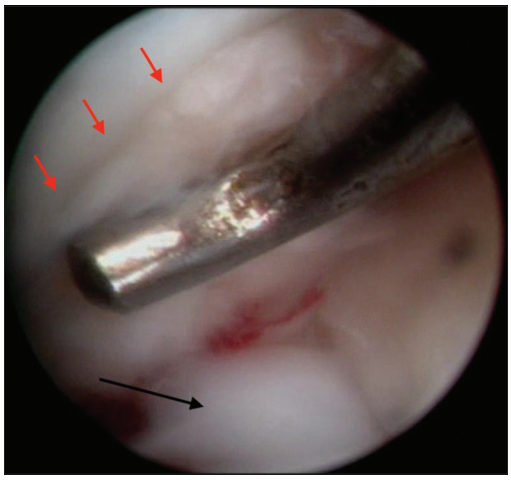

Figure 1: Fibrocartilage regeneration after the microfracture technique. Right knee arthroscopy picture (viewing from the anterolateral portal) of a 53-year-old female who underwent MF for the focal chondral defect of the medial femoral condyle 8 years ago. The probe is over the fibrocartilage regeneration area which is seen as soft, less shiny, and irregular surface as compared to the hyaline cartilage seen at the left upper corner; and both separated by the red arrows at the integration zone. Also seen is the fluffy whitish area of the hypertrophic cartilage (black arrow) at the bottom, the possible reason for the frequent catching sensation to the patient and indication for re-arthroscopy. MF technique has a limitation of regenerating fibrocartilage like regeneration that is poor in quality and fails early.

various variations available by different manufacturers such as mosaicplasty (Smith and Nephew, Andover, USA) and OATS (Arthrex, USA). The technique is expected to provide hyaline or hyaline-like repair as against MF which provides a fibrocartilage repair tissue.[14] It is now 25 years since the procedure was first described in 1994 and the long-term results must be reviewed.

Hangody *et al.*[15] (2010) analyzed the results of multi-center, mosaicplasty procedure in athletic population at a maximum of 17 years and reported good to excellent results in 91% of femoral, 86% of tibial, and 74% of the patellofemoral mosaicplasty cases. Donor site morbidity leading to a patellofemoral pain was observed in 5% of cases. Second look arthroscopy was done in 21 patients and revealed good, congruent, and smooth surface in 16 patients and degenerative changes in 5 cases. They recommended mosaicplasty as an useful alternative for the treatment of the chondral or the OC defects of size 1–4 cm^2 with an expectation of a slight deterioration at a mean 9.6 years in the competitive athletes. Gudas *et al.*[16] (2012) analyzed Tegner scores, X-rays and MRI of osteochondritis dissecans (OCD) athletes treated either with MF or OCT at 10 years follow-up. OCT resulted in a significantly higher rate of return to preinjury level sports activity as compared to MF. Another study by Gudas *et al.*[17] (2013) compared the results of 34 athletes each, treated with debridement, MF, and OCT along with the ACL reconstruction, and followed for a minimum period of 34 months. The authors concluded that the OCT cases led to a significantly better IKDC subjective and Tegner score as compared to the MF and the debridement group, while the post-operative ACL stability was similar in all the groups. Liu *et al.*[18] (2019) reviewed the long-term results of an OC transplantation at a mean duration of 10.2 years (10.0–10.7 years) in 15 cases and found a statistically significant high results in clinical score (KSS score improved from 38.86 ± 4.09 to 85.07 ± 2.19, $P < 0.05$) and the functional score (from 3.33 ± 4.88 to 82.67 ± 4.58, $P < 0.05$). A Level I randomized clinical trial by Solheim *et al.*[19] (2018) compared a minimum 15 years long-term results of MF ($n = 20$) with OCT ($n = 20$) having a mean lesion size of 3.5 cm^2 (range 2–5 cm^2) in young age group (18–50 years). The main outcome score was Lysholm score and that remained significantly better at 12 months, 5 years, 10 years, and 15 years in OCT group compared to the MF group signifying better long-term results of OCT.

A systematic Level II review of literature by Goyal *et al.*[20] (2013) found a distinct advantage of OCT over MF in younger patients and with smaller chondral lesions. Another meta-analysis by Haien *et al.*[14] (2018) comprising five studies and 294 patients compared OCT with MF and revealed that there is a distinct advantage of OCT while referring to the index of return to activity, ICRS scores, and the rate of failure; while there was no significant difference in rate of excellent or good results and the rate of osteoarthritis. The study was silent about the size of the defect while comparing between OCT and MF.

The recent status of OCT seems superior to MF as there is a very high trend toward greater longevity, durability, and improved outcomes, even in high demand patients and with mid-size lesions.[12] Compared to this, recent MF status favors it to be preferred only in small lesions with less post-operative demand patients for a shorter duration of expected recovery. However, limitations of OCT stands same as they were 25 years ago, namely, a donor site morbidity [Figure 2], limited number of grafts [Figure 3], and the high surgical skills. Any evolution in the technique that can ease the harvesting and implantation procedure while decreasing the donor site issues will make this technique more surgeon-friendly; however, no progress is seen toward this in the current literature.

Autologous chondrocytes implantation (ACI)

The ACI procedure was originally described by Brittberg *et al.* in their landmark paper in 1994.[21] The classical ACI procedure used periosteum membrane harvested from the proximal tibia to cover the implanted chondrocytes over the

defect and hence this procedure is also known as periosteum based ACI (P-ACI). The first-generation procedure had two major issues, periosteal hypertrophy requiring a high incidence of re-arthroscopy and an additional surgery to harvest the periosteum. The procedure evolved and an artificial collagen membrane was introduced instead of the periosteum patch, thus called the collagen membrane ACI (C-ACI) or the second generation ACI. To avoid many disadvantages of the P-ACI and the C-ACI like suturing [Figure 4], access to the difficult-to-reach areas, etc.; a further evolution took place, wherein the chondrocytes were implanted on the artificial membrane or scaffold in the laboratory itself and then the whole matrix or scaffold was implanted into the defect. This further modification in the technique was called the matrix associated ACI or the third generation ACI. Due to a high technicality, a higher cost and two stage surgeries; ACI was advocated as a second line of treatment traditionally.[22] However, there is recent evidence that favors its use as the first line of treatment in certain selected indications.[6,22]

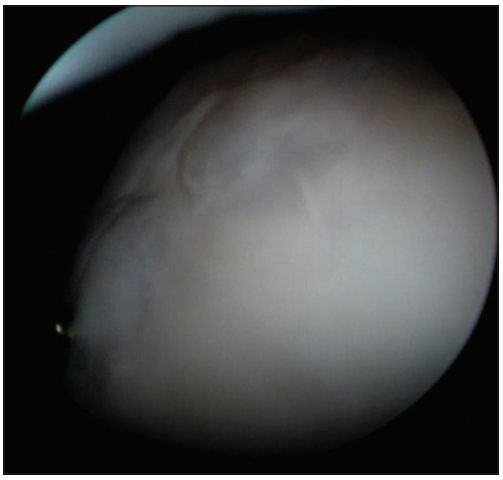

Figure 2: Graft site morbidity due to hypertrophic donor site post-mosaicplasty. A 3 years follow-up arthroscopy was done in a 17 years old patient who was operated for osteochondritis dissecans of the right medial femoral condyle (viewing from the anterolateral portal). The graft donor area, the non-weight bearing zone of the lateral femoral condyle, showed a hypertrophied area due to cartilage overgrowth causing pain on knee flexion. One of the limitations of the mosaicplasty procedure is donor site morbidity in form of post-operative pain or catching sensations.

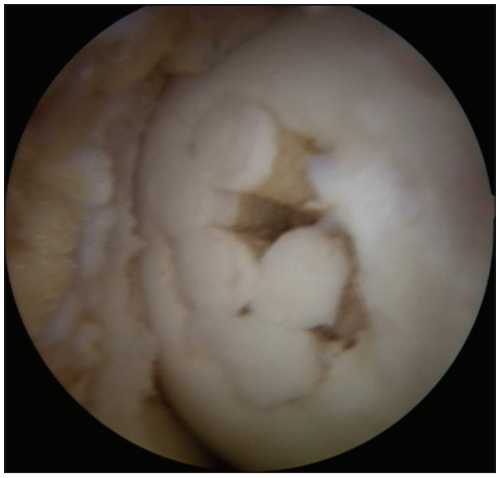

Figure 3: Limited donor osteochondral plugs in mosaicplasty. A 27-year-old male patient underwent left knee arthroscopy for a large osteochondritis dissecans of around 2.5 × 2.5 cm^2. The surgeon could harvest 6 cylindrical OC plugs of 6.5 mm each, but one plug got decapitated, leaving the surgery in jeopardy as there was no more donor area available. This signifies a limitation of the mosaicplasty procedure which should not be performed in larger lesions.

Peterson *et al.*[23] (2010) published the long-term results of P-ACI done in 341 patients with a mean age of 33.3 years and a mean lesion size of 5.3 cm^2. A total of 224/341 patients reported at a mean follow-up of 12.8 years (9.3–20.7 years), of which 92% confirmed that they will opt for the procedure again if the situation arises again and 74% of the patients said that they were better than before or continued to improve. Rosa *et al.*[24] (2016) reported the long-term results of P-ACI in 15 cases done for symptomatic chondral defect of the size 5.08 cm^2 (range 2–9 cm^2). At mean follow-up of 148 months (range 125–177 months), there was a significant improvement in all the clinical scores such as IKDC, Tegner, and KOOS scores, while the MOCART score decreased significantly. Periosteal hypertrophy was present in 26.6% of the cases while 13.3% cases had a failure due to the graft

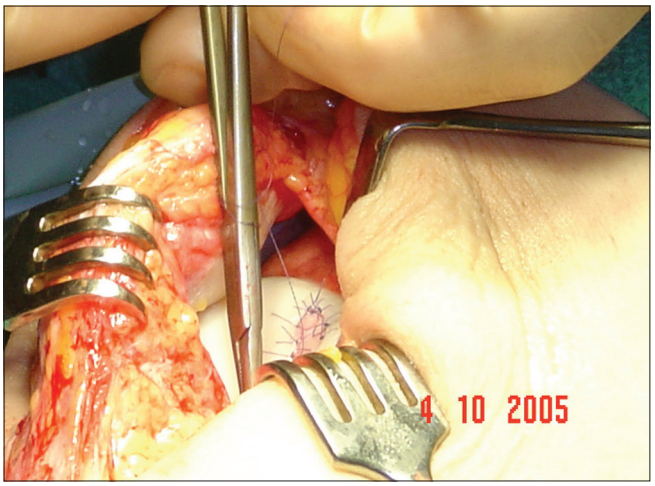

Figure 4: Suturing of the periosteum or the collagen membrane during autologous chondrocyte implantation (ACI). The periosteum based ACI or collagen membrane based ACI, both require respective membranes to suture over the cartialge defect before implantation of the autologous chondorcytes. Taking deep sutures is a tedious job, requires patience and skill, large arthrotomy and have a chance of frequent breaking due to very thin material. Newer generation ACI evolved to avoid the suturing part and thereby incrased the surgical compliance.

detachment. Ogura *et al.*[25] (2017) assessed the long-term results of P-ACI technique done in the adolescent age group having a symptomatic full thickness cartilage defect size of a mean 6.2 cm^2 at a mean follow-up of 9.6 years (median, 13 years; range, 2–19 years). The survival rate of P-ACI was 89% at both 5 years and 10 years and the successful cases did not show signs of the progression of osteoarthritis on a final follow-up. Another arthroscopy to perform the periosteal hypertrophy shaving was needed in 68.9% cases which was a known complication of the P-ACI procedure. Various recent series confirm that there were good results of P-ACI but had a very high incidence of its associated complications such as periosteal hypertrophy. The procedure also evolved over a period of time, thereby offering improving results. There are no confirmed reports of the onset of osteoarthritis at a duration more than 10 years, but MOCART score did deteriorate in one study.[24,25]

Historically, graft hypertrophy has been considered as a major complication of ACI procedure. However, a Level II study by Niethammer *et al.*[26] (2018) proposed a new concept that graft hypertrophy may be an adjustment reaction to the cartilage regeneration process after the ACI procedure and not an indicator of a failure. Twenty patients treated with matrix-based ACI having graft hypertrophy were compared with 21 matched pair (age, defect size, and BMI) patients of non-hypertrophic group in a cohort of total 91 cases having isolated ICRS Grades III-IV defects. In all the cases, T2-weighted relaxation time of ACI continued to improve with the value decreasing from 52.1 ms at 3 months to 33.3 ms at 4 years. The T2-weighted relaxation time was also constant and comparable to the surrounding healthy hyaline cartilage after 12 months. Authors did not find a reduced cartilage quality in the patients with a graft hypertrophy after ACI.

Knutsen *et al.* published the results of a randomized trial comparing P-ACI with MF at 2 years[27] (2004), 5 years[28] (2007), and at 14–15 years[29] (2016). In all the three studies, results of the ACI were not superior to the MF and hence they concluded that there is no extra benefit with a two staged expensive ACI surgery. However, there long-term comparison was found irrelevant by Fu and Soni[30] because the study was initially designed in 1999–2000 when the P-ACI was only a few years old procedure. The ACI procedure has evolved tremendously after that, and P-ACI is hardly used nowadays. An editorial review by Belk and McCarty[6] (2020) further stated that the comparison of MF with the historical ACI (P-ACI) may not be appropriate and it would be better if MF is compared with the newer-generation techniques of ACI. Na *et al.*[31] (2019) did a systemic review of Level I and II studies comparing ACI with MF at mid-term. They reported that the newer generation ACI (C-ACI and MACI) had significantly better results than MF using KOOS, Tegner, and IKDC scores. However, the failure rate remained same between the MF and the ACI in the review. Goyal *et al.*[32] reviewed Level I and II studies and compared the various generations of the ACI. The C-ACI and MACI were proved better procedures as compared to P-ACI with a weak evidence. The reason for the week evidence was stated as short duration of follow-ups, small number of patients, medium size defects, and a younger age group in the reviewed studies. They also found strong evidence in favor of MACI for an accelerated weight bearing post-operative regime.

Brittberg *et al.*[33] (2018) published Level I randomized trial comparing the efficacy and the safety of MACI with that of MF treated for the chondral defects equal to or more than 3 cm^2 in size. The study was performed at over 11 sites in Europe comprising 128 patients (n = 65, MACI; n-63, MF) who signed the informed consent for the study. At 5 years, the results of MACI were statistically significant high with KOOS-pain and KOOS-function sub-score (P = 0.022), statistically better with KOOS-activities of daily living (ADL) (P = 0.007), and statistically less significant with KOOS-quality of life (QOL) and KOOS-other symptoms. MRI evaluation (n = 120) showed improved but not statistically significant defect filling in both the groups. No remarkable adverse event or efficacy issues were noted in either group. Kreuz *et al.*[34] (2018) assessed 21 patients treated with MACI for full thickness ICRS Grade IV chondral defects at 12 years. MRI morphological evaluation showed a moderate to complete filling in 10/14 patients. Clinical scores such as IKDC, Lysholm, and KOOS subscale ADL and QOL showed a significant correlation with the cartilage signals on MRI; both suggesting promising results of MACI at a long-term follow-up. Historically, it is also believed that the results of MACI at patellofemoral joint are less better than a MACI of tibiofemoral joint. A Level III studies by Ebert *et al.*[35] (2017) compared matched groups of tibiofemoral MACI patients (n = 94, medial; n = 33, lateral) with patellotrochlear MACI patients (n = 35, patella; n = 32, trochlea) using KOOS, VAS, and SF-36 clinical scores at 24 months. They concluded that PF group showed a statistically significant improvement similar to TF group, when biomechanical correction was simultaneously performed for the patellar mal-tracking.

Many newer variations of the third generation ACI have been also been tried such as NeoCart®, Spheroids, and gel based ACI.[2,36,37] Anderson *et al.*[36] (2017) did a FDA trial for the symptomatic full thickness femoral chondral defects using ACI (NeoCart®) in 29 patients and analyzed the results using the MOCART score. The MRI analysis using the MOCART score showed a significant improvement with the repair tissue gradually evolving and becoming durable at a 24 months follow-up and then remaining stable from 24 to 60 months. Siebold *et al.*[37] (2016) performed a follow-up arthroscopy examination of the ACI procedure (spheroids)

in 57 defects (41 patients) at a median time of 10 (6–72) months. The macroscopic ICRS-cartilage repair assessment was rated "normal" or "nearly normal" in 52/57 (91.3 %) and "abnormal" in 5/57 (8.8 %) cartilage lesions. Goyal[38] published few case reports of long-term success of gel-based ACI, recently.

After establishment of the ACI as a reliable procedure, there are many attempts to increase its chondrogenic potential and have a better hyaline repair yield. The gene expression of the cultured chondrocytes carry lots of information and can give signals about the cultured cell's chondrogenic potential. Normally, the chondrocytes de-differentiates when grown in a monolayer media during the culture process. Aurich *et al*.[39] (2018) isolated chondrocytes from the articular cartilage lesion site itself and compared their re-differentiation potential in a 3-D alginate bead culture with the monolayer expansion of chondrocytes isolated from the classical chondral biopsy site. Chondral lesion chondrocytes displayed non-degenerative phenotypes, characterized by a relatively high mRNA expression of aggrecan and Type II and X collagen, but a low Type I collagen expression and a low ratio of Type I to II collagen mRNA expression. Whereas, the dedifferentiation in monolayer culture led to a significantly altered degenerative mRNA expression profile. These data suggested that the re-differentiation in the alginate beads after a monolayer expansion resulted in chondrocytes with a greater chondrogenic potential, compared to the expanded dedifferentiated chondrocytes. The gene expression of the transplanted chondrocytes may also have an influence on the maturity of the graft, and a measurement of these genes using polymerase chain reaction tests can be a good prognosticator of the future graft maturity. Albrecht *et al*.[40] (2017) documented the gene expressions (collagen Type I, collagen Type II, aggrecan, versican, and interleukin-1β) of the transplanted chondrocytes from the residues of the implanted MACI at the time of implantation and then correlated these gene expressions with the graft maturity at 2 years on MRI. Improvement of the T2 index at 2 years significantly correlated with the gene expression of collagen Type I A1, collagen Type A2, aggrecan, COL1A1, COL2A1, and the versican genes; while there was no correlation with the expression of interleukin-1β signifying the roles of these markers in the future prediction of the graft maturity post-MACI. Niemeyer *et al*.[41] (2016) tried to correlate a high cell dose with the better chondrogenic potential of the cultured cells. They performed a Level I randomized clinical trial to assess the role of cell dose on the early morphological changes (MOCART score) on MRI after an ACI. There was a better improvement in the MOCART score after 3 months in high cell dose cases; however, there was no difference in the MOCART score after 12 months irrespective of the cell dose.

The post-operative recovery is faster with an arthroscopy procedure with better patient compliance. However, it is not known if the arthroscopic ACI procedure has any influence on the cell viability. Biant *et al*.[42] (2017) analyzed the cell viability of the implanted autologous chondrocytes in arthroscopic procedure versus open procedure in a controlled laboratory setting. Cell membrane had ≥92% viable cells at the time of accepting delivery in the cadaveric laboratory. After either an arthroscopic (n = 8) or open (n = 8), implantation was complete, the cells were captured from the implanted grafts and assessed using a confocal laser scanning microscopy. The open procedure showed 16 times more viable cells as compared to the arthroscopic procedure and the operative time was significantly shorter in the open procedure as compared to an arthroscopic procedure (6 vs. 32 min; $P < 0.001$). This study obviously and strongly recommended a mini-arthrotomy as a procedure of choice as compared to an arthroscopic implantation for the ACI.

Many controversies surround the use of ACI but as noticed by many, it does not make any sense comparing P-ACI with the other cartilage repair procedures (e.g., MF, and OCT) in 2020. The P-ACI has long evolved and is much better a procedure than what it was 25 years ago in the form of the newer generations ACI. The current status of ACI procedure is also very promising with the support of many long-term studies giving good results. However, the biggest hurdle is that we are looking forward to the newer generation of ACI while relying on the results of outdated P-ACI procedure. We must wait many more years to have the long-term results of the newer generation ACI as not enough time has passed for the newer generation ACI to give the long-term results. Meanwhile, scientists continue to work on better cell isolation, cell expansion, cell culture, and characterization techniques. The next decade should come with more robust studies that can characterize chondrocytes to yield a better hyaline regenerate, find out ways that can express markers before the implantation indicating the chondrogenic potential of the cells, and our ability to detect the good and the bad cultured cells.

Osteochondral Allografts (OCA)

OCA transplantation is one of the techniques of choice to repair large chondral defects without causing any donor site morbidity. The many advantages of the allograft include a flexibility in the selection of the graft size and location, single stage treatment, and high chances of regeneration of the hyaline cartilage.[43] However, it does have many limitations such as a short shelf life, size-matched donor requirements, potential challenges of bone healing, limited availability, and a relatively high price.[5]

Nielsen *et al*.[44] (2017) analyzed 142 patients (149 knees, and mean age 31.2 years) who underwent OCA transplantation

for a mean follow-up of 6 years and found 75.2% of knees returned to the sport or a recreational activity. Females, reinjury and a large graft size were the common variables in patients who could not return to the active sports. León *et al*.[45] (2019) retrospectively reviewed 60 patients who underwent femoral unipolar fresh OCAs with a concomitant realignment osteotomy. Failure rate was 23.3% (14 grafts) at mean 8.6 years (1.4–20.1 years) which was defined as the conversion to either a total knee arthroplasty or a revision allograft or a graft removal. The persistent post-operative malalignment was considered as a major risk factor for failure as it was present mainly in the failed grafts (failure case: 28.6% vs. non-failure cases: 4.3%; $P = 0.023$). Graft survivorship was as 87.3%, 85.0%, 74.8%, 65.2%, and 59.8% at 5, 10, 15, 20, and 25 years, respectively. A systematic review of literature by Familiari *et al*.[46] (2018) revealed a mean survival rate of 86.7%, 78.7%, 72.8%, and 67.5% at respective 5, 10, 15, and 20 years; based on the 19 studies comprising 1036 patients. The maximum failures were noticed in the revision cases, the patellar lesions, and the bipolar lesions.

As the indications of OCA is largely for the large chondral and OC defects occurring due to avascular necrosis, large OCD, or large traumatic lesions; there are no comparative trials between OCA and other cartilage repair methods.[43] With the increasing use of tissue engineering technologies, the newer treatment options may prove an alternative to treat the large defects or a control group to assess the long-term results of OCA.

Scaffolds, stem cells, and tissue engineering

While various autogenic and allogenic options are being practiced for nearly three decades, none has been found to be a gold standard. Cell biologists and tissue engineers are working in search of the alternative therapies that can go beyond the limits of autogenous and allogenic solutions and can achieve a final solution in the form of a durable hyaline cartilage regenerate with adequate mechanical properties. The solution must also be a single stage, surgeon-friendly solution that must allow increase in its practical usage.

Scaffolds

The tissue engineers are able to develop newer biomaterials that can mimic the characteristics of the human tissues.[47] Cartilage tissue engineering strategies comprise the use of an appropriately chosen scaffold in combination with the seeding cells; either *ex vivo* on *in vivo*.[48] These scaffolds have become hugely popular because they serve the purpose of single stage, off the shelf products while utilizing the autologous cells. Further, the synthetic scaffolds do not have the risk of transmitting the bacterial contamination and losing the phenotype during the cell manipulation, which is possible with the biological materials. A clinical success with this technology would ease lot of burden on cartilage repair surgeons by reducing cost, high demanding surgeries, and two stage surgeries. The scaffolds can be laden with the cells *ex vivo* and then implanted over the cartilage defect; or the scaffold is implanted along with an adjuvant procedure *in vivo*. Although there are some early promising results of these scaffolds, long-term effectiveness and safety are important concerns. Further, synthetic scaffolds should have the ability to self-degrade and be replaced by the regenerating tissues. These scaffolds can be monophasic for a pure chondrogenic repair or biphasic having osteogenic and chondrogenic potential to treat the OC defects. Monophasic scaffolds are commonly used as an adjuvant scaffold to an existing procedure of the cartilage repair; like in association with the MF, the ACI, or the stem cells. For the regeneration of the SC bone, scaffolds have a challenge to regenerate two different tissues having two different characteristics and healing potentials. Biphasic scaffolds are expected to reproduce the different biological and functional requirements of the bone and the cartilage due to its different biomimetic properties. The commonly available monophasic scaffolds are the collagen membrane (e.g., Chondro Gide®, Geistlich Pharma AG, Wolhusen, Switzerland), Hyalofast, and CarGel (Smith and Nephew Inc.); while the commonly available biphasic OC scaffolds are MaioRegen®, TruFit® (Smith and Nephew, Andover, MA, USA) and Agili-C (CartiHeal, Kfar Sava, Israel), etc.

AMIC is a technique that uses an implantation of a Type I/III porcine collagen membrane, for example, Chondrogide over the MF procedure to improve its chondrogenic potential as well as a long-term repair. However, there are many studies that show better results of AMIC as compared to MF at short-term, but a very few long-term reports. Bertho *et al*.[49] (2018) evaluated 13 patients treated with AMIC procedure for the chondral defects (mean size of 3.7 cm^2, range 2.2–6.9 cm^2; mean depth of 0.5 mm, range 0.4–0.8 mm) having an ICRS Grades III and IV chondral defects in a prospective Level IV study. In 11/13 patients, AMIC procedure showed significant improvements in the subjective IKDC score and KOOS scores with a mean increase of 27 and 28 points, respectively, at a median follow-up of 24 months (range, 12–42 months; minimum, 1 year). Volz *et al*.[50] (2017) did a randomized clinical Level I trial comparing the results of MF with AMIC for the medium size chondral defects (mean defect size 3.6 cm^2) in the age group of 37 ± 10 years. While the results were consistent at 2 years between the two groups, MF cases started deteriorating while the AMIC cases continued to show good results till 5 years. MRI defect filling was also more complete in AMIC group, signifying AMIC as a better cartilage repair procedure at 5 years as compared to MF. Gao *et al*.[51] (2019) did a systematic review of the literature related to AMIC and did not find high-quality, randomized

controlled studies comparing the AMIC technique with the established procedures such as MF or ACI and thus recommended high powered long-term randomized trials to support the AMIC procedure.

CarGel is a chitosan-based polymer biomaterial that is put on a MF treated cartilage defect. The CarGel works as a scaffold to contain the superclot to the defect and to allow the cells to grow in the scaffold in a more organized way. CarGel patients (n = 21/41) showed a better defect filling, integration, and tissue appearance on arthroscopy; a significant surface architecture, cell viability and distribution, more organized repair tissue with better collagen stratification on histology at a minimum duration of 12 months as compared to the MF (n = 17/39) patients in a multicenter randomized controlled trial done by Méthot *et al*. (2014).[52] Steinwachs *et al*.[11] (2019) retrospectively reviewed 91 patients treated with the Cargel + MF. While there was a significant decrease in pain and swelling and a significant increase in MOCART-II score; none of the case showed an allergic reaction or infection or a decrease in the range of motion. Shive *et al*.[53] (2015) analyzed the mid-term results of an international, multicenter randomized control trial of Cargel +MF with MF alone. At 5 years, a blinded MRI demonstrated a significantly higher defect filling and close to normal T2 relaxation time in patients treated with CarGel + MF group as compared to the MF group alone. Both the groups showed a significant improvement in the WOMAC score at 5 years with an equal safety profile. The study confirmed the superiority of CarGel over MF in the superior quantity and quality of the repair tissue.

MaioRegen® is a biomimetic, cell free, and tri-phasic scaffold that attempts to resemble the structure of the OC tissues. The superficial layer mimics the chondral surface (100% Type I collagen), the intermediate layer mimics the tidemark (60% Type I collagen and 40% hydroxyapatite) and the deeper layer mimics the SC bone (30% Type I collagen and 70% hydroxyapatite).[54,55] Perdisa *et al*.[56] (2018) evaluated the results of the OC cell free biomimetic scaffolds in 27 patients of ICRS Grades III and IV OCD with mean defect size of 3.4 ± 2.2 cm^2 at 5 years. The mean IKDC subjective score improved from a mean 48.4 ± 17.8–82.2 ± 12.2 at 2 years and further improved to 90.1 ± 12.0 further at 5 years. The mean Tegner score increased from 2.4 ± 1.7 to 4.4 ± 1.6 at 2 years and then reached to almost the pre-operative level of 5.0 ± 1.7 at 5 years. However, MRI did show abnormalities, more in the SC bone with no persistent improvement from 2 to 5 years in the MOCART score. Authors did not find any correlation between the imaging and the clinical scores. Christensen *et al*.[55,57] (2016) evaluated ten patients operated with MaioRegen for the OC defect, out of which two patients had a failure while the remaining eight patients did not show a complete regeneration of the SC bone on CT. On MRI, 6/8 patients had no or very minor (<10%) SC bone formation, while 2/8 had 50–75% SC bone formation at 2.5 years. Although there was no evidence of SC bone regeneration on imaging, the clinical outcome scores improved which was similar to the findings of the study by Perdisa *et al*.[56] In contrast, a study by Brix *et al*.[58] (2016) showed that 5/8 patients had excellent or good SC ossification of the MaioRegen implant at 18 months following the implantation and 7/8 patients showed a complete integration of the scaffold into the border zone. The surface of the implants was intact but the cartilage quality was not good as revealed by the T2 mapping of the implanted area and the surrounding healthy cartilage. Mathis *et al*.[59] (2018) analyzed the results of a cell-free multi-layered nanocomposite MaioRegen® scaffold for the treatment of OC lesions (mean size 1.0–3.5 cm^2) in 14 patients with a mean age of 33.1 ± 10.7 years. Although the clinical results were encouraging, MRI showed a very poor integration (86% showed a minor or poor filling) at 1 year. A systemic review of 16 studies on MaioRegen by D'Ambrosi *et al*.[46] concluded that MaioRegen showed an effective and a significant clinical improvement in the 1st year after surgery in all the studies that continued to improve till 2 years in 7/16 studies. Only one study reported the results till 5 years and showed a significant improvement. As all the studies in the review were of low evidence and many studies were of short durations, authors did not confirm the clinical superiority of the MaioRegen compared to the conservative treatment or the other cartilage techniques. The histological results reported in 2/16 studies confirmed the absence of any residue of scaffolds suggesting a complete resolution of the graft by the regenerating tissues, indicating the safety of the scaffold.

The TruFit (Smith and Nephew, Andover, MA, USA) plug is a synthetic, biphasic, acellular scaffold, consisting of polylactide-co-glycolide copolymer with calcium sulfate in the bony phase to stimulate the bone ingrowth. Dhollander *et al*.[60] (2015) studied the morphological analysis of synthetic OC plug (TruFit) done in 20 patients for OC defects at a mean follow-up of 34.15 months. The clinical improvement was not comparable with MRI findings where there were persistent SC changes in all patients and a poor defect filling in 30.7% of the cases at 24 months of follow-up. The osteoconductive bone growth was not seen, nullifying the very purpose of the biphasic scaffolds. A systematic review by Verhaegen *et al*. (2015) reported a deterioration of the TruFit plug results after showing an early improvement. Radiologically, there was conflicting evidence on the properties of the newly formed cartilage while none showed an evidence of a bony ingrowth.

Agili-C is aragonite based biphasic, OC scaffold with the superficial layer made up of a modified aragonite and hyaluronic acid while the deeper layer made up of calcium carbonate in aragonite crystals. The laboratory studies revealed the product as safe, biodegradable with a good cell

recruiting and OC regeneration potential.[61] A preliminary study by Kon *et al*.[62] with a tapered shape Agili-C implants did not find any superiority over the conventional cylindrical implants; however, there was no implant removal with the tapered Agili-C implant compared to 10.5% failures in the cylindrical implants at 12 months. The scaffold appears safe with this limited experience but has no significant clinical data yet, to support its use.

Cells

The laboratory and a limited clinical trials of the mesenchymal stem cells (MSCs) have shown their promising potential to influence the chondral repair.[63,64] MSCs must have an ability to reproduce, differentiate, promote angiogenesis, and release the trophic factors and the anti-inflammatory cytokines.[47] The MSCs can be sourced from different areas such as the bone marrow, adipose tissues, synovium, and cord blood.[65] Each sourced stem cells can have certain advantages and disadvantages and with the use of the newer engineering technologies, we can narrow down to those stem cells that can be the most suitable for the human cartilage regeneration.[63] Although, all these technologies are in the experimental stages, they hold lots of promises as evident by the various studies.

The synovial MSCs are highly proliferative and have a high potential to undergo chondrogenesis. Sekiya *et al*.[66] (2015) studied ten patients for a minimum follow-up of 3 years (average 52 months, and 37–80 months) having chondral defects of the knee treated with the synovial MSCs that were expanded with a 10% autologous human serum for 14 days. The synovial MSC suspension was placed on the cartilage defect with a syringe under the arthroscopic control and held for 10 min, while keeping the defect as gravity neutral. On a follow-up, MRI score was statistically significant as compared to the pre-operative scores. The second look arthroscopy done in four cases showed a better quality cartilage repair while the histological analysis showed a hyaline cartilage in three cases and a fibrocartilage in one case. The author recommended that this methodology might be a better option to avoid more complicated and invasive OCT and ACI procedures, but this procedure must prove its supremacy over the MF. Baboolal *et al*.[67] (2018) demonstrated that a specially made device can mobilize the synovial stem cells to up to 105 folds as compared to the use of a cytology brush. They further demonstrated that these cells have a higher affinity to bind to the various fibrous scaffolds. The technology can be used to concentrate cells to the operated defect and increase the repair potential of a joint.

Kyriakidis *et al*.[68] (2020) published the mid-term results of a case series treated using matrix induced culture expanded adipose tissue derived MSCs embedded in a trimmed-to-fit commercially available biodegradable matrix for the treatment of the focal chondral lesions. Twenty-five consecutive patients with an average lesion size of 3.5 cm^2 (range 2–6) and median age of 30.5 (range 16–43) showed significant improvements in the clinical scores at a mean 3 years follow-up. Two years follow-up MRI showed a complete filling and the integration to the border zone in 65% of the patients. Two patients who underwent post-operative biopsies and the histological analysis, demonstrated the presence of hyaline-like tissue. Koh *et al*.[69] (2016) did a Level II randomized prospective trial assessing the clinical and the radiologic efficacy of adipose-derived stem cells (ADSCs) with a fibrin glue and MF (ADSCs + MF) (n = 40) versus the MF (n = 40) alone, in an age group of 18–50 years and having ICRS Grade III/IV symptomatic chondral defect with defect size ≥3 cm^2. At 2 years, 65% patients in ADSCs + MF group had a complete covering of the cartilage defect as compared to 45% in MF alone group; whereas normal or nearly normal signal intensity was seen in 80% of the ADSCs + MF group patients as compared to 72.5% patients in the MF alone group. The KOOS-pain and KOOS-symptoms sub-scores improved significantly in the ADSCs + MF group as compared to the MF alone group; while the KOOS-activity of daily living, KOOS-sports and recreation, KOOS-QOL sub-scores did not show any significant difference between the two groups. The second look arthroscopy showed a good healing in both the groups without any significant difference between the two.

Bone marrow aspirate concentrate (BMAC) is a mixture of the various marrow elements and MSC harvested from the bone marrow. The BMAC technology is getting popular because of easy harvest, easy processing method, and easy ethical clearances if not manipulated.[70] The stem cells present in the bone marrow concentrate can be further cultured as they have more ability to differentiate into either the chondrocytes or the osteocytes. BMAC also have a higher concentrations of the growth factors that stimulate the extra-cellular matrix synthesis and a decreased chondrocytes catabolic activity.[70] The present literature shows early clinical data supporting a better hyaline repair. Cotter *et al*. (2018)[70] evaluated 1832 articles related to BMAC thru a PubMed and ovoid search and found promising results in the clinical application of BMAC. These bone marrow concentrate cells can either be injected into the joint, or culture expanded and used in conjunction with the scaffolds or can be used as an independent procedure.

There are many preliminary studies that have shown better but also variable results with BMAC or BM-MSCs, and hence the future research must find out the components that influence these results in the different preparations of BMAC.[70] The technique needs to evolve at too many fronts such as a more refined BMAC usage, cell isolation and expansion procedures, the ability to produce more collagen

and aggrecan, differentiation environments, injection timing, and quantity. Bone marrow aspirate cells yielded from the posterior iliac crest have the highest concentration of MSCs, while a yield from the other sources have a lower yield.[70] The future studies need to investigate if the yield has any role in the better results. A study by Mahmoud *et al*.[71] showed a better histological appearance of the cartilage repair tissues with a better hyaline cartilage content with 1.25 and 6.25 million bone marrow derived MSCs/ml as compared to 0.125 million MSCs/ml; showing the influence of number of cells on the quality of regenerate. Moreover, cells in the BMAC are questioned to be MSCs by the International Society for Cellular Therapy as these isolated cells do not show a trilineage differentiation.[72] A multicenter randomized clinical trials assessing the optimum number of cells required, the application timing, the selection criteria, the outcome assessment, and adequate control groups are needed.[70]

Gobbi *et al*.[73] (2014) used scaffold made up of collage Type I/III membrane embedded with BMAC and implanted in the large (mean 8.3 cm^2) full thickness chondral defects of the knee in 25 patients. All the patients reported significant clinical outcomes as reported in Lysholm, VAS, KOOS, and Tegner scores at 3 years. Gobbi and Whyte[74] (2016) studied (Level II) the results of a single stage hyaluronic acid-based scaffold with an activated bone marrow aspirate concentrate (HA-BMAC) in 50 patients (mean age, 45 years) with ICRS Grade IV lesions (lesion size, 1.5–24 cm^2) and compared the results with those of MF at 5 years. At 2 years, 64% patients were normal or nearly normal as per IKDC objective score as compared to 100% patients in HA-BMAC group. At 5 years IKDC objective, Tegner, and KOOS scores were higher with HA-BAMC group as compared to the MF group; while Lysholm and IKDC subjective scores were similar in both the groups. The poor outcome of MF group was attributed to the larger lesions (4 cm^2) and multiple lesions. Authors concluded that though MF can provide equivalent to HA-BMAC results at short-term, results of HA-BMAC are better at mid-term. Gobbi *et al*.[75] (2017) prospectively compared the mid-term results of BMAC-hyaluronan based scaffold (Hyalofast) for the treatment of ICRS Grade IV lesions in the patients older than 45 years with the patients younger than 45 years in a Level II prospective cohort study and found it to be a viable and effective option that is mainly affected by the lesion size and number and not by the age. MRI showed a complete filling of the defect in 80% versus 71% in the age group >45 years versus <45 years, respectively.

The present literature on various MSCs and scaffolds is very limited with a very short duration of follow-up and a limited number of cases. Most of the stem cells and scaffold related technology is comparing themselves with the MF procedure. It is already known that though MF can be a first line of treatment for the selected cases, it is not the gold standard. Hence, comparing stem cells and scaffold with MF are like comparing it with a non-ideal technique. MSCs and scaffolds need to be superior to MF only in the preliminary stage, but finally these technologies must prove themselves as better than more hyaline (like) producing techniques. Not only that, but stem cells and scaffolds must also overcome the limitation of OCT and ACI procedures. Large scale validation of the MSCs and the scaffolds related experimental studies, clinical trials, and long-term clinical effects will finally determine the future of the stem cells technology. The technologies also must develop to have a better isolation, expansion, and higher concentrations of the MSCs at the defect site, while it must also simultaneously produce better regenerate with an optimum number of cells. The mechanism by which the optimal MSC dosing can be determined is yet to be found, while we also need to confirm the prochondrogenic effect of a higher number of cells. The scaffolds must be made that can attract more cells and hold cells to the defect site, while providing an optimum environment for an ideal regenerate. Simultaneous researches are also needed to identify less invasive approaches to implant the MSCs and scaffolds to the defect site. Cartilage tissue engineering technology is further constrained by the associated lesions of the SC bone, BME and the limb alignment issues etc., if at all it progresses to a clinical success levels.[76] In all, there are good evidences of MSCs and scaffolds for a short-term against MF, and weak evidence for the mid-term. High quality studies with a comparison to OCT or ACI with long-term results are expected in the future.

Chondral/OC paste

Chondral or OC chips or paste of allogenic or autogenic origin have also been experimented but have very limited presence in the clinical literature. Christensen[57] (2016) performed an experimental comparison on Göttingen minipig using an autologous dual-tissue transplantation (combined autologous bone and cartilage chips) with autologous bone grafting alone for the treatment of the OC injuries. The presence of cartilage chips in a dual-tissue transplantation facilitated the formation of the fibrocartilage as opposed to the fibrous tissue in an isolated autologous bone graft group at both 6 and 12 months, favoring the role of autologous chondrocytes in promoting the cartilage repair. Stone *et al*.[77] (2017) evaluated the long-term (mean 16.8 years, range 10.6–23.2 years) results of an articular graft paste done in 74 patients for severe OC lesions at a mean age of 45.3 (range 13–69 years). The procedure was able to delay TKA in 41.9% (31 patients) to a mean age of 60.2 years. The procedure also improved the pain, function, and activity levels for a mean duration of 16.6 years in the rest of the cases. Particulated Juvenile Articular cartilage (PJAC) (DeNovo NT) is a minced cartilage allograft from the juvenile donors. Wang *et al*.[78] (2018) reviewed 27 patients treated with PJAC for the full-

thickness patellofemoral cartilage lesions at a mean follow-up of 3.84 years. There were clinical improvements in the mean IKDC and KOOS-ADL scores; while MRI showed a persisted prolonged T2 relaxation time from the repaired area. Although clinically encouraging, results were not morphologically positive. A lot of work needs to be done on this technology to keep its existence alive, as the various previously described techniques are more promising at the current time and have more powerful evidence.

IMAGING IN THE CARTILAGE REPAIR

Arthroscopy is a gold standard for the evaluation of the chondral lesion before the surgery and after the surgery. However, it is an invasive procedure and cannot adequately depict the deeper cartilage layer and the SC bone.[79,80] Whereas, MRI is an effective and non-invasive tool to detect and quantify the pre-operative cartilage lesions as well as to assess the post-operative repair status. The SC bone cannot be assessed thru arthroscopy because of the overlying cartilage, but MRI can give a detailed assessment of the SC bone in the OC lesions, and can give us a clue about the pathology occurring in the OC unit.[35,79] Recent MRI technology provides us with an opportunity to do the morphological and quantitative biochemical assessment of the lesion, as both have their own importance.[81] MOCART score is a good system to do the morphological assessment of the pre-operative cartilage as well as the repaired cartilage; as it provides a detailed overview of the defect size, depth, filling, integration, homogeneity, surface integrity, etc.[39,82] The quantitative MRI techniques do the biochemical assessment of cartilage such as a delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC), T2, T2*, T1ρ, and sodium imaging or gagCEST[80,81] and help to assess the collagen content and the orientation, water content, proteoglycan and glycosaminoglycan content etc. For example, the graft maturation can be assessed by measuring the T2 relaxation time values of the transplant and comparing it with healthy native surrounding cartilage, with a high T2 time indicating a less stiff cartilage compared to the native cartilage. At present, the morphological assessment of the repair tissue using the MOCART score is the main role of MRI in the clinical practice. Quantitative biochemical or compositional MRI is mostly used in the research and the clinical trials at present as these need to be standardized and further validated. Future expectations will be a combination of the morphological and quantitative MRI that can give the clinician a detailed structural and biochemical information about the repaired cartilage.[82]

Various studies have compared the results of different procedures such as MF,[7] AMIC,[49] OCT,[83] MACI,[32,33] and ADSCs[68] with the post-operative MRI using either the morphological or the biochemical studies; the comparison being mostly consistent but not always. On the other hand, studies like that of Årøen *et al*.[84] were able to demonstrate the sensitivity of MRI in delineating the quality of cartilage surrounding a focal defect using the T2 mapping and dGEMRIC studies. More comparative researches with a longer follow-ups need to be done, not only to have a consistent MRI based results assessment but also to find the best MRI based analysis to judge the results.

THE CURRENT STATUS AND FUTURE EXPECTATIONS

With a detailed review of each technique, the important question is to find out the best option amongst the available techniques. Riboh *et al*.[85] (2017) did a Level I meta-analysis of 19 RCT from 15 separate cohorts including 855 patients published till 2015 to analyze the comparative efficacy of the various cartilage repair treatments. At 2 years, the re-operation rate between the MF, OCT, and ACI was same. At 5 years and at 10 years, the OCT had a lower re-operation rate as compared to the MF but at 10 years, the OCT had a higher re-operation rate than C-ACI. Tegner and Lysholm scores were comparable at 2 years between MF, OCT, and ACI; however, no long-term comparable clinical outcome data were available. Post-operative biopsy showed better quality hyaline repair in the OCT and the C-ACI cases than in the MF. The C-ACI and MACI had much lower rate of graft hypertrophy than the P-ACI. They ranked the best procedure as the C-ACI, the OCT, and the MACI in a decreasing order, while considering all the outcome measures. A cartilage repair procedure should be optimum enough in quality to allow a return to sports at pre-operative/preinjury levels. Krych *et al*.[86] did a meta-analysis of studies reporting the return to sports at a minimum 2 years following either MF, OCT, OCA, or an ACI procedure. Forty-four studies (18 Level I/ II, and 26 Level III/IV) comprising 2549 patients with an average age of 35 years and follow-up of 47 months were reviewed. The highest rates of return were revealed after the OCT (93%), followed by the OCA (88%), the ACI (82%), and the MF (58%). The faster return to sports was also revealed with the OCT (5.2 ± 1.8 months), followed by the MF (9.1 ± 2.2 months), the OCA (9.6 ± 3.0 months), and then the ACI (11.8 ± 3.8 months). The heterogeneity of the patient age, lesion size, pre-operative Tegner score, etc., was not significant determinants for the rate of return to the sport. The current status of cartilage repair does not favor one technique but favors different techniques depending on the lesion variables. Long-term results of OCT and modern ACI are favorable but have their own limitations, and thus the need for an optimum solution.

However, the gold standard for the cartilage repair is not yet reached and it is not sighted very soon; but there is a light at the end of the long tunnel. One single treatment to treat all types of cartilage lesions will not be possible but a consensus

will reach soon, for the best options depending on the size, the depth, the location, and the demands of the patient. Consensus will develop to better classify and designate each type of lesion and then the guidelines will be made for each designated type of lesion. The most common techniques used currently such as MF, OCT, and ACI will serve as a launchpad to the future surgeries such as the augmented procedures, the scaffold based procedures in adjunction with a better cell harvest, isolation, culture, and characterization techniques. The newer generation techniques will focus on a single stage, over the shelf products with the aim of regenerating hyaline cartilage using better cell, scaffold, and a tissue engineering technology.

CONCLUSION

The MF, the OCT, and the ACI procedure will stay for long with their limited indications. It is up to the surgeons to identify the limitation of each technique and choose the optimum best for their individual case. At present, MF is the treatment of choice for small lesions in the young patients with low post-operative demands and midterm expectations. The technologies to add scaffolds as an adjuvant to MF must get more robust in future so as to expect better MF results in large lesions or for a longer duration of the time. Better results and a better hyaline cartilage regenerate from an augmented MF can decrease the burden on the OCT technique which is presently a treatment of choice for small to mid-size lesions with long-term expectations of the results. OCT is currently performed to get excellent results in small lesions in the high demand patients or to get good results in the mid-size lesions but with a due consideration to the limited graft availability, a small percentage of donor site morbidity and high technical skills. Unless better harvest and implantation techniques are soon invented, the OCT is bound to lose its presence against the more user-friendly techniques like the ACI. The newer generations/third generations ACI are currently used irrespective of the size of lesions when the patient and the surgeon both are comfortable with the high cost and a two stage surgery. The size of the lesion should influence the selection of the ACI procedure, where an ACI can be chosen as the first line of treatment for the large lesions and can be avoided in the smaller lesions. The future expectations from ACI are to get a better cell harvest, culture, and characterization techniques so as to yield a better hyaline regenerate. Scaffolds, tissue engineering, and cell science, all are in very early stages at present but probably holds a promising future. Lots of work need to be done on the cells and the scaffolds, which has a great potential to eliminate all the existing techniques and emerge as a gold standard. But only time can tell…

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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