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Outcomes following gel-based autologous chondrocyte implantation for articular cartilage defects of the knee

Dinshaw N. Pardiwala [a,*], Sachin Tapasvi [b], Deepak Chaudhary [c], Ashish Babhulkar [d], Jacob Varghese [e], David Rajan [f], Abhay Narvekar [g], Parag Sancheti [h]

[a] Department of Centre for Bone and Joint, Kokilaben Dhirubhai Ambani Hospital, Mumbai, India
[b] Department of Orthopaedic, The Orthopaedic Specialty Clinic, Pune, India
[c] Department of Centre for Arthroscopy and Sports Medicine, BLK-Max Super Speciality Hospital, New Delhi, India
[d] Department of Shoulder and Sports Injuries, Deenanath Mangeshkar Hospital, Pune, India
[e] Senior Consultant and HOD, Director of Orthopedics and Department of Joint Replacement & Sports Medicine, VPS Lakeshore Hospital, Kochi, India
[f] Department of Orthopaedic, Ortho One Orthopaedic Speciality Centre, Coimbatore, India
[g] Department of Centre for Orthopedic Care, P.D. Hinduja Hospital, Mumbai, India
[h] Department of Joint Replacement, Sancheti Institute for Orthopaedics & Rehabilitation, Pune, India

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ABSTRACT

Background: Gel-based autologous chondrocyte implantation (GACI) enables a simpler and more effective delivery of chondrocytes with reproducible three-dimensional structural restoration of the articular cartilage surface. There is limited documentation of medium-term outcomes. This study assessed safety and effectiveness of GACI for treatment of cartilage defects of the knee.

Methods: This multicentric retrospective study was conducted across eight hospitals in India. Patients who had undergone GACI (CARTIGROW®) between 2008 and 2014 for the treatment of focal articular cartilage defects of the knee (mean defect size 4.5 ± 5.8 cm^2) in limbs with normal alignment were analyzed. Primary outcomes were changes in Lysholm Knee Scoring Scale score, and Knee Outcome Sports Activity Scale (SAS).

Results: A total of 107 patients (110 knee joints) with mean age 31.0 ± 10.5 years were included. The mean follow-up was 9.8 ± 1.5 years (range 7.85–13.43). Majority had osteochondritis dissecans (n = 51; 46.4%). The mean Lysholm Knee Scoring Scale score (81.23 ± 13.21 vs. 51.32 ± 17.89; p < 0.0001) and SAS score (80.93 ± 8.26 vs. 28.11 ± 12.28; p < 0.0001) improved significantly at follow-up as compared to pre-operative. Magnetic Resonance Observation of Cartilage Repair Tissue score in 39 patients at minimum 2 years follow-up was 84.5 ± 4.3. Among 30 patients who were playing sports before treatment, 17 patients (56.7%) could return to the same or higher level of sports post-transplantation. No major intra-operative or post-operative complications were noted. Four patients warranted revision surgery.

Conclusion: GACI is an effective treatment option for large focal articular cartilage defects of the knee with a low complication rate and revision rate and significant improvement in functional scores.

* Corresponding author at: Department of Centre for Bone and Joint, Director – Arthroscopy Service, & Head – Centre for Sports Medicine, Kokilaben Dhirubhai Ambani Hospital, Mumbai, India.

E-mail addresses: pardiwala@outlook.com (D.N. Pardiwala), stapasvi@gmail.com (S. Tapasvi), deepakchaudhary@hotmail.com (D. Chaudhary), docshoulder@gmail.com (A. Babhulkar), varjac@gmail.com (J. Varghese), davidvrajan@gmail.com (D. Rajan), narvekar72@gmail.com (A. Narvekar), parag@sanchetihospital.org (P. Sancheti).

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1. Introduction

Autologous chondrocyte implantation (ACI) has been established as an effective treatment option for large articular cartilage defects of the knee since it results in a hyaline-rich cartilage repair [1–6]. ACI involves implantation of chondrocytes harvested from a non-weight bearing area of the articular cartilage of the knee joint and expanded *ex-vivo*. ACI has shown benefits in terms of pain relief, quality of life parameters, and improvements in functional scores for treating symptomatic chondral defects in the knee of the size range 2–9 cm^2, with durability of benefits for up to 10–13 years [7–9]. Although the initially described ACI techniques involved implanting the cultured chondrocytes into the debrided articular cartilage defect under a periosteal cover, collagen membrane, or impregnated within a matrix (MACI), technological advances have enabled gel-based delivery systems that enable a simpler and more reproducible three-dimensional structural restoration of the articular cartilage surface [10–12]. Gel-based ACI (GACI) has been available for clinical use for almost two decades now, and although clinical studies with GACI are published, there is limited documentation of its medium-term or long-term outcomes [13–18].

GACI involves a technique in which cultured chondrocytes are mixed with fibrin glue *ex-vivo* and implanted as an injectable form that solidifies within 4 min of cell delivery. This latest generation of ACI facilitates an even cell distribution within the defect, enables a three-dimensional structural restoration of articular cartilage surface topography, ensures a stable cartilage repair construct well-attached to subchondral bone, and potentially decreases risk of graft hypertrophy [19]. Moreover, this delivery system has simplified the surgical technique substantially and improved the ability of the surgeon to address defects of varied shape, depth, and location.

GACI (CARTIGROW®) has been widely used in India since 2008 and is available from Regrow Biosciences Pvt. Ltd, Mumbai, India. The product has received Marketing Authorization from the DCGI, CDSCO, Ministry of Health & Family Welfare, Government of India.

In this study, we retrospectively evaluated the 7–14 years outcomes in patients treated with GACI for large focal articular cartilage defects of the knee. Our study hypothesis was that GACI is an effective treatment option, with a low complication rate, for large chondral defects of the knee, and results in significant improvement in functional scores when evaluated 7–14 years following the procedure.

2. Methods

2.1. Study design and patient selection

This multicentric retrospective study was conducted across eight hospitals in India. We analyzed data of patients who had undergone GACI for the treatment of focal articular cartilage defects of the knee between 2008 and 2014 and who had a minimum 7-year follow-up after surgery. We included all patients aged 18–60 years, with isolated focal articular cartilage defects of the knee joint, of grades III or IV severity as per the International Cartilage Repair Society (ICRS) classification, or unstable osteochondritis dissecans, and normal coronal limb alignment. Patients were excluded the study if they had mal-aligned knees, and if GACI was combined with other reconstructive procedures such as anterior cruciate ligament reconstruction or staged limb alignment corrective osteotomy, patients preoperative or postoperative medical records were incomplete, or if minimum 7 years of follow-up was not available. The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by Institutional Ethics Committee and informed consent was waived for this retrospective study.

2.2. Study procedure

The GACI procedure was carried out in two stages. In the first stage, arthroscopy was performed to delineate the osteochondral defect, and once confirmed to be appropriate for GACI, a hexagonal osteochondral cylinder of 6 mm in diameter was harvested to obtain a full thickness articular cartilage punch biopsy. The preferred site for chondral biopsy is the non-weight-bearing lateral or medial edge of the trochlea above the sulcus terminalis.

This cartilage biopsy was then transferred to a GMP certified cell culture laboratory for chondrocyte harvest and multiplication. Bioprocessing and cell culture were performed in a biosafety level-2 (BSL-2), Grade B cleanroom environment. All tissue samples were processed within 72 hours of collection for cell isolation using a standardized procedure. Cartilage tissues were washed, minced and enzymatically digested. The isolated chondrocytes were then expanded in monolayer culture in tissue culture flasks with Dulbecco's Modified Eagle's Medium (DMEM). The chondrocytes were cultured for 21–28 days until they reached confluency and total number of 48–50 million. Quality control testing was performed at all stages including at receipt, in-process and prior to release of the final product to the hospital. Flow cytometry (FACSCanto™ II flow cytometry system, BD Biosciences, San Jose, USA) was performed on every batch to identify chondrocytes with CD44 and CD151 markers.

In the second stage, the first step was to prepare the cartilage defect and undermine the edges of the recipient site. Perforations of 1 mm at the base were created without penetrating the subchondral bone to avoid bleeding. The undermined

edges and perforations ensured shear stability to the final solidified scaffolding of the cell-gel mixture. Thereafter, a standardized CARTIGROW® formulation procedure was followed to prepare two 1 ml syringes with a "Y" mixing connector. The first syringe contained fibrinogen and the second syringe contained cultured chondrocytes and thrombin. The mixture of chondrocytes and thrombin-fibrinogen was directly implanted drop-wise on to the defect area to achieve complete filling of the defect and restoration of the articular surface topography, creating a three-dimensional scaffold inhabited by the cultured chondrocytes (Fig. 1). No other materials or membranes were used over the recipient area since extracellular matrix formation begins in the GACI recipient site within 4-7 days.

The initially viscous mixture was allowed to solidify at the recipient site, and the implantation was checked for construct adherence and stability, prior to arthrotomy closure. No donor site morbidity was observed or reported in any case of this series. This was primarily due to a small single biopsy harvest being performed. Moreover, during the second stage of ACI implantation, it was consistently observed that the contained biopsy site was completely filled with a consolidating and firm blood clot which can be expected to eventually heal with reparative fibrocartilage. A few surgeons routinely removed this consolidating clot and substituted it with the remaining GACI once the recipient site was implanted. Patients followed a standard post-operative rehabilitation program: non-weight-bearing ambulation with a walker or crutches immediately post-GACI for 4–6 weeks, followed by partial weight-bearing ambulation for another 2–3 weeks. Using a continuous passive motion (CPM) machine or active assisted knee range of motion exercises, a range of 140° of motion was achieved within 8 weeks following GACI. In addition, patients were allowed early mobilization for ranges 0–90° using a CPM machine. Muscle strengthening exercises, such as isometric quadriceps exercise and hamstring co-contraction exercises, were initiated early. At 12 weeks post-GACI, patients could perform stationary bike activities without resistance. Patients could start to walk lightly at 13 weeks and to jog at 6 months. High-intensity exercises and sports activities were introduced 9 months post-GACI. Deviation from the rehabilitation program was at the physician's discretion based on patient's condition.

2.3. Data collection

The following pre-operative and post-operative data were collected retrospectively and reviewed: clinical findings; imaging studies functional scoring data, including Lysholm Knee Scoring Scale and Knee Outcome Sports Activity Scale (SAS). We also documented duration of symptoms, surgical treatment undertaken prior to GACI, reported complications, requirement for revision surgery, and results of relook arthroscopic evaluation when performed.

2.4. Study outcome

The primary outcome measure was change in Lysholm Knee Scoring Scale, and Knee Outcome Sports Activity Scale (SAS). The secondary outcome measure was MRI assessment of cartilage repair using Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART). We also assessed complications following GACI, time to resume sports following GACI, need for revision surgery following GACI, and quality of cartilage repair during relook arthroscopy.

2.5. Statistical analysis

Continuous and quantitative variables were summarized using descriptive statistics and compared using Student's *t*-test or nonparametric test, as applicable. Categorical data were presented as frequency count (n) and percentages (%) and were

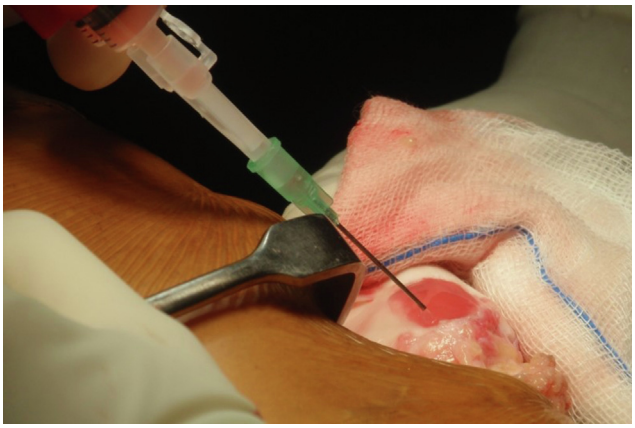

Fig. 1. Gel-based ACI for patellar ICRS grade IV chondral defect. Following recipient site preparation, the fibrin-cell mixture is directly implanted on to the defect area to achieve complete filling of the defect and three-dimensional restoration of the articular surface topography.

compared using the χ^2 test or Fisher's exact test. *P*-values < 0.05 were considered significant. All analysis was performed using SAS version 9.4.

3. Results

A total of 107 patients (110 knee joints) fulfilled all criteria and were included in the study. This included three patients who had undergone bilateral GACI. The mean age was 31.0 ± 10.5 years, and the mean BMI was 25.7 ± 4.6 kg/m^2. The majority of patients were male (68.2%). The mean duration since the diagnosis of cartilage defect was 0.67 ± 1.52 years, and the mean follow-up following GACI was 9.8 ± 1.5 years (range 7.85–13.43).

3.1. Characteristics of cartilage defects

Of the total 110 treated knee joints for GACI, cartilage lesions were located at the medial femoral condyle (MFC) in 69 (63%) patients, lateral femoral condyle (LFC) in 21 (19%) patients, and trochlea/patella/tibial region in 20 (18%) patients. Among all cartilage defects, 39 of the articular cartilage defects (35.4%) were ICRS grade III, 20 (18.2%) were ICRS grade IV, and 51 (46.4%) were osteochondritis dissecans (ICRS OCD II to IV). The mean defect size was 4.5 ± 5.8 cm^2 (range: 1.2–15 cm^2). The most common etiology for articular cartilage defect was traumatic injury, including sports injury in 56 patients (52.3%), and osteochondritis dissecans in 51 patients (47.6%). Nine patients had undergone a failed attempt at arthroscopic cartilage repair prior to GACI, and included eight bone marrow stimulation procedures with microfracture, and one mosaicplasty.

3.2. Clinical outcomes

The mean Lysholm Knee Scoring Scale score improved from pre-operative 51.32 ± 17.89 to post-operative follow-up 81. 23 ± 13.21. This improvement was statistically significant (p < 0.0001). Similarly, SAS score significantly improved (p < 0.0001) from mean pre-operative 28.11 ± 12.28 to mean post-operative 80.93 ± 8.26 at latest follow-up (Fig. 2).

3.3. Cartilage repair assessment

39 patients had undergone a postoperative MRI at minimum 2 years follow-up. MOCART scores ranged from 45 to 100 with a mean of 84.5 + 4.3, indicating a high rate of articular cartilage repair (Fig. 3). Five patients underwent a relook arthroscopy at minimum one year follow-up to study quality of cartilage repair (Fig. 4). Repair assessment was graded as normal (ICRS grade I) in 3 patients, and nearly normal (ICRS grade II) in 2 patients. One patient underwent a postoperative biopsy that confirmed a hyaline-rich cartilage repair.

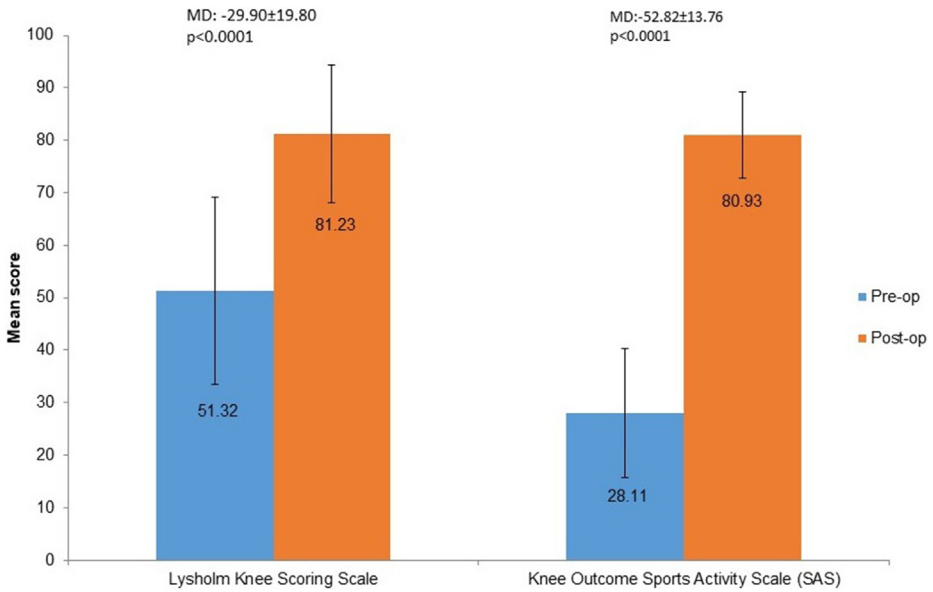

Fig. 2. Comparison of pre-operative and post-operative scores in patients with knee defects.

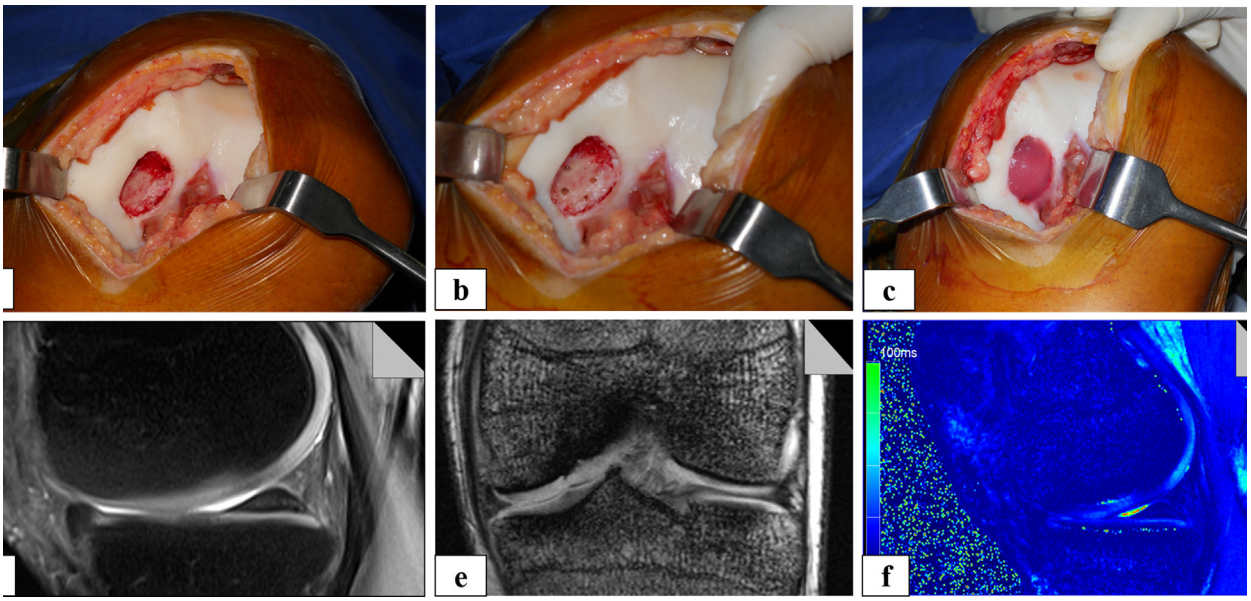

Fig. 3. Osteochondritis dissecans of left knee medial femoral condyle (MFC) treated with gel-based ACI. (a)(b)(c) Intra-operative images: exposure of the 24 × 20 mm MFC defect site, recipient site preparation, and ACI implantation. (d)(e) Two years post-operative MRI reveals complete defect filling with homogeneous repair, intact smooth surface, and complete interface integration (MOCART score = 95). (f) T2 STAR cartilage mapping 2 years post-surgery reveals T2 values of repaired cartilage similar to those of adjoining normal cartilage, indicating successful hyaline cartilage repair.

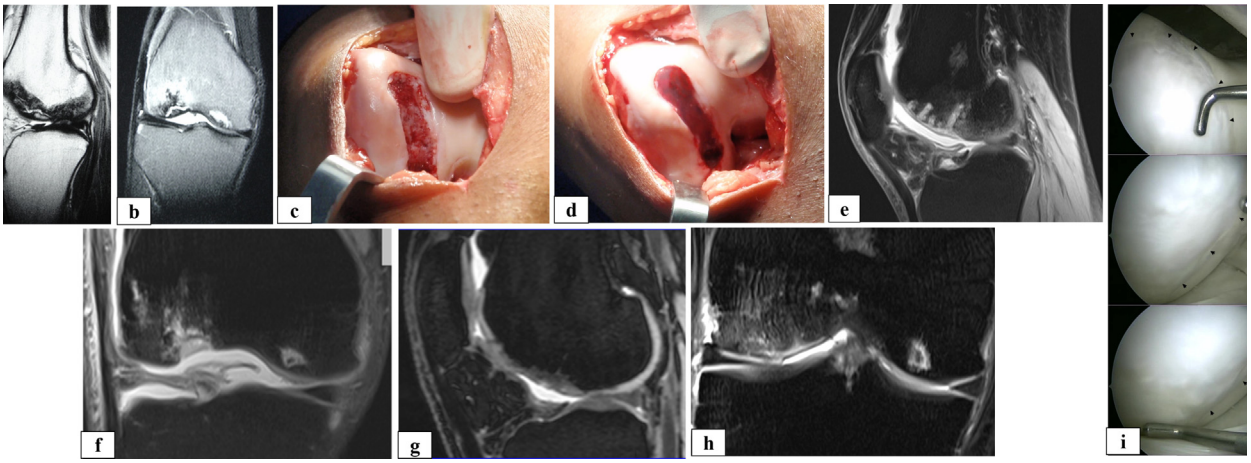

Fig. 4. Gel-based ACI for right knee lateral femoral condyle ICRS grade IV single chondral defect measuring 5.5 × 1.5 cm (8.25 cm^2). (a)(b) MRI delineates the unstable osteochondral lesion of the lateral femoral condyle secondary to avascular necrosis. (c) Recipient site preparation. (d) Gel-based ACI implantation. (e)(f) Post-operative MRI 6 months post-ACI reveals a stable cartilage repair. (g)(h) Post-operative MRI 24 months post-ACI reveals complete defect filling with homogeneous repair and an intact smooth surface. (i) Relook arthroscopy 1 year post-ACI reveals an ICRS grade II (nearly normal) cartilage repair with repair in level with surrounding cartilage, with a demarcating border < 1 mm., and intact smooth surface.

3.4. Return to sport

Among 30 patients who were playing recreational or competitive sports prior to treatment, 17 patients (56.7%) returned to the same or higher level of sports post-transplantation. Of these, 50% played cricket; 30% played football; and the remaining 20% engaged in other sports, such as tennis, badminton, wrestling, hockey, and golf. Mean duration to resume sports was 8.32 ± 1.82 months.

3.5. Complications and revision surgery

No major intra-operative or post-operative complications were noted. However, three patients had mild superficial infections and delayed wound healing; there were no deep infections and revision surgical procedures for infection. Total four

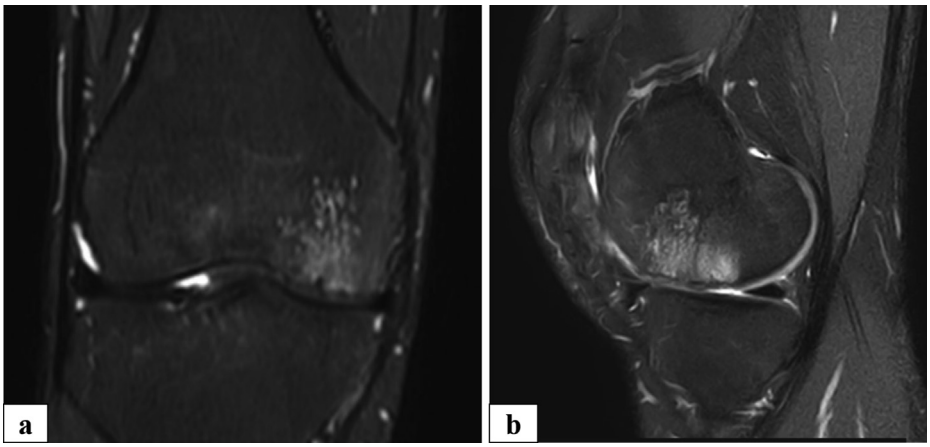

Fig. 5. Failed ACI of medial femoral condyle that was subsequently revised with osteochondral autograft transfer. (a) and (b) Coronal and sagittal MRI 14 months following ACI reveals no healthy cartilage at the repair site with significant bone oedema.

patients warranted revision surgery and included one arthroscopic debridement, two mosaicplasty, and one total knee replacement (Fig. 5).

4. Discussion

Gel-based ACI is an effective treatment option with a low complication rate for repair of large focal articular cartilage defects of the knee, and results in significant improvement in functional scores (Lysholm Knee Scoring Scale score, and Knee Outcome SAS score) when evaluated 7–14 years following the procedure. MOCART scores for 39 patients who had undergone a post-operative MRI at minimum 2 years follow-up ranged from 45–100 with a mean of 84.5 ± 4.3. All five patients who underwent relook arthroscopy at a minimum 1 year period following surgery revealed normal or nearly normal articular cartilage (ICRS cartilage repair assessment grade I/II). Among 30 patients who were playing sports prior to treatment, 56.7% (n = 17) returned to the same level of sports post-transplantation. The mean duration to resume sports was 8.32 ± 1.82 m onths. 3.48% knees (4 of 110) warranted revision surgery within 7–14 years follow-up period.

Articular cartilage has a limited capability for spontaneous healing and untreated full-thickness chondral defects often lead to degenerative joint disease. ACI, with its ability to ensure a durable hyaline-rich articular cartilage repair, has been an accepted treatment option to relieve symptoms and improve function in full-thickness articular cartilage defects of the knee [20,21]. Since ACI offers long-term chondroprotective benefits, it is an optimal treatment option for large-sized (>4 cm^2) lesions in young adults or active middle-aged patients, and in patients with high physical demands [3,22].

However, conventional ACI presents several disadvantages. These primarily involve surgical complexity and unpredictable topographic restoration of the articular surface. Periosteal grafting, besides requiring an additional operation to harvest the periosteum, warrants a more extensive approach to facilitate periosteal suturing. Moreover, lesions that are posterior on the femoral condyles are difficult to access, and water-tight suturing of the periosteal graft with the surrounding cartilage to prevent subsequent leakage of injected cells is challenging. Periosteal edge overlapping, periosteal delamination, graft delamination, and graft hypertrophy are often noted with the conventional ACI technique [23,24]. Cutting and repeated manipulation of the seeded membrane in ACI techniques with collagen membranes may lead to loss of critical chondrocytes or detachment of the collagen membrane from the defect [25].

The ACI techniques that overcome these challenges are available. In injectable GACI technique [CARTIGROW®] a three-dimensional construct of the cultured chondrocytes is created in a scaffold of fibrin glue [26]. Fibrin helps to maintain the shape of the graft, restores a convex condylar topography, and decreases subchondral bleeding within the cartilage repair [27]. In addition to ensuring a stable cartilage repair construct well-attached to the subchondral bone, this delivery system has simplified the surgical technique substantially and improved the ability of the surgeon to address and access defects of varied shape, size, depth, and location. Moreover, GACI technique uses characterized chondrocytes which result in improved structural repair compared with the uncharacterized, dedifferentiated chondrocytes of conventional ACI, which may have lost their ability to reexpress the articular cartilage phenotype *in vivo* [28,29]. Studies with short-term follow-up have demonstrated GACI to be safe and effective as assessed using MOCART (Magnetic Resonance Observation of Cartilage Repair Tissue) and IKDC (International Knee Documentation Committee) scores [13]. However, there is limited documentation of outcomes beyond 2 years.

This study reports primarily the functional outcomes 7–14 years following GACI for large focal articular cartilage defects of the knee. The mean defect size of the articular cartilage lesions addressed in this study was 4.5 ± 5.8 cm^2. There was statistically significant improvement (p < 0.0001) in mean Lysholm Knee Scoring Scale scores from pre-operative 51.32 ± 17.89

to post-operative at latest follow-up 81.23 ± 13.21. These outcomes with GACI are similar to previously reported studies with conventional ACI [30–32]. No major intra-operative or post-operative complications were noted. Among 30 patients who were playing sports prior to treatment, only 56.7% (n = 17) returned to the same level of sports post-transplantation. The mean duration to resume sports was 8.32 ± 1.82 months. Although the time taken to return to sports was comparable to 9.1 ± 2.2 months after conventional ACI as reported in a recent *meta*-analysis, the low rate of return to the same level of sports post-transplantation is a concern and athletes undergoing this procedure primarily to allow a continuation of sports should be counselled accordingly [33].

Of knees treated with GACI 3.48% knees (4 of 110) warranted revision surgery within the follow-up period. Two patients underwent mosaicplasty at 2 and 3 years post-GACI, respectively. Further, one patient with osteochondritis dissecans underwent arthroscopic debridement 2 years post-GACI for persistent mechanical symptoms and pain, whereas one patient underwent a knee replacement 6 years post-GACI.

The treatment goal, especially in young patients with large chondral lesions, is directed towards ensuring a durable hyaline-rich articular cartilage repair which restores the chondral surface both in topography and in ultrastructure. Although we were unable to document the ultrastructure of the cartilage repair in this study, we did evaluate the radiological success of cartilage repair with post-operative MRI.

Conventional ACI has been noted to be safe with minimal adverse events reported in literature. The most important side-effect is graft rejection occurring in 0−7.6% patients. Other less serious adverse effects, such as swelling, hemorrhage and arthrofibrosis have also been reported. No patient had any significant adverse events in our study and GACI was found to be safe and tolerable.

This study had some inherent limitations. Being a retrospective multicentric study, there is a lack of control group and this could have resulted in an overestimation/underestimation of a treatment effect. In addition, comparison with other techniques could not be performed.

5. Conclusion

In conclusion, gel-based ACI is an effective treatment option, with a low complication rate, for large chondral defects of the knee, and results in significant improvement in functional scores when evaluated in the medium-term. The functional outcomes of gel-based ACI are comparable to conventional ACI, with the added benefit of ease of delivery and decreased graft hypertrophy.

Author contributions

Study concept, and/or design, or data acquisition, analysis and/or interpretation: Dinshaw Pardiwala. The drafting of the work or reviewing it critically for important intellectual content was done by all authors. All authors read and approved the final manuscript. All authors agree to be accountable for the accuracy and integrity of the work.

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Ethical approval

Ethical approval was obtained from Institutional Ethics Committee (Regrow Biosciences IEC) (registration number: ECR/309/Indt/MH/2019).

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article.

CRediT authorship contribution statement

Dinshaw N. Pardiwala: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Sachin Tapasvi:** Writing – review & editing, Writing – original draft. **Deepak Chaudhary:** Writing – review & editing, Writing – original draft. **Ashish Babhulkar:** Writing – review & editing, Writing – original draft. **Jacob Varghese:** Writing – review & editing, Writing – original draft. **David Rajan:** Writing – review & editing, Writing – original draft. **Abhay Narvekar:** Writing – review & editing, Writing – original draft. **Parag Sancheti:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

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

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