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ORIGINAL ARTICLE

Gel-Based Autologous Chondrocyte Implantation (GACI) in the Chondral Defects of the Knee: An Observational Study

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Abstract

Introduction Gel-based autologous chondrocyte implantation (GACI) is known to have superior results when compared to conventional autologous chondrocyte implantation (ACI) in terms of delivery of chondrocytes to the articular cartilage surface with reproducible three-dimensional structural restoration. This study aims to evaluate the short-term outcomes of gel-based autologous chondrocyte implantation (GACI) for the treatment of large focal articular cartilage defects of the knee.

Methods This was a prospective observational study among 25 patients who underwent GACI. Primary outcome measures included Lysholm Knee Scoring Scale and IKDC score and secondary outcome measures included MRI assessment of cartilage repair using MOCART.

Results Mean age of the population was 39.8 ± 7.5 years. The study found a highly significant improvement in both Lysholm knee score (pre-op: 45.1 to post-op: 72.4) and IKDC score (pre-op: 36.7 to post-op: 78.5) ($p < 0.001$) at the final follow-up of 24 months, even with the mean defect size being 4.5 ± 5.8 cm^2. Postoperative MRI showed a mean MOCART score improvement from 39.4 to 67.4 at the final follow-up. No major complications were observed.

Conclusion GACI is an effective and safe treatment option for large focal articular cartilage defects around the knee, with significant improvement in functional scores and low revision rates at medium-term follow-up.

Keywords Cartilage defects · Knee · Gel-based ACI · GACI

Introduction

ACI (autologous chondrocyte implantation) has been shown to be an effective therapeutic option for significant articular cartilage lesions in the knee [1–3] by promoting hyaline-rich cartilage repair [4–6]. ACI involves the implantation of chondrocytes that are harvested from a non-weight-bearing region on the articular cartilage of the knee joint which is later expanded ex vivo. ACI has shown benefits in terms of pain relief, quality of life parameters, and improvements in functional scores for treating patients with symptomatic chondral defects in the knee of the size range 2–9 cm^2, with the durability of benefits for up to 10–13 years [7–9]. The original ACI techniques involved implanting cultured chondrocytes into the debrided articular cartilage defect and securing them with a periosteal flap, a collagen membrane, or a matrix impregnating the cells (MACI). Recent advancements have introduced gel-based delivery systems that have streamlined and enhanced the process of creating three-dimensional recreations of the articular cartilage surface. These innovations offer a more efficient and consistent method for reconstructing the intricate structure of the cartilage within a three-dimensional framework. [10–12]. Gel-based autologous chondrocyte implantation (GACI) has been accessible for clinical application for nearly 20 years. Nonetheless, there exists a scarcity of comprehensive records pertaining to the intermediate and extended outcomes associated with this approach.

GACI employs a technique in which cultured chondrocytes are amalgamated with fibrin glue outside the organism

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and subsequently introduced as an injectable substance that solidifies within a span of 4 min post-cell implantation. This progressive iteration of autologous chondrocyte implantation (ACI) ensures consistent dispersion of cells across the affected area, permits a comprehensive three-dimensional reinstatement of the articular cartilage surface's structure, and establishes a sturdy framework that maintains secure adherence to the underlying subchondral bone. This approach also holds promise for diminishing the potential occurrence of graft hypertrophy [13]. Furthermore, this delivery mechanism has notably streamlined the surgical intervention and amplified the surgeon's capability to address anomalies of diverse configurations and depths within the cartilage. GACI has been extensively applied in the Indian context since 2008. The primary objective of this study was to assess the functional and radiological outcomes over an intermediate duration for individuals subjected to GACI treatment. In addition, the study sought to scrutinize the safety profile, occurrences of complications, and overall contentment levels of patients who underwent the procedure.

Materials and Methods

Study Design and Patient Selection

This prospective observational investigation was executed at a tertiary care facility over the period spanning from July 2019 to July 2021. The study encompassed a cohort of 25 eligible patients who willingly underwent Gel-based Autologous Chondrocyte Implantation (GACI). The selected participants, falling within the age range of 18–60 years, exhibited isolated focal defects within the articular cartilage of the knee joint. These defects were categorized according to the International Cartilage Repair Society (ICRS) grading system as having a severity of grade III or IV. In addition, patients presenting with unstable osteochondritis dissecans and maintaining normal coronal limb alignment were included. Exclusions from the study encompassed individuals with concurrent ligament injuries, prior history of knee surgical interventions, and other neuromuscular conditions that could potentially impede early rehabilitation processes. The study design received ethical clearance from the Institutional Ethics Committee, and informed consent was secured from participants prior to the initiation of data collection procedures.

Study Procedure

CHONDRON® (Regrow Biosciences Pvt. Ltd, Mumbai, India) is a gel-based autologous cartilage implantation (GACI) procedure that was performed in two stages.

In the first stage, arthroscopy and biopsy of the cartilage are obtained. Once the osteochondral defect is delineated and the patient was confirmed to be a suitable candidate for GACI, the articular cartilage of full thickness is harvested using punch biopsy in the form of hexagonal osteochondral cylinders of 6–8 mm diameter. The preferred site for harvesting the cartilage was the non-weight-bearing region of the superomedial or lateral femoral condyle as shown in Fig. 1. This full-thickness cartilage biopsy sample was then transferred to the GMP-certified culture laboratory (Regrow Biosciences Pvt. Ltd, Mumbai, India) with the culture medium in a sterile container. Any loose bodies and damaged or unstable cartilage were carefully removed without penetrating the subchondral bone.

In the laboratory, cells were isolated after receiving a cartilage biopsy sample via enzymatic digestion in collagenase solution. The cells were isolated in a 25 cm^2 tissue culture flask containing DMEM (Dulbecco's modified Eagle media) and fetal-bovine serum. These separated cells were grown in primary culture for 14 days. Throughout the culture phase, the media in the tissue culture flask was changed every 3 days as shown in Fig. 2. In about 4 weeks, the target number of approximately 48 million cells is cultivated, which is then transported back to the hospital with sterilization and continuous cold chain maintenance (2–8 °C) as shown in Fig. 3.

During the second phase of the procedure, a minimally invasive incision along the medial parapatellar region was executed, measuring approximately 4–5 cm in length. This approach provided access to the knee joint. Subsequently, the site afflicted by the chondral defect was treated with the application of gel-based autologous chondrocyte implantation (GACI) using the CHONDRON® product. The objective was to ensure complete filling of the defect and to attain a three-dimensional reestablishment of the articular surface's topographical structure, all while directly observing the process. The implantation involved the direct injection of the composite into the defect, with the knee oriented parallel to the ground to negate the influence of gravity. The initially viscous mixture was allowed to solidify within the designated recipient site. The placement of the implant was meticulously inspected to verify its attachment and stability by conducting controlled movements of the knee throughout its complete range of motion. The incision created for arthrotomy was subsequently closed in a sequential manner. A representative case exemplifying a 5×5 cm osteochondral defect situated on the medial femoral condyle is visually depicted in Figs. 4 and 5.

Rehabilitation Program

All subjects participating in the study adhered to a standardized postoperative rehabilitation regimen. This protocol

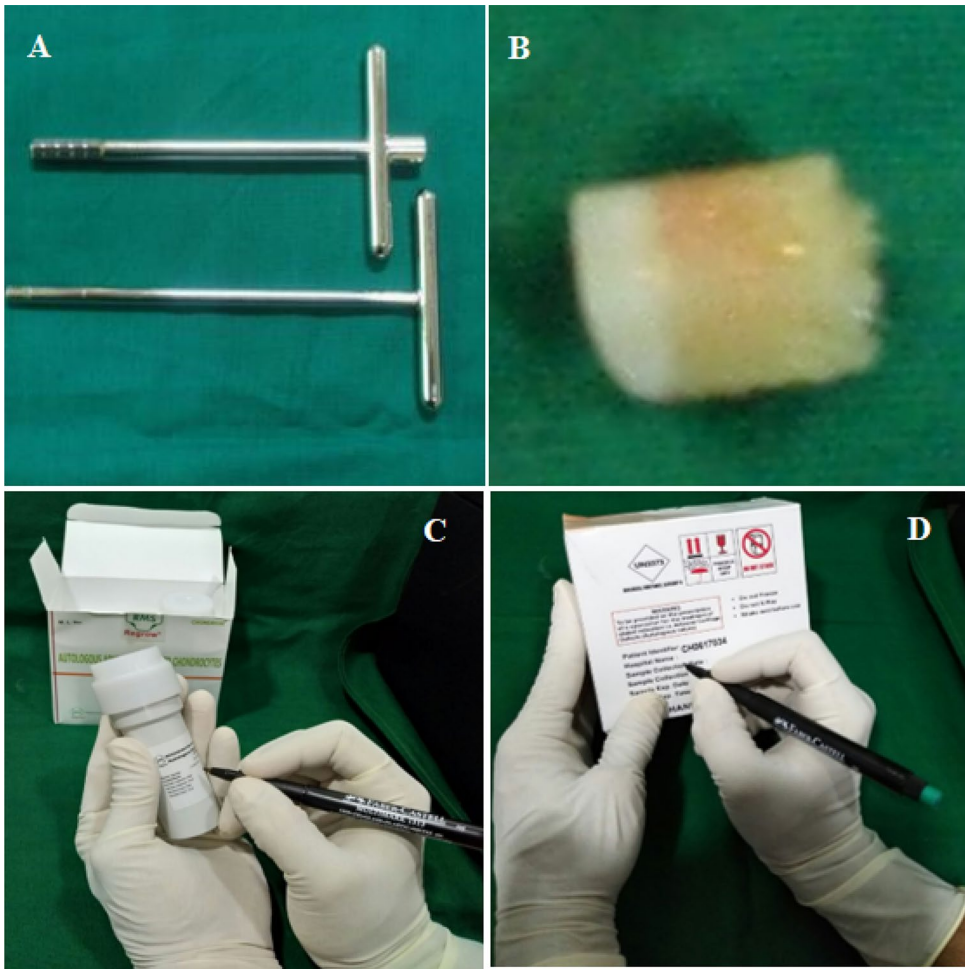

Fig. 1 **A** Cartilage harvester (7 mm); **B** 7 mm core of cartilage biopsy from non-weight area of the femoral condyle; **C**, **D** labeling of the sample which is to be sent to laboratory for culture of chondrocytes

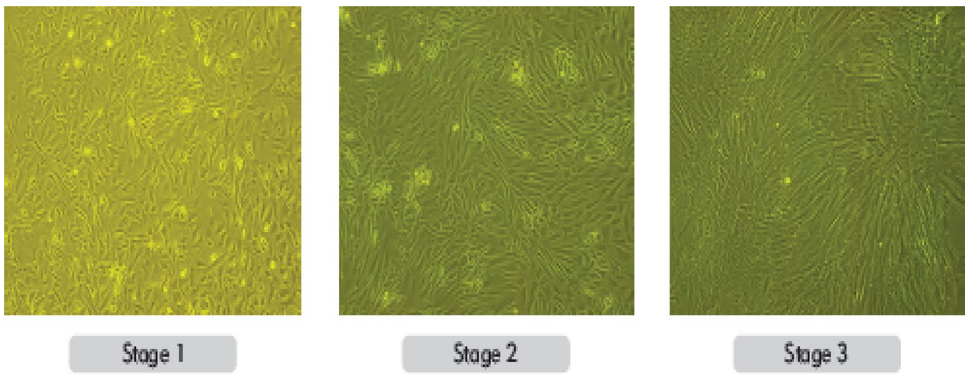

Fig. 2 Serial passage of chondrocytes in the laboratory

facilitated immediate engagement in active knee range of motion exercises, although weight-bearing activities were prohibited during the initial four weeks following gel-based autologous chondrocyte implantation (GACI). Throughout this period, patients utilized a range of motion (ROM) knee brace set in extension, a practice universally adopted among all participants. Commencing at the 4-week mark, partial weight-bearing was gradually introduced, and in cases where a knee flexion range of 140° had not been attained by the eighth week post-implantation, a continuous passive motion (CPM) machine was employed. Throughout the rehabilitation process, patients were advised to initiate quadriceps and hamstring strengthening exercises from the outset. Upon reaching the 12-week milestone after the surgical intervention, subjects were permitted to fully bear weight and engage in cycling activities without resistance. Slight modifications to the rehabilitation regimen were discretely incorporated

Fig. 3 Autologous adult live cultured chondrocytes (CHONDRON®) implant containing passage 3–48 million live chondrocytes

by the investigators when deemed necessary to align with the individual progress of patients.

Study Outcome

The study's principal endpoints were centered around alterations observed in the Lysholm Knee Scoring Scale and the Knee Outcome Sports Activity Scale (SAS) subsequent to the intervention. In addition to these primary metrics, the secondary endpoints encompassed an evaluation of cartilage repair utilizing magnetic resonance imaging (MRI) through the application of the magnetic resonance observation of cartilage repair tissue (MOCART) methodology. Furthermore, the investigation involved an assessment of several ancillary variables, including the duration of symptoms experienced prior to gel-based autologous chondrocyte implantation (GACI), rates of infection, occurrences of wound complications, and the occurrence of subsequent revision surgeries.

Statistical Analysis

Descriptive statistics were used to summarize continuous and quantitative variables, and Student's *t* test or nonparametric test, as appropriate, was used to compare them. Categorical data were reported as frequency count (*n*) and percentages (%), and the Chi-square test or Fisher's exact test was used to compare them. p values < 0.05 indicated statistical significance. All analyses were conducted using SPSS® version 26.

Results

The demographic details of the study population are shown in Table 1. This study comprised 25 patients who underwent gel-based autologous chondrocyte implantation for chondral defects of the knee. Gender distribution was nearly equal between females ($N = 13$, 52%) and males ($N = 12$, 48%) in our study, with the majority of the patients aged between 20 to 30 years ($n = 12$, 48%). A total of 28% of patients belong to the normal category as per BMI grading, whereas 40% of patients belong to the overweight category and 32% of patients belong to class 1 obesity. All the patients presented with complaints of pain, and difficulty in walking, climbing stairs, and difficulty in doing athletic activities with the duration of symptoms ranging from 1 week to 6 months before surgery. All patients followed same rehabilitation protocol till 3 months, after which tailored rehabilitation program was followed, which was personalized for each patient demands.

The severity of cartilage injury was categorized based on the size of the cartilage defect according to ICRS grading. All the patients in the study had cartilage defect on the medial condyle of the femur with majority of the patients having cartilage defect measuring between 26 and 30 mm ($N = 12$, 48%) (Table 1). The operative time was calculated from the time of skin incision to skin closure in minutes. The mean time for 1st stage procedure was 30 ± 12.34 min and for 2nd stage procedure was 65 ± 17.19 min. The length of hospital stay varied from 1 to 2 days following 1st stage surgery and 2–3 days following 2nd stage surgery. None of the patients experienced any wound complications or infections following the surgery.

International Knee Documentation Committee (IKDC) score: The mean pre-op IKDC score was 36.68 ± 14.23 which improved to 72.52 ± 23.56 at the end of 24-month follow-up which was statistically significant ($p = 0.000$) as shown in Table 2 and Fig. 6.

LYSHOLM score: In this study of 25 patients who underwent GACI, the mean pre-op LYSHOLM score was 42.84 ± 20.34 which was indicative of severe disability due to cartilage injury. Postoperatively at 1 month, the mean LYSHOLM score was 45.12, which further increased to 72.44 at 24 months, indicating minimal disability. The increase in LYSHOLM score between pre-op and 1, 6, 12, and 24 months post-op was found to be statistically significant (p value $= 0.000$) as shown in Table 3 and Fig. 7.

MOCART score: The pre-op mean MOCART score value was 39.40. All patients were evaluated at 24 months with post-op MRI and the post-op mean MOCART score value was 67.40. This significant increase in the MOCART score pre-op and post-op indicates a decrease in disabilities as shown in Table 4 and Fig. 8.

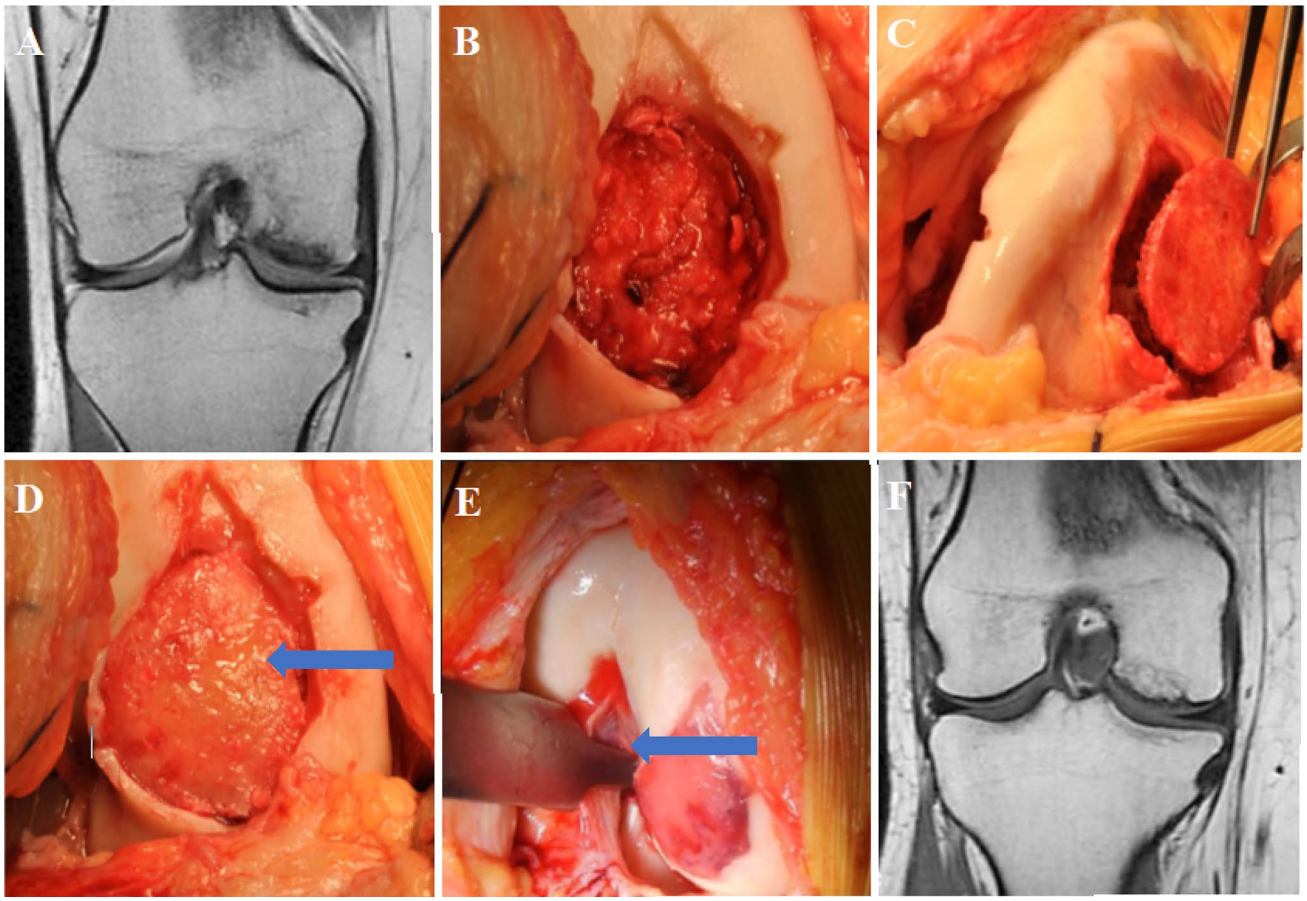

Fig. 4 **A** Pre-op MRI image showing 5×5 cm osteochondral defect in the medial femoral condyle; **B** preparation of osteochondral defect; **C**, **D** placement of bone graft in osteochondral defect (as shown with blue arrow); **E** placement of CHONDRON implant in the osteochondral defect (as shown with blue arrow); and **F** 2-year follow-up MRI image showing complete healing of osteochondral defect in the medial femoral condyle

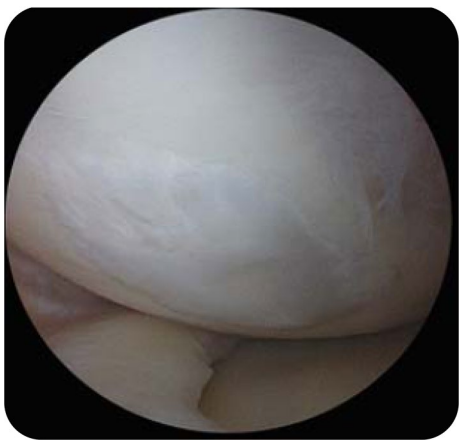

Fig. 5 Evidence of cartilage regeneration in the medial femoral condyle in re-look arthroscopy at the end of 2nd-year follow-up

Table 1 Cartilage defect size in the medial femoral condyle

Cartilage defect size (mm)	No (%)
< 20	2 (8%)
21–25	5 (20%)
26–30	12 (48%)
> 30	6 (24%)

No correlation was observed between BMI and IKDC ($r=0.127$; $p=0.18$) and BMI and Lysholm score ($r=0.018$; $p=0.41$). No correlation was observed between mean articular cartilage defect size and IKSC score ($r=0.110$; $p=0.58$) and mean articular cartilage defect size and Lysholm score ($r=0.023$; $p=0.20$).

Table 2 Follow-up IKDC scores among study participants ($N=25$)

Time scale		Mean	Standard deviation	Standard error of the mean	Correlation	Significance	Paired differences (95% CI)	*T* (*df*)	Significance (2-tailed)
Pair 1	Pre-op IKDC score	36.68	4.190	0.838	0.638	0.001	−2.043	−4.640 (24)	0.000
	IKDC score 1 month	40.36	4.982	0.996					
Pair 2	Pre-op IKDC score	36.68	4.190	0.838	0.247	0.233	−10.471	−10.221 (24)	0.000
	IKDC score 6 months	49.80	6.007	1.201					
Pair 3	Pre-op IKDC score	36.68	4.190	0.838	0.139	0.509	−22.379	−11.805 (24)	0.000
	IKDC score 12 months	63.80	11.292	2.258					
Pair 4	Pre-op IKDC score	36.68	4.190	0.838	0.169	0.418	−30.382	−13.554 (24)	0.000
	IKDC score 24 months	72.52	13.270	2.654					
Pair 5	IKDC score 1 month	40.36	4.982	0.996	0.539	0.005	−7.230	−8.815 (24)	0.000
	IKDC score 6 months	49.80	6.007	1.201					
Pair 6	IKDC score 1 month	40.36	4.982	0.996	0.356	0.081	−19.067	−11.062 (24)	0.000
	IKDC score 12 months	63.80	11.292	2.258					
Pair 7	IKDC score 1 month	40.36	4.982	0.996	0.323	0.115	−26.968	−12.784 (24)	0.000
	IKDC score 24 months	72.52	13.270	2.654					
Pair 8	IKDC score 6 months	49.80	6.007	1.201	0.642	0.001	−10.390	−8.003 (24)	0.000
	IKDC score 12 months	63.80	11.292	2.258					
Pair 9	IKDC score 6 months	49.80	6.007	1.201	0.592	0.002	−18.238	−10.463 (24)	0.000
	IKDC score 24 months	72.52	13.270	2.654					
Pair 10	IKDC score 12 months	63.80	11.292	2.258	0.926	0.000	−6.607	−8.516 (24)	0.000
	IKDC score 24 months	72.52	13.270	2.654					

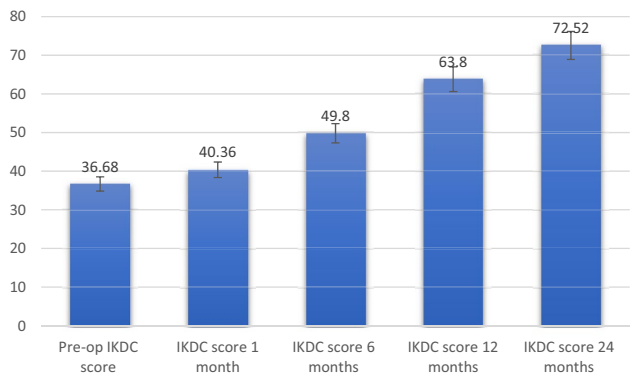

Fig. 6 Error bar showing difference in pre- and post-op IKDC scores

Discussion

The current therapies for cartilage restoration that operate on the bone marrow stimulation principle include transcortical Pridie drilling, microfracture therapy, and abrasion arthroplasty. These therapies involve creating small perforations in the subchondral bones to allow bleeding into the defect [14]. Such bone marrow stimulation principle works with the stimulation of resident mesenchymal stromal cells, growth factors, and cytokines which direct cartilage regeneration [14, 15]. This therapy is, however, associated with the formation of fibrous-fibro-hyaline cartilage which reduces the biomechanical efficacy when compared to hyaline cartilage and offers improvement of symptoms. Koelling et al.

Table 3 Follow-up LYSHOLM scores among study participants ($N=25$)

Time scale		Mean	Standard deviation	Standard error of the mean	Correlation	Significance	Paired differences (95% CI)	*T* (*df*)	Significance (2-tailed)
Pair 1	Pre-op LYSHOLM score	42.84	5.580	1.116	0.816	0.000	−0.818	−3.219	0.004
	LYSHOLM score 1 month	45.12	6.009	1.202					
Pair 2	Pre-op LYSHOLM score	42.84	5.580	1.116	0.752	0.000	−6.985	−9.078	0.000
	LYSHOLM score 6 months	51.88	7.557	1.511					
Pair 3	Pre-op LYSHOLM score	42.84	5.580	1.116	0.722	0.000	−14.979	−13.511	0.000
	LYSHOLM score 12 months	60.52	9.315	1.863					
Pair 4	Pre-op LYSHOLM score	42.84	5.580	1.116	0.606	0.000	−25.584	−15.211	0.000
	LYSHOLM score 24 months	72.44	12.042	2.408					
Pair 5	LYSHOLM score 1 month	45.12	6.009	1.202	0.871	0.000	−5.210	−8.999	0.000
	LYSHOLM score 6 months	51.88	7.557	1.511					
Pair 6	LYSHOLM score 1 month	45.12	6.009	1.202	0.798	0.000	−13.011	−13.304	0.000
	LYSHOLM score 12 months	60.52	9.315	1.863					
Pair 7	LYSHOLM score 1 month	45.12	6.009	1.202	0.629	0.000	−23.403	−14.394	0.000
	LYSHOLM score 24 months	72.44	12.042	2.408					
Pair 8	LYSHOLM score 6 months	51.88	7.557	1.511	0.939	0.000	−7.226	−12.608	0.000
	LYSHOLM score 12 months	60.52	9.315	1.863					
Pair 9	LYSHOLM score 6 months	51.88	7.557	1.511	0.746	0.000	−17.200	−12.629	0.000
	LYSHOLM score 24 months	72.44	12.042	2.408					
Pair 10	LYSHOLM score 12 months	60.52	9.315	1.863	0.817	0.000	−9.046	−8.559	0.000
	LYSHOLM score 24 months	72.44	12.042	2.408					

reported the migration of chondrogenic progenitor cells to the chondral defect of the knee from bone marrow through subchondral bone to form hyaline-like cartilage [16].

The articular cartilage has a limited healing potential and untreated full-thickness chondral defects frequently progress to end-stage degenerative arthritis. ACI is a well-accepted therapeutic option for symptom relief and functional improvement in full-thickness articular cartilage abnormalities of the knee [17, 18]. ACI is the best therapeutic option for large-sized (>4 cm^2) lesions in young people or active middle-aged patients [19], as well as those with significant physical demands because it provides long-term chondroprotective effects. Traditional ACI, on the other hand, has significant drawbacks, including surgical complexity and unexpected topographic restoration of the articular surface [1].

The conventional ACI techniques often necessitate periosteal grafting which requires a more extensive approach and is frequently associated with complications such as periosteal edge overlapping, periosteal delamination, graft

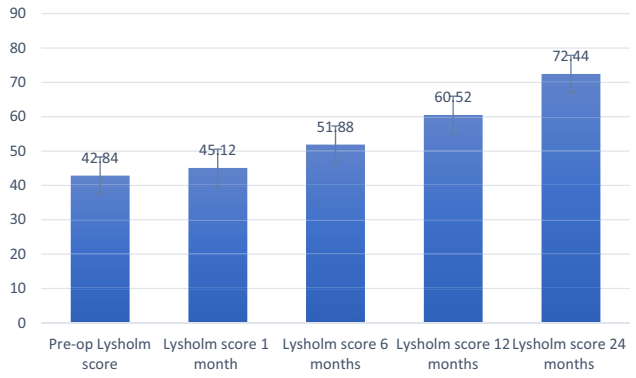

Fig. 7 Error bar showing difference in pre- and post-op LYSHOLM scores

delamination, and graft hypertrophy. Moreover, within traditional methodologies, achieving an impermeable seal between the periosteal graft and the adjacent cartilage poses a considerable challenge. This is essential to forestall the potential subsequent leakage of injected cells [20, 21]. Likewise, in ACI techniques employing collagen membranes, the cutting and repetitive manipulation of the seeded membrane can lead to detrimental outcomes such as the depletion of essential chondrocytes or the detachment of the collagen membrane from the defect site [22]. Conventional ACI has been noted to be safe with minimal adverse events reported in the literature [9, 23–25]. Graft rejection is the most significant complication that occurs in up to 7.6% of patients. Other less serious adverse effects such as swelling, hemorrhage, and arthrofibrosis have also been reported, however, were not observed in any of our patients with GACI found to be safe and tolerable [9, 25].

To overcome all these setbacks, an injectable gel-based ACI technique [CARTIGROW®] has been developed in which a 3D construct of the cultured chondrocytes is created in a fibrin glue scaffold [26]. Fibrin helps maintain the structure of the graft, restores a convex condylar topography, and decreases subchondral bleeding within the cartilage repair zone [27]. In addition to ensuring a stable cartilage repair structure firmly attached to the subchondral bone, this delivery system has considerably simplified the surgical procedure and enhanced the surgeon's capacity to treat and access defects of various shapes, sizes, depths, and locations. Moreover, this technique uses highly differentiated chondrocytes which produce better structural repair and re-expresses articular cartilage phenotype in vivo better than uncharacterized cells [28, 29].

Studies with short-term follow-up have demonstrated GACI to be safe and effective as assessed using MOCART and IKDC scores which reports primarily the functional outcomes at 12 months following GACI for large focal defects of the articular cartilage around the knee [30, 31]. These outcomes with GACI are similar to previously reported studies with conventional ACI [6, 32–34]. No major intraoperative or postoperative complications were noted.

Lane et al. demonstrated that a mere 80% of individuals subjected to ACI treatment managed to resume their prior high levels of activity, regardless of factors such as BMI, age, or the specific attributes of the cartilage lesion. This concern should be made aware to athletes and other high-demand individuals undergoing this procedure [35]. Utilizing gel-based autologous chondrocyte implantation (ACI) proves to be a feasible therapeutic avenue for addressing substantial focal articular cartilage defects within the knee joint, accompanied by a low incidence of complications. Our investigation, encompassing a cohort of 25 patients, each with an average age of 29.43 years and an average articular cartilage defect measuring 4.5 ± 5.8 cm^2, revealed noteworthy advancements in pain alleviation and overall quality of life over a 24-month period. These improvements were substantiated both radiologically and clinically, as discerned from functional assessment scores. Notably, a substantial enhancement in functional metrics, as denoted by the IKDC,

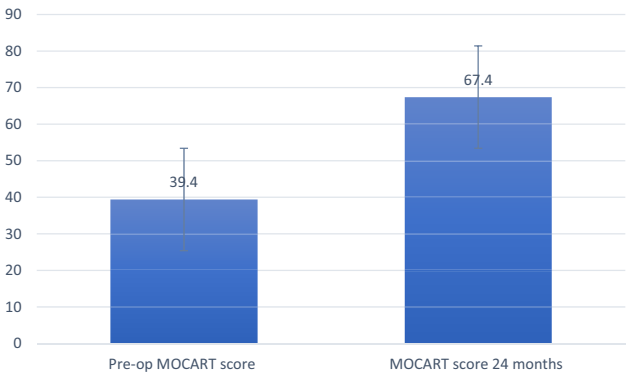

Fig. 8 Error bar showing difference in pre- and post-op MOCART score

Table 4 Follow-up MOCART score among study participants ($N=25$)

Time scale		Mean	Standard deviation	Standard error of the mean	Correlation	Significance
Pair 1	Pre-op MOCART score	39.40	6.178	1.236	0.710	0.000
	MOCART score 24 months	67.40	16.963	3.393		

Lysholm Knee Score, and MOCART Score, was evident upon evaluation at the culmination of the 24-month follow-up period. The MOCART scores, deduced from postoperative MRI assessments conducted on the 25 patients who underwent the procedure and were followed for a minimum of 24 months, demonstrated an average value of 67.40.

This study is subject to several notable limitations. First, the sample size remains relatively small, and the follow-up duration is of a limited scope. Second, the utilization of an open arthrotomy procedure for GACI implantation during the secondary phase introduces a potential confounding factor. Lastly, the absence of a comparative cohort diminishes the capacity for direct contrast and evaluation. To ascertain the genuine efficacy of gel-based autologous chondrocyte implantation (GACI) for addressing chondral defects within the knee, further investigation necessitates extensive, long-term, and prospectively designed randomized control trials.

Conclusions

Gel-based autologous chondrocyte implantation (GACI) emerges as a feasible therapeutic avenue characterized by a minimal incidence of complications, rendering it a suitable choice for managing substantial chondral defects situated within the knee joint. Furthermore, the approach manifests a noteworthy enhancement in functional evaluation scores, as evidenced by medium-term follow-up assessments.

Author Contributions Conceptualization—NSA and MJ; data collection—NJ and GPN; manuscript writing—MJ, TJ, NJ, and AN; and manuscript revision and proof reading—MJ and TJ. All the authors agreed to publish the manuscript.

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Data Availability Not applicable.

Declarations

Conflict of Interest Not applicable.

Institutional Ethics Committee AMH/DNB-015/04-19 dated 5th July, 2019.

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

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