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Scaffold impregnated chondrocyte implantation in patients with focal chondral defects

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Abstract:
Focal articular cartilage defects of the knee have limited healing potential, making durable regenerative treatment a clinical challenge. Therefore, it is of interest to compare the scaffold-assisted autologous chondrocyte implantation using a chitosan–chondroitin sulfate–silk fibroin scaffold with conservative treatment in 20 patients (10/group) over 12 months. The scaffold-assisted group showed significant improvements in Magnetic Resonance Observation of Cartilage Repair Tissue (31.7±6.8 to 75.0±17.3), International Knee Documentation Committee (34.8±0.4 to 50.5±7.8) and Lysholm scores (56.2±3.2 to 79.2±13.1) (all p=0.002). At 12 months, outcomes were significantly better following scaffold-assisted implantation than conservative treatment (all p<0.001), without major post-operative complications. Thus, data shows that scaffold-assisted autologous chondrocyte implantation as a promising tissue-engineering strategy for focal knee cartilage defects.

Keywords: Articular cartilage, knee, autologous chondrocyte implantation (ACI), tissue engineering, scaffold, chitosan, silk fibroin, chondroitin sulfate, Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART)

Background:
Articular cartilage is a highly specialized form of avascular connective tissue which acts as a low friction surface to allow the gliding movement of articulating surfaces and to distribute the weight evenly across synovial joints. Mature articular cartilage is avascular, alymphatic and aneural, making the regenerative capacity of cartilage very limited after trauma or degeneration **[1]**. This is the case in focal chondral defects, which often develop into chronic pain, joint stiffness, decreased range of motion and later, established OA, especially in young and active people. Focal cartilage defects are a prevalent cause of disability in the world, especially due to a rising number of sports injuries, road accidents and the degeneration of cartilage in aged persons, for which biological treatment methods capable of restoring hyaline cartilage and not merely fibrocartilage are in growing demand **[2].** Arthroscopic debridement, arthroscopic lavage, abrasion arthroplasty and microfracture are the standard surgical procedures performed for focal cartilage defects. These may relieve symptoms, but their long-term effects are unpredictable. Marrow stimulation techniques primarily produce fibrocartilaginous repair tissue, which is harder to experience the same biomechanical qualities as native hyaline cartilage and in some instances does not last long if subjected to the repetitive physiological loading **[3]**. A systemic review and meta-analysis of autologous chondrocyte implantation (ACI) with microfracture found that cartilage repair with ACI was more durable and had better and superior long-term function results than cartilage repair by microfracture, especially in the medium-size and large chondral defects **[4].** Since its inception, the field of autologous chondrocyte implantation has experienced many changes and is now considered one of the most potent biologic treatments for treating symptomatic focal cartilage lesions of the knee. Advances in the last few years include the harvesting of healthy articular cartilage from a non-weight-bearing region, isolation and culture of chondrocytes in a controlled laboratory setting and finally replacement of these cells within the defect using a biodegradable scaffold or matrix **[5]**. In recent years, the clinical benefit of both the autologous chondrocytes and mesenchymal stem cell-based therapy has been widely established, both in terms of clinical function and in terms of cartilage repair: in fact, the latter (ACI assisted by scaffolds) has proven to be the therapy with the highest long-term survival and patient satisfaction **[6].** These recent innovations in tissue engineering have added support from 3D biodegradable scaffolds (materials, that have many similarities with cartilage's own extracellular matrix), which has been proved to enhance cartilage repair. The matrix-assisted autologous chondrocyte implantation (MACI) technique offers a favorable microenvironment for cell attachment, proliferation, differentiation and synthesis of the extracellular matrix and an enhanced handling and stability of the graft during the implantation **[7]**. With structural cartilage repair and functional recovery strongly improved, HA-CR has recently shown promising clinical results reviewing the scaffold-based cartilage regenerative techniques introduced so far **[8].** In the research for the biomaterials for cartilage tissue engineering, silk fibroin/chitosan/chondroitin sulfate composite scaffolds have attracted much attention thanks to its outstanding biocompatibility, biodegradability and the capability of promoting chondrogenesis **[9]**. Silk fibroin has outstanding tensile properties, programmed degradation by cells, weak immunogenicity and excellent cellular adhesion properties, together with chondroitin sulfate that is involved with the organization and preservation of the extracellular matrix and chondrogenic phenotype. Silk fibroin based composite scaffolds have been consistently shown to support cell survival, the deposition of extracellular matrix and cartilage regeneration both *in vitro* and *in vivo* in experimental studies **[10].** The biological performance of tissue-engineered constructs has been greatly enhanced by the use of nanotechnology and scaffold engineering. Well-structured three-dimensional scaffolds allow taking up nutrients, removing waste products and making cells vascular independent and support even matrix formation outside the scaffold **[11]**. The architecture, pore size and

mechanical properties of the scaffolds are now critical for successful cartilage regeneration. Though a variety of natural and synthetic biomaterials have been studied, the latest progress suggests biomimetic composite scaffolds offer better structural support with a differentiated phenotype of chondrocytes in culture **[12].** His new developments of regenerative medicine are focused on restoring biological hyaline cartilage instead of repairing cartilage defects in the simplest way of filling them. New tissue engineering methods combine biomaterial scaffolds, tissue autologous cells, growth factors and recent advances in manufacturing techniques in order to produce tissue constructs with future potential to be integrated over time into the surrounding native cartilage. These multi-specialty approaches have received increased focus in recent reviews and are one of the most promising areas of current orthopaedic science and could significantly contribute to future management of focally damaged articular cartilage **[13, 14].** Therefore, it is of interest to evaluate the clinical feasibility, safety and preliminary effectiveness of scaffold-assisted, autologous chondrocyte implantation (SAACI) as a biologically based method for regenerating cartilage in focal defects of the knee.

Materials and Methods:

Study design and setting:

A Prospective Controlled Clinical Study was conducted jointly between Department of Orthopaedics, Katihar Medical College, Al-Karim University and Katihar Engineering College, Al-Karim University, Katihar, Bihar, India. The study protocol was reviewed and ethically approved prior to study commencement, by the Institutional ethics committee. All participants gave a written informed consent before being enrolled.

Study population:

All the patients attending the orthopedic OPD with symptomatic focal articular cartilage defects of knee joint were screened for the eligibility of the study. Twenty patients (20-50 years) who met the preset criteria were enrolled in the study as prospective patients. Two groups were set up. Ten patients who are receiving conventional conservative treatment with analgesics, physio, activity modification and rehab were analyzed as the control group. The 10 patients in the ACI group received tissue-engineered composite scaffolds during the surgical procedure of scaffold-assisted autologous chondrocyte implantation (ACI). Unilateral involvement or bilateral involvement was acceptable, but if bilateral disease occurred, only the knee which met the criteria for the study was included for evaluation.

Inclusion criteria:

Patients who met all the pre-defined criteria were included in this study - age between 20-50 years, symptomatic focal articular cartilage defect in the femoral condyles, tibial condyles or patella and defect area ≥2 - ≤6 cm^2. Patients with multiple or single cartilage defect were accepted in the study if the size of each cartilage defect was not more than 6 cm^2 in a single articular surface. Other eligibility criteria were the knee pain classified as persistent, *i.e.* persisting despite conservative care, or damage to the cartilage of the knee was at least partly regarded as relates to trauma or degeneration.

Exclusion criteria:

Patients under 20 years or more than 50 years were excluded, as well as those with cartilage defects less than 2 cm^2 or more than 6 cm^2 and for those with a body mass index (BMI) >30 kg/m^2. Patients with diabetes mellitus, hypertension, tuberculosis, bronchial asthma, malignancies and other major systemic diseases were excluded. Other exclusion criteria were identified as known cases of hypersensitivity to study materials, congenital skeletons anomalies, severe malnutrition and associated meniscal injuries and ligament injuries around the anterior cruciate ligament (ACL), posterior cruciate ligament (PCL), medial collateral ligament (MCL) and lateral collateral ligament (LCL) which were adequately managed with routine conservative care.

Matching of study group:

The baseline demographic and clinical variables, as well as lesions size, location and clinical features, were harmonized to minimize selection bias and maximize comparability between groups when comparing the operative and control groups.

Tissue engineering protocol:

The scaffold-assisted ACI was performed in three consecutive steps: (1) arthroscopic collection of cartilage fragments, (2) isolation of chondrocytes and cell culture and (3) open cell transplantation of the cell-seeded scaffold.

Scaffold fabrication:

In the Department of Biomedical Engineering, a composite scaffold from biodegradable materials chitosan (2% w/v), chondroitin sulfate (3% w/v) and silk fibroin (17% w/v) was prepared. Other laboratory equipment that were used in scaffold preparation and cell cultivation included Dulbecco's Modified Eagle Media (DMEM), fetal bovine serum (FBS), collagenase Type II, trypsin, antibiotic-antimycotic (penicillin-streptomycin solution), amphotericin B, glutamine, phosphate buffered saline (PBS), tissue culture flasks, CO_2 incubator, centrifuge, lyophilizer and the EDC-NHS cross-linking solution.

Scaffold preparation:

The composite polymer solutions of chitosan, chondroitin sulfate and silk fibroin were produced in a sterile condition. This polymer mixture was placed in the freezer at −20°C overnight and then the mixture was lyophilized (freeze-dried) under vacuum for about 48 hours. A porous scaffold was formed and chemically crosslinked with 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and N-Hydroxysuccinimide (NHS) to provide better structural stability. After cross-linking scaffolds were washed several times with distilled water and then lyophilized again before sterilization.

Scaffold characterization:

Scanning electron microscopy:

After a gold sputter coating, scaffold morphology was analyzed by scanning electron microscopy (SEM; QUANTA 200F). The pore size of the scaffold was 32-150 µm with an average pore size, which showed a porous scaffold structure capable of an interconnected pore system suitable for cell attachment and proliferation.

Porosity:
The porosimetic values of the scaffolds were obtained with a Micromeritics Model 9310, USA Mercury Intrusion Porosimeter. The fabricated scaffold had an average of about 80% porosity.

Swelling study:
Samples of scaffolds were cut into pieces of size 1 cm × 1 cm and the pre-soaking weight (W_0) of each piece was measured before they were immersed in distilled water and taken out for a given time interval (W_1) every 24 hours for the following 24 hours. The swelling ratio was determined by the following formula: $SR = (W_1 - W_0) / W_0$.

Hemocompatibility:
Clean human blood was used to carry out hemocompatibility test. There was an excellent level of blood compatibility, with a percentage hemolysis of 0.92% by the fabricated scaffold in accordance with ISO standards.

Stage I: Arthroscopic cartilage harvest:
Regionally anaesthetized, diagnostic arthroscopy was carried out through the standard anterolateral and anteromedial portals. A detailed examination of the knee joint was performed to find the cartilage defects, meniscal defects, ligament tears and loose bodies. About 200-300 grams of sound cartilage were removed from the intercondylar notch, superior ridge of the medial femoral condyle, or superior ridge of the lateral femoral condyle of the femur, respectively, which would not bear weight. The harvested cartilage samples were then placed in sterile normal saline and shipped to the cell culture lab in less than 1 hour.

Stage II: Isolating chondrocytes and expansion:
The cartilage tissue was carefully rinsed in phosphate-buffered saline and cut into smaller pieces. It was digested sequentially with 0.25% of trypsin and collagenase Type II. After an overnight digestion in a humidified 5% CO_2 incubator the cell suspension was filtered through nylon mesh of 70 microns and centrifuged for 10 minutes at a speed of 2500 rpm. A cell pellet was then resuspended in complete DMEM containing 10% fetal bovine serum, penicillin, streptomycin, amphotericin B and glutamine. Primary chondrocytes were seeded in tissue culture flasks, cultured at 37°C and maintained in 5% CO_2 until 80-90% confluent. Afterward, cells were re-passaged with 0.25 %of trypsin and cell viability was determined by Trypan Blue exclusion with the help of a hemocytometer.

Cell seeding on scaffold:
Complete medium was used to pre-condition the scaffolds at room temperature overnight before they were sterilized. In total, 5×10^5 viable chondrocytes were seeded onto each scaffold. The constructs of cells and scaffolds were cultured in the normal culture conditions for 2 weeks, changing the medium every 3 days. Scanning electron microscopy was used to verify cell attachment and morphology prior to implantation.

Stage III: Scaffold implantation:
The open arthrotomy was performed in a standard manner depending on the location of the cartilage defect. Once the lesion had been exposed, the cartilage areas damaged by the injury were used to get rid of it and to create stable vertical edges of cartilage. A sterile template was used for measurement of defect dimensions. A number of microdrill holes were made in the subchondral bone about 1 mm wide using a Kirsner wire to ensure marrow stimulation. The cell-seeded scaffold was then cut to fit the defect and inserted into the defect using a "press-fit" technique. For further fixation, 6-0 polyglactin (Vicryl) sutures were returned to positions of 12, 3, 6 and 9 o'clock. Passive knee range of motion was evaluated before the routine layered wound closure and implant stability was confirmed.

Post-operative rehabilitation:
Post-operative treatment consisted of 24 hours of intravenous antibiotics and five days of prophylactic oral antibiotics after surgery. Once on post-operative day 3 and when needed following soakage, dressing changes were carried out. Sutures were taken off after 14 days or later when the wound was dry and healed. Rehabilitation consisted of immobilization 12-24 hrs after operation, starting with continuous passive motion within 24 hrs after operation for the purpose of obtaining full range of motion within 1 week after operation, partial weight bearing from the second week after operation and complete weight bearing 6-12 weeks after operation. After six months, patients were allowed to resume low impact sports and high impact sports 9-12 months based on clinical recovery.

Outcome measures:
Patients' clinical and radiologic evaluations were performed at regular post-treatment visits. Structural cartilage repair was the primary outcome measure by Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score on Magnetic Resonance Imaging (MRI). Secondary outcome measures consisted of the International Knee Documentation Committee (IKDC) score, the pain relief score, functional recovery score, range of motion, graft incorporation score and complication scores.

Statistical analysis:
Microsoft Excel was used to input data and IBM SPSS Statistics version 29.0 was used to analyze data. Data were presented as Mean ± SD for continuous variables and frequencies and percentages for categorical variables. Independent Student's t-test, Mann-Whitney U-test were used for continuous data and Chi-square test and Fisher's exact test for categorical data, when comparisons were made between the two groups, operative and control. Paired t-tests and repeated-measures analysis as

appropriate were used to look for within-group changes over follow-ups. A p value < 0.05 was deemed to be statistically significant.

Results:

This prospective study involved a total of 20 patients with symptomatic focal articular cartilage defects in the knee. There were ten ACI cases and ten patients in the normal (conservative) management group. The operated and control groups had similar baseline characteristics. No statistically significant differences were observed in age (p = 0.62), sex distribution (p = 0.53), defect size (p = 0.59), or lesion location (p = 0.71). These results indicate no detected baseline differences in the variables presented; they do not, by themselves, establish that the groups were well matched or that selection bias was reduced **(Table 1).** Among the six patients with 12-month data after scaffold-assisted autologous chondrocyte implantation (SAAChI), mean MOCART scores increased from 31.7 ± 6.8 at baseline to 75.0 ± 17.3 at 12 months. Mean IKDC scores increased from 34.8 ± 0.4 to 50.5 ± 7.8 and mean Lysholm scores increased from 56.2 ± 3.2 to 79.2 ± 13.1. The reported baseline-to-12-month comparisons were statistically significant for all three outcomes (p = 0.002). These are within-group changes; they do not establish that the improvement was greater than in controls **(Table 2).** In the conservatively managed group, mean MOCART scores decreased from 30.5 ± 3.8 at baseline to 18.0 ± 3.9 at 12 months (p = 0.031). Mean IKDC scores decreased from 34.3 ± 1.5 to 30.4 ± 0.8 (p = 0.041), while mean Lysholm scores decreased from 55.4 ± 2.8 to 34.8 ± 4.6 (p = 0.028). The reported baseline-to-12-month comparisons were statistically significant for each outcome **(Table 3).** At 12 months, mean scores were higher in the operated group than in controls for MOCART (75.0 ± 17.3 vs 18.0 ± 3.9; mean difference, 57.0; p < 0.001), IKDC (50.5 ± 7.8 vs 30.4 ± 0.8; mean difference, 20.1; p < 0.001) and Lysholm (79.2 ± 13.1 vs 34.8 ± 4.6; mean difference, 44.4; p < 0.001). Thus, the reported 12-month scores favored the operated group on all three measures. Higher MOCART scores indicate better MRI-assessed repair-tissue morphology and higher IKDC and Lysholm scores indicate better reported knee status or function **(Table 4).**

Table 1: Baseline characteristics of the study population

Variable	Operated Group (n=10)	Control Group (n=10)	p value
Mean age (years)	44.2 ± 3.2	45.0 ± 2.6	0.62
Female sex	4 (40.0%)	5 (50.0%)	0.53
Male sex	6 (60.0%)	5 (50.0%)	
Mean defect size (cm²)	4.7 ± 0.8	4.5 ± 0.7	0.59
Medial femoral condyle	5 (50.0%)	3 (30.0%)	
Lateral tibial condyle	5 (50.0%)	5 (50.0%)	
Other locations	0	2 (20.0%)	0.71

Table 2: Clinical and radiological outcomes (mean value) following scaffold-assisted autologous chondrocyte implantation (n=10)

Parameter	Baseline	6 Months	12 Months	p value*
MOCART score	31.7 ± 6.8	64.2 ± 11.6	75.0 ± 17.3	0.002
IKDC score	34.8 ± 0.4	49.8 ± 7.2	50.5 ± 7.8	0.002
Lysholm score	56.2 ± 3.2	72.8 ± 11.4	79.2 ± 13.1	0.002

**Paired comparison between baseline and 12 months.*

Table 3: Clinical and radiological outcomes (mean value) in conservatively managed controls (n=10)

Parameter	Baseline	6 Months	12 Months	p value*
MOCART score	30.5 ± 3.8	25.0 ± 4.7	18.0 ± 3.9	0.031
IKDC score	34.3 ± 1.5	26.8 ± 0.8	30.4 ± 0.8	0.041
Lysholm score	55.4 ± 2.8	41.0 ± 4.4	34.8 ± 4.6	0.028

**Baseline versus 12 months.*

Table 4: Comparison of mean values in between operated and control groups at 12 months

Outcome	Operated Group	Control Group	Mean Difference	p value
MOCART score	75.0 ± 17.3	18.0 ± 3.9	+57.0	<0.001
IKDC score	50.5 ± 7.8	30.4 ± 0.8	+20.1	<0.001
Lysholm score	79.2 ± 13.1	34.8 ± 4.6	+44.4	<0.001

Discussion:

This prospective study compared the effectiveness of scaffold assisted autologous chondrocyte implantation (ACI) with a tissue engineered composite scaffold that is a blend of chitosan, chondroitin sulfate and silk fibroin for the treatment of focal defects in the articular cartilage of knee joints. At the 12-month follow-up, patients with successful implants had progressive radiological improvement (MOCART score) along with clinically meaningful (IKDC/Lysholm score improvement) functional improvement. In contrast, in those treated conservatively, MRI studies and clinical scores worsened, demonstrating little flaw healing potential of physiological treatment of focal cartilage defects. In a 48-month case series, Kreuz *et al.* also reported improved Lysholm and IKDC scores after scaffold-assisted autologous chondrocyte grafting, with moderate-to-complete defect filling on MRI in 43 of 44 patients **[15]**. Many findings drew from the current study were quite good, one of which, was employing a biologically active scaffold system for autologous chondrocytes implantation. Tissue-engineered scaffolds include an environment (3D ECM) which helps to promote adhesion, proliferation, maintenance of differentiated phenotype and production of extracellular matrix by chondrocytes. Physiological studies have revealed that collagen based and collagen/hybrid scaffolds promote structured cartilage regeneration with enhanced structural integration with native cartilage. In an orthotropic model, Szychlinska *et al.* showed that a type I collagen scaffold devoid of an exogenous cell population was sufficient to promote cartilage regeneration, which underscored the significance of the architecture of a scaffold to medical applications for cartilage repair without exogenously sourced cells **[16]**. Similarly, the positive results of the MRI in the current study indicate the composite scaffold created an adequate physiological setting for the maturation of repair tissue. Cartilage regeneration is a complex biological process that depends not only on implanted chondrocytes but also on the activation of endogenous regenerative mechanisms. Murphy *et al.* recognized that activated SSCs are important progenitors for cartilage regeneration and showed that stimulating the progenitor cells had a significant effect enhancing repair of osteochondral defects **[17]**. Therefore, pre-implantation of a scaffold with micro-drilling of the subchondral bone was added in the current study to stimulate bone marrow and recruit bone

marrow mesenchymal progenitor cells. This integrated treatment may have played a role in the systematic gain in MOCART score that was seen in the follow up. Development in cell-based tissue engineering has been highlighting the need for integration of living cells with biomimetic scaffolds that are able to mimic the structural and biochemical features of native cartilage. Huang *et al.* summarized what they have learned about cell-based cartilage repair techniques and proposed that the major factors determining a successful clinical outcome are the use of suitable cell sources, scaffold composition and maintenance of the chondrocyte phenotype throughout culture **[18]**. The present study employed these principles: (1) harvesting of a patient's own cartilage, (2) controlled cartilage expansion in the laboratory and (3) repopulation of the scaffold with the expanded cartilage. While four cases turned out to be failed cases for culture failure due to contamination and/or poor cellular adaptation, patients with successful histology had sustained radiological and functional improvement, thereby confirming the feasibility of this regenerative approach. In addition, advances in biomaterials, bio fabrication techniques and biological signaling have further advanced the design of scaffolds in recent years. Modern tissue-engineering strategies combine scaffold materials, regenerative cells and growth factors and advanced manufacturing technologies for improved cartilage repair and functional outcome, as well as their use, was highlighted by Yang *et al.* **[19]**. In the present study, the composite used can be modified to have sufficient porosity, mechanical strength and biodegradability to allow the gradual ingrowth of new cartilage matrix. These modern ideas of biomaterial-assisted cartilage repair correlate well with the MRI findings of an improved structure. MSCs have been identified as a potential biological modifier for cartilage repair as well. Allogeneic MSCs also are very immunomodulatory and have important regenerative potential for cartilage healing, according to the review by Aldrich *et al.* **[20]**. The use of autologous chondrocytes in the present study did not involve stem cells but, the stem cells could have been recruited through stimulating the marrow, as is possible with drilling the subchondral surface of the bone, which provides an appropriate microenvironment for the chondrocytes to function in. Silk fibroin has been widely studied as a scaffold due to its mechanical properties, good biocompatibility, controlled biodegradation and promoting cartilage specific extracellular matrix (ECM) formation. Previously, silk fibroin scaffolds produced with additive manufacturing techniques have been shown to promote cartilage tissue development and chondrocyte proliferation making silk fibroin to be a good biomaterial for cartilage engineering **[21]**. The biomechanical stability and structural stability of the scaffold during tissue regeneration in early stages may have been due to the integration of silk fibroin within the scaffold. More recently, Yu *et al.* described that collagen-silk fibroin composite scaffolds that were treated using the ultrasonically method showed promising ability to chondrogenesis, increase the extracellular matrix and better repair of cartilage in an experimental model **[22]**. The findings here agree with the age-dependent increase in MOCART scores in the present study and seal the evolution of repair tissue within the implanted scaffold. Likewise, Luo *et al.* used regenerated silk fibroin to prepare osteochondral defect repair scaffolds which were integrated with cartilage sealing hydrogels and proved to have good integration, cartilage regeneration and osteochondral defect restoration **[23]**. Their results confirm that enhanced design of the scaffold is essential to the success rate for cartilage reconstruction. The scaffold used in the current study, containing both nano silk fibroin and chitosan and chondroitin sulfate, might also have helped to stabilize the structure and provide biological integration. Hydrogel based silk biomaterials have recently been developed as another interesting platform for cartilage tissue engineering. In the second article, Akdag *et al.* summarized advanced silk-based hydrogels and explained why they possess great water retention, injectability, cytocompatibility and ability to deliver cells and bioactive molecules in cartilage defects **[24]**. While the scaffold used in the present investigation is freeze-dried and porous, the goals are comparable; to provide a supportive microenvironment in three-dimensional space which enhances cellular function and tissue regeneration and a hydrogel can be used as well. Articular cartilage biomimetic strategies for tissue engineering focused on successful clinical application reported over the last years, suggesting that a combination of scaffold technology, regenerative cells, biological signaling molecules and precise surgical approaches plays a major role in achieving successful outcomes of cartilage repair **[25]**. Several of this was incorporated into the present study by the use of ACHs, biodegradable composite scaffolds and marrow stimulation with subchondral drilling. For successfully implanted patients, the encouraging clinical and radiological results indicate that biomimetic tissue-engineering strategies are a good strategy for the management of focal articular cartilage defects. A recent review likewise highlights scaffold-based and marrow-stimulating approaches as promising options, while noting that outcome evidence remains heterogeneous across studies **[26].** Although these promising results were gained, a few limitations should be noted. A small number of patients were successfully cultured for this study; 4 of them failed to expand in the laboratory. The follow-up period was set at 12 months, but the formation of regenerated cartilage may require more than 12 months to be followed. Repeat biopsy was felt as ethically unpalatable and hence there was no histological confirmation of hyaline cartilage formation. However, both consistent improvement of MOCART and IKDC scores and Lysholm scores are indicative of a treatment that is both feasible and biologically effective with scaffold-assisted autogenous chondrocytes transplantation. Additional multicenter studies with large numbers of patients, uniform cell culture and longer follow-up periods are warranted, as well as advanced imaging or histological correlation to validate the preliminary results presented and reinforce the clinical importance of tissue engineering for cartilage regeneration.

Conclusion:

Scaffold-assisted autologous chondrocyte implantation was associated with higher 12-month MOCART, IKDC and Lysholm

scores than conservative management. These findings are preliminary, given the small sample and the discrepancy in the reported operated-group sample size. Larger studies with complete follow-up are needed to confirm these results and assess longer-term outcomes.

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