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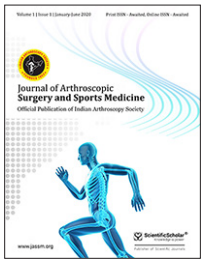

Review Article

Allogeneic chondrocyte implantation: What is stopping it from being a standard of care?

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ABSTRACT

Allogenic chondrocyte implantation refers to harvesting of donor chondrocytes, growing them in culture plates with growth factors and implanting them with/without biocompatible scaffolds into cartilage defects. Despite its huge potential, it suffers several drawbacks with respect to source, biomaterial, preservation, cell-culture conditions as well as clinical utility. Through this letter, we attempt to provide an account of these limitations that are stopping it from being a standard of care.

Keywords: Allogenic chondrocyte, Implantation, Scaffolds, Cartilage defect, Osteoarthritis

PROBLEM STATEMENT

Hyaline articular cartilage is composed of nests of chondrons dispersed in highly-organized, dense extracellular matrix of collagen (Type II), proteoglycans (aggrecan), and glycosaminoglycans (hyaluronan).[1] It is a unique tissue lining the joint surface - strong enough to allow weight-bearing yet smooth enough to allow for frictionless motion. Being an avascular, aneural, and alymphatic structure, and lacking a stem cell niche of its own, it has poor intrinsic capacity for spontaneous healing. Thus, defects here either as a result of trauma in young (particularly in sportsperson) or age-related attrition, tend not to heal, which in the long-term leads to osteoarthritis, a debilitating illness affecting millions worldwide.[2]

TECHNIQUES CURRENTLY IN PLACE

Realizing the need for early intervention to prevent the chain of deterioration, scientists over the years have advocated a myriad of techniques to repair the cartilage defects. While giving the defect site access to bone marrow stem cells using procedures such as Pridie drilling and microfracture techniques have been cheap and easy to perform, they have failed to mirror the articular cartilage biochemically and biomechanically owing to fibrocartilage invasion, which does not favor long term clinical outcomes.[3] Restorative techniques such as mosaicplasty or osteochondral autografts have managed to overcome the said disadvantages but come with the liability of donor site morbidity and increased risk of graft failure due to failed integration of the autograft with the surrounding tissue.[4] With the emerging pandemic of cellular therapy in the past two decades, autologous chondrocyte transplantation has been increasingly considered but the process suffers from major drawbacks, including the need of two surgeries – one to harvest

cells from the patient and one for surgical implantation of the cultured cells; and insufficient chondrocyte number to fill larger sized defects.[5] Against this background, chondrocytes from allogeneic sources have been explored as an alternative for cartilage regeneration.

OVERVIEW OF ALLOGENEIC CHONDROCYTE IMPLANTATION

In allogeneic chondrocyte implantation, chondrocytes are harvested from cadaveric articular cartilage, and implanted with/without biocompatible scaffolds into cartilage defects, after growing them in culture plates with growth factors and serial passage through monolayer cultures. Resemblance of the neocartilage to hyaline cartilage, lack of ethical concerns for harvesting chondrocytes, lack of the need for double surgery, reduced patient morbidity, availability of a large chondrocyte depot are the possible reasons why the technique ought to be the "next big thing."[6,7] Despite the huge potential, limitations exist with respect to culture and clinical domains, and we attempt to provide an account of the same [Table 1], with potential solutions to tackle them. Various important studies[5-18] conducted to highlight the

Table 1: Challenges during allogenic chondrocyte implantation and potential ways to mitigate.

Steps	Existing Standards	Hurdles	Potential Solutions
Source of Chondrocytes	Adult cadaveric articular cartilage.	Lesser efficiency in matrix synthesis compared to juvenile sources.	Post-amputation limbs, Infant syndactyly surgical waste, Nasal chondrocytes.
Laboratory Culture	Ex-vivo expansion of chondrocytes by serial passage through monolayer cultures in a biocompatible scaffold and in the presence of chondrogenic growth factors.	Dedifferentiation and terminal differentiation of chondrocytes.	3D culture techniques - Pellet culture, Alginate encapsulation, suspension culture.
		Need for an ideal biomaterial scaffold.	Collagen, hyaluronic acid, fibrin.
		Need for an ideal growth factor Efficient growth factor delivery system.	Non-serum based growth factors: IGF-1, TGF-beta, PRP, SOX-9, and GDF-5 Chip based delivery systems for sustained chondrogenesis.
Preservation	Cryopreservation of harvested articular cartilage.	Challenging to cryopreserve tissue systems – difficult to maintain matrix-cell relationship.	Isolated chondrocyte preservation, Vitrification, Cartilage bio-banking.
Clinical Trials	Preliminary stages based on promising results in animal studies.	Variations based on age, gender, size of lesion, site of lesion need to be studied.	Extrapolation of existing data from autologous chondrocyte implantation technique-based clinical trials.
Consent and Patient Acceptance	Skepticism pertaining to autologous/cadaveric based tissue/organ donation as well implantation.	Cultural, religious/racial, financial constraints.	Address individual concerns, generate awareness among the population.
Surgical Implantation	Implantation of harvested chondrocytes under Periosteal patch.	Periosteal hypertrophy, harvest site pain.	Usage of fibrin glue for chondrocyte suspension, Search for the ideal scaffold continues.
	Collagen membrane.	Inflammatory reaction, delamination, failed integration.	
	Biomaterial based scaffold.	Immunological reaction, mechanical stability of the scaffold, failed integration.	
Implantation Hurdles	Primarily used to fill articular cartilage defects>3-5cm in diameter, especially in young individuals with refractory symptoms and continued progression of cartilage degeneration.	Ideal number of chondrocytes to be transplanted.	Artificial intelligence based neural networks.
		Immune rejection of transplanted chondrocytes – steroids inhibiting wound repair.	Alternate immune suppressants – azathioprine, cyclosporine, MMF.
		Transmission of occult donor diseases – infectious, genetic.	Screening assays, standardization protocols, immunotherapeutic protection.
Post-Operative	Generic rehabilitation protocols until full weight bearing.	Post-operative complications and recipient joint morbidity.	Supplementation with pre-transplant rehabilitation protocols.

scope and utility of allogenic chondrocyte implantation have been briefly discussed in [Table 2].

LIMITATIONS AND POSSIBLE WAYS TO CIRCUMVENT THE CHALLENGES

Source of chondrocytes

It is seen that chondrocytes from adult sources are less efficient in synthesizing the matrix *in vitro* and subsequently face difficulty initiating repair *in vivo*, compared to juvenile sources.[19] Apart from the ethical concerns associated, juvenile sources may not be able to keep up with the demand-supply discrepancy.

As a potential solution, infant cartilage tissue obtained from polydactyly/syndactyly surgical wastes can act as substitutes.[20] In addition, nasal chondrocytes, harvested from cadaveric sources or post-septoplasty/submucosal resection specimens can be considered since they have been shown to have a faster *in vitro* proliferation rate compared to articular cartilage, thus needing less cell seeding densities.[21] The depot can also be increased using chondrocytes from post-amputation limbs.[20]

Need for cryopreservation

Despite having adequate number of chondrocytes for transplantation, developing an effective preservation strategies is a must since we cannot be waiting for a source every time a patient needs an articular defect repair. Tissue preservation systems have been well established compared to isolated chondrocyte preservation but remain more challenging nevertheless since there is a need to not only store the cells and the matrix but also maintain the intricate relationship between them.[22] Vitrification of cells, which allows transition into a glass-like amorphous state, without passing through the intermediate crystalline stage is all set to be a forerunner in the field of chondrocyte bio-banking.[22]

Culture conditions

While having an allogeneic source reduces the number of times chondrocytes need to be expanded to increase their number, its need cannot be completely negated. During *in vitro* serial monolayer expansion, chondrocytes tend to be replaced by complex cartilage phenotype containing Type I collagen and low-level proteoglycan synthesis which would lead to transplant failure either due to dedifferentiation into fibrocartilage or terminal differentiation into hypertrophic cartilage.[23] 3D culture techniques using pellet culture, alginate encapsulation, suspension culture help overcome this by promoting redifferentiation at every stage and allowing for higher cell seeding densities.[24]

While transplanting chondrons (chondrocytes with pericellular matrix) would reduce the numbers available for transplantation considerably, chondrocytes when transplanted alone would fail to integrate with the surrounding tissues.[1,25] This necessitates the use of a natural/synthetic biomaterial scaffold for chondrocyte culture and transplantation. An ideal scaffold is an elusive find considering that it has to be biodegradable and non-toxic, geometrically appropriate with the correct pore-size and morphology to allow for nutrient and by-products diffusion and provide an ideal micro-environment for chondrocyte growth while hosting differential matrix component distribution. A variety of pro-chondrogenic natural and synthetic scaffolds including collagen, agarose, fibrin, hyaluronic acid, poly-L-Lactic acid have been considered but the search continues.[26,27]

Enhancing chondrogenesis *in vitro* is done using growth factors. Serum-based growth factors not only have limited availability and increasing variability worldwide but also are known to reduce *in vitro* chondrogenesis.[19,28] Non serum-based factors (IGF-1, TGF-beta, PRP, SOX-9) could be used but effective ways to deliver these short-lived factors for sustained chondrogenesis *in vivo,* and their quality control still remains an issue.[29,30] Micro and nanochips containing these growth factors could be embedded in the scaffolds at graded concentrations which would help mimic the natural structure of articular cartilage.[31]

Clinical hurdles

Implantation of the cultured cells under a periosteal cover is not only technically challenging but may also lead to periosteal hypertrophy with consequent pain, in addition to harvest site pain thus reducing the quality of life.[32] Collagen scaffolds alleviate this problem but would lead to inflammatory reaction and graft failure, delamination or failed integration, necessitating repeat surgery, reiterating the need for an effective synthetic scaffold.[33] The scaffold, in addition to being near perfect as a laboratory material, has to be immunogenically non-reactive and mechanically compatible.

Although articular cartilage is pauci-immunogenic, studies in rabbit model show immunogenic anti-graft rejection response to the implanted chondrocytes, slowly destroying the regenerated cartilage, unlike autologous chondrocytes.[34] Use of corticosteroids in the patient to overcome this would interfere with the subsequent repair process. Alternative immunosuppressants such as cyclosporine, mycophenolate mofetil, or azathioprine could be tried but need substantiation.

The ideal number of chondrocytes needed to be transferred to fill defects of varying size is beyond human intelligence but artificial intelligence-based approach using deep neural networks could be path-breaking in this regard.[35]

Table 2: Important studies pertaining to allogenic chondrocyte implantation.

Article	Aims	Outcomes
Boopalan *et al.*[6]	**Compare ACT with allogenic chondrocyte transplantation** in the treatment of experimentally created articular cartilage defects in rabbit knee joints.	Allogenic chondrocyte transplantation seems to be as effective as ACT in cartilage regeneration, with the added advantages of increased cell availability and reduced morbidity of a single surgery.
Perrier-Groult *et al.*[7]	To investigate **tolerance of allogeneic HACs by the human immune system,** developing a humanized mouse model implanted with allogeneic cartilage constructs generated *in vitro.*	No sign of T-cell or macrophage infiltration was seen in the cartilaginous constructs and no significant increase in subpopulations of T lymphocytes and monocytes was detected in peripheral blood and spleen.
Man *et al.*[8]	To explore the **effect of allogeneic chondrocytes transplantation with the CS- DBM hybrid scaffold** via one-step operation to repair the full-thickness cartilage defect in rabbits.	The CS/DBM scaffold was found to be an ideal biomaterial for cartilage tissue engineering. Allogenic chondrocytes delivered with the CS/DBM scaffold could effectively repair rabbit cartilage injury via one-step operation.
Takizawa *et al.*[9]	Investigate the **regenerative effects of human chondrocyte sheets and synoviocyte sheets for articular cartilage regeneration** in a xenogeneic model using immune-deficient rats to establish a human translational model.	Results indicate that layered chondrocyte sheet transplantation contributes to articular cartilage regeneration.
Tani *et al.*[10]	To examine the **efficacy of using vitrified-thawed cryostored chondrocyte sheets** in treating full-thickness articular defects induced in the knees of rabbits.	Significantly better pain-alleviating effects and tissue repair were achieved by using vitrified–thawed chondrocyte sheet transplantation compared with no treatment (an osteochondral defect alone). No significant differences were observed between the transplantation of conventional fresh chondrocyte sheets and vitrified chondrocyte sheets.
Wu *et al.*[11]	Explore the application of 3D micromass stem cell culture for chondrocyte and osteoblast induction prior to bioreactor-based cells-loaded scaffold culture for treatment behavior of **chondrocyte and osteoblast-loaded β-TCP bioceramic scaffolds for articular cartilage defect treatment.**	Chondrocyte/osteoblast-loaded β-TCP bioceramic scaffolds had several advantages for the treatment of cartilage defects: (i) Good cartilage regeneration ability; (ii) wide allogenic BMSCs availability; (iii) no need additional surgery for patients; (iv) no donor site defect formation in patients; (v) less possible blood loss and infection. This work suggested micromass stem cell culture and bioreactor-based cells-loaded scaffold culture can be applied to prepare chondrocyte/osteoblast-loaded β-TCP bioceramic scaffold.
Choi *et al.*[5]	To evaluate the results of **autologous bone marrow cell stimulation and allogenic chondrocyte implantation using 3-dimensional gel-type fibrin matrix** in an animal model.	Suggested that autologous bone marrow cells stimulation and implantation of allogenic chondrocytes are both useful methodologies for regenerating hyaline-like cartilage in full-thickness cartilage defects in animal model.
Lee *et al.*[12]	To assess the occurrence of **apoptotic chondrocyte death** in the areas of defect in the articular cartilage following chondrocyte transplantation in the knee of the rabbit.	During the remodeling stage after chondrocyte transplantation, there is a rapid and significant decrease in total cellularity along with a concomitant significant increase in apoptosis, especially in the superficial layers. Therefore, apoptosis may be one of the factors responsible for the decrease in total cellularity of transplanted chondrocytes during the remodelling stage of chondrocyte transplantation.
Boopalan *et al.*[13]	To study the **effectiveness of *in vitro* expanded allogenic chondrocyte transplantation** for focal articular cartilage defects in rabbits.	Articular cartilage defects treated with allogenic chondrocyte transplantation result in better repair tissue formation with hyaline characteristics than those in control knees.

(*Contd...*)

Table 2: (*Continued*).

Article	Aims	Outcomes
Toyoda *et al*.[14]	Evaluate the efficacy of **PD sheets** as an allogeneic alternative to standard chondrocyte sheets was examined using an orthotopic xenogeneic transplantation model.	Efficacy-associated genes that may contribute to hyaline cartilage regeneration via PD sheet transplantation. The identified characteristics could act as markers to predict the *in vivo* efficacy of using PD sheets.
Maehara *et al*.[15]	Investigate the characteristics of **PD** sheets fabricated from the chondrocytes of young polydactyly donors.	PDs proliferated rapidly to establish a layered structure with sufficient extracellular matrix and formed sheets that could be easily manipulated without tearing. PD sheets exhibited characteristics thought to be important to chondrocyte sheets as well as proliferative capacity that may facilitate provision of a stable supply in the future.
Guo *et al*.[16]	To investigate the effect of **allogeneic chondrocytes-calcium alginate gel composite** under the intervention of **LIPUS** for repairing rabbit articular cartilage defects.	Allogeneic chondrocytes-calcium alginate gel composite can effectively repair articular cartilage defect. The effect of LIPUS optimized allogeneic chondrocytes-calcium alginate gel composite is better.
Dhollander *et al*.[17]	To evaluate the **implantation of alginate beads containing human mature allogenic chondrocytes** for the treatment of symptomatic cartilage defects of the knee. MRI was used for the morphological analysis of cartilage repair.	The correlation between clinical outcome and MRI findings was poor. Further validation of these scoring systems is mandatory. The promising short-term clinical outcome of the allogenic chondrocytes/alginate beads implantation was not confirmed by the short-term MRI findings.
Lin *et al*.[18]	Animal model to study the effects on a 4-week healing process of chondral defects by the **implantation of allogenous chondrocyte-seeded HA/Col II microspheres** that had been cultured *in vitro* for 7 days prior to implantation compared with unseeded HA/Col II microspheres or an untreated wound.	More GAG staining appeared in the defect implanted with chondrocyte-seeded HA/Col II microspheres, which demonstrated a higher level of hyaline cartilage regeneration. Due to the short healing period assigned to this study, the repaired cartilage showed limited incorporation into the surrounding host cartilage and some loose connection to the subchondral bone.

ACT: Autologous chondrocyte transplantation, CS/DBM: Chitosan hydrogel/demineralized bone matrix, LIPUS: Low intensive pulsed ultrasound, PD: Polydactyly-derived chondrocyte

The implanted chondrocytes could serve as a new parenteral means to transmit diseases – infectious diseases could be screened for but occult congenital diseases, autoimmune diseases, and malignancies could be manifested only in the recipient post-transplant. Optimal screening assays and standardization of transplant protocols are a must before the procedure can kick in as a standard of care.[36]

Post-chondrocyte transplant, the patient needs to be put on a safe, customized, optimal rehabilitation program, ranging from progressive partial weight-bearing to subsequent complete weight-bearing in order to obtain full joint motion and function. Pre-transplant rehabilitation protocols could also be put in considering the complex joint biomechanics.[37]

The fact that the cells are obtained from allogeneic sources gives immense scope for rejection of the procedure by the patients and convincing the mass about the pros of the procedure can be a challenge. The laboratory and preservation-related costs may also prevent widespread use of the technique, particularly in developing countries.[13-18]

CONCLUSION

Cartilage repair is an ever-evolving field with huge scope for improvement and exploration, allogeneic chondrocyte implantation being just another cusp of it. There is no doubt about its immense potential but it probably suffers from the "*middle child syndrome*" – its precursors (surgical techniques) have been relied upon by many due to their low cost, its contemporaries (autologous transplants) have passed through reliable clinical trials, and its potential successors (stem cell therapy, gene editing, and bio-printing) are even more enticing. Adequate large-scale studies to prove long-term clinical efficacy of the technique, assessment of benefit versus risk in patients, age, gender, and lesion-size-based variation in results need to be validated before accepting it as a standard of care.

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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