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Challenges in osteochondral repair– a critical review

Jalaja Aswathy[1,2], Josna Joseph[3] and Annie Abraham[1,*]

[1] Department of Biochemistry, University of Kerala, Kariavattom, Thiruvananthapuram 695581, India
[2] Phytochemistry and phytopharmacology Division, KSCSTE-Jawaharlal Nehru Tropical Botanic Garden and Research Institute, India
[3] Dept. Clinical Immunology & Rheumatology, Christian Medical College, Vellore, Tamil Nadu 632004, India

* Correspondence author; E-mail: annieab@keralauniversity.ac.in.

Abstract: Osteochondral (OC) tissue repair is a significant challenge in managing osteoarthritis patients, as osteoarthritis (OA) progressively deteriorates both cartilage and subchondral bone, reducing quality of life. Restoring OC regions with complete structural and functional recovery is crucial. Despite availability of various OC constructs for OA joint repair, ensuring their stability and bone support remains problematic. The primary obstacle in attaining favourable patient outcome is designing constructs tailored to individual needs. This critical review addresses the various challenges in OC tissue repair, including (i) anatomical complexities, (ii) biological approaches to restoring the OC interface, and material selection, (iii) cell sources for reconstruction, and (iv) recreating a coordinated microenvironment. The findings arising out of this introspection, underscore the need for innovative strategies to overcome these OC tissue repair limitations, aiming at restoring OC unit structure and function in OA patients.

Keywords: osteochondral unit; osteoarthritis; stem cells; osteochondral construct; scaffolds

1. Introduction

Osteochondral (OC) repair in osteoarthritis is the therapeutic strategy to restore damaged joint surfaces and underlying bone in individuals suffering from osteoarthritis (OA). OA is a chronic degenerative disease affecting the elderly, especially women [1]. The pathological condition of OA is characteristically progressive by cartilage breakdown, the collapse of the subchondral bone, fibrosis, hypertrophy of the synovial tissue and degeneration of menisci, and finally, osteophyte formation [2,3]. This osteophyte formation, followed by softening, fibrillation, and abrasion of the cartilage lead to the denudation of underlying bone and OC

defects. The reconstruction of OC defects in OA patients is challenging as anatomical restrictions, pathological limitations, host response factors, and translational challenges exist. According to the data provided by the World Health Organization (WHO), OA remains a significant global health concern, affecting 528 million individuals ie, about 6.5% are suffering with OA around the world. WHO's statistical findings underscore the widespread prevalence of OA, and the average age of onset is above 55, and 60% of them are women [4]. Age-standardized prevalence rates (ASRs) show that the global rate of osteoarthritis (OA) is 6.34%, with an annual rise of 0.12% [5]. The prevalence of OA in rural and urban India is estimated to be 3.9% and 5.5%, respectively [6]. There is an increased concern about this disease since an estimated 18% of post-menopausal women worldwide and 22–39% of the Indian population suffer from OA [7,8]. Previously, OA was considered as a joint disorder; later, studies revealed that it affects the whole joint organ [9]. To address this clinically, various approaches have been developed to promote repair *via* replacement or regeneration of the OC unit. These strategies involve microfracture, mosaicplasty, autologous chondrocyte implantation, tissue replacement, and tissue engineering approaches using biomaterials and stem cells. These interventions aim to enhance cartilage healing, reduce pain, improve joint function, and potentially slow down disease progression. OC repair promises to improve the quality of life for affected individuals, but further research is needed to optimise this technology to understand its long-term efficacy and safety. Therefore, this review offers insights into various challenges in OC repair, existing sophisticated technologies, ongoing technical advancement, and clinical trials in OC tissue restoration.

2. Anatomical challenges

2.1. OC unit/OC tissue anatomy

OC tissue is arranged as a discrete zone, and the level of zonal discrimination accounts for Extra Cellular Matrix (ECM) composition, collagen orientation, and chondrocyte phenotype, morphology, organization, and number [10]. The height of the OC unit varies significantly from one individual to another and this variability is due to the different knee joint size, shape, biomechanics, *etc.* The average height of OC tissue ranges from about 3 mm, and 90% of it is constituted by cartilage the remaining 5% by calcified cartilage zone, and the other 5% by subchondral bone plate respectively [11]. Unlike most tissues, articular cartilage is devoid of blood vessels, nerve innervation, and lymphatics [12–14] and the movement of nutrients and the excretion of waste is primarily *via* diffusion to-and-from neighbouring tissues. This exchange is possible only through synovial fluid, a viscous liquid that bathes the cartilage surfaces within joints [15–17]. In addition to the synovial fluid, proteoglycans and glycoproteins like lubricin [18] in the articular cartilage that lines up the bone surface in the OC unit act as flexible connective tissue in the synovial joints throughout the body, responsible for movement with almost zero friction [18–21]. The delicate balance of nutrient exchange is crucial for sustaining cartilage's unique structure and function, maintaining optimal synovial fluid composition and circulation for cushioning joints, and enabling smooth movement. While considering these facts another significant challenge for OC

damage healing is the lack of blood vessels for delivering nutrients, oxygen, and immune cells necessary for the repair process. Also repair of injury of a perichondrium-like fibrous membrane that surrounds the cartilage and the post-injury recovery is also inefficient due to lack of blood vessels and blood supply [1,13], though during the initial development stage of perichondrium, the regenerative potential of early mesenchymal progenitor cells aid to some extent [22,23]. Hence, without an adequate blood supply, the repair of cartilage defects can be slow and less effective [14,24–26]. Preparing an OC unit that is tailored to each individual's anatomy requires precise imaging, measurements, and surgical planning. The production of customized OC units becomes a more difficult and challenging task while considering all the functionalised requirements of a native OC unit [27–30].

Articular cartilage, despite its high water content (~80%), exhibits remarkable mechanical properties. The compressive modulus, a key indicator of cartilage stiffness, typically ranges from 0.53 to 1.82 MPa. Tensile strength, measuring the resistance to deformation before failure, is approximately 17 MPa. It is important to note that these values can vary depending on factors such as age, loading conditions, and disease progression state [31,32]. The special characteristic of articular cartilage is its dense ECM with a sparse distribution of highly specialized chondrocytes. Chondrocytes are adapted to low-oxygen (hypoxic) environments, and their metabolism and functions are optimized for these conditions [33]. When cartilage is injured or needs to be regenerated, creating an environment that mimics its natural hypoxic state is crucial for successful regeneration [33–35]. Depending upon the ECM composition type and arrangement of the chondrocytes, the articular cartilage is differentiated into different zones. They are the superficial tangential zone, the transition/middle zone, and the radial/deep zone. The orientation of collagen fibres and chondrocytes, proteoglycan, and water content in each zone is varied to act as an anatomic and functional bridge, providing the line of resistance to compressive forces [12,36,37]. These zonal variations in cartilage with varying cell densities and ECM compositions affect the healing potential and biomechanical properties of repaired tissue, making it difficult to reproduce the native tissue structure [25,37–39]. In addition to cartilage, the OC constitutes of subchondral bone made of the subchondral bone plate and the calcified cartilage zone which acts as the transition into articular cartilage often referred to as the ‘tide mark’ with the lead cellular population of hypertrophic chondrocytes [12]. During joint development, the subchondral bone is formed *via* endochondral ossification of the cartilage template at the secondary ossification centres of the bone epiphyses. This subchondral trabecular bone is highly vascularized and it provides nutrition to cartilage in addition to that from synovial fluid [40]. There for preparing a customised OC unit for regeneration pose specific hurdles when considering the anatomy of cartilage and bone due to the hypoxia sensitive nature of chondrocyte and the highly vascularised nature of bone.

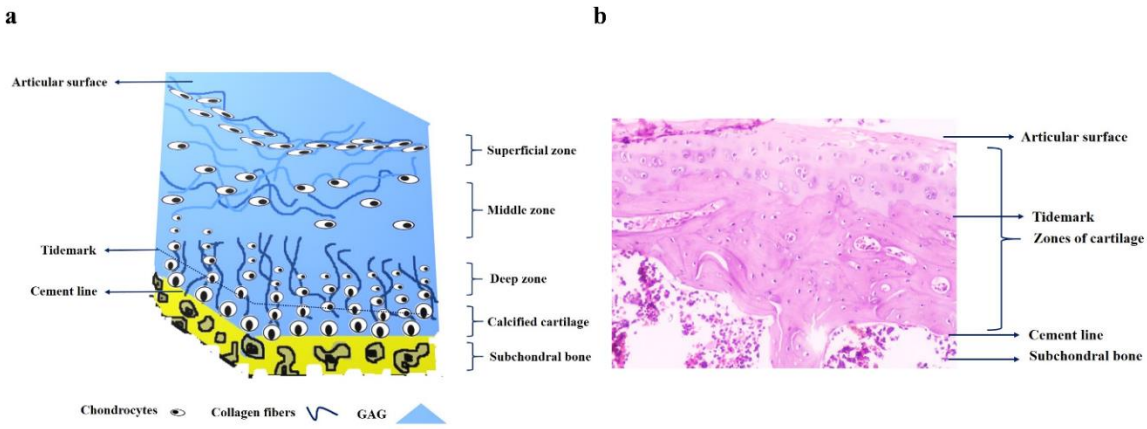

Figure 1. Osteochondral (OC) unit. (a) Diagrammatic representation of OC unit (b) H&E staining of murine OC unit.

2.2. Engineering approaches to restoring the OC interface

An understanding of the structural and functional properties of OC units realizes that the lack of vascularisation and deficiency in nutrient circulation to specific compartments along with the stringent mechanical strength requirements and hierarchical tissue structure would pose the main challenge in restoring an OC unit with the aid of tissue-engineered construct. The existing standard procedures such as total knee transplantation with artificial material are successful in relieving pain and improving function, but the articular cartilage and subchondral bone are not fully restored and would deteriorate over time [41]. The high failure rates associated with total knee replacements (TKRs) underscore the necessity for innovative treatment strategies. Factors contributing to TKR failure include fractures induced by wear and fatigue, stress concentration, inclusions, and high carbon levels in biomaterials [42]. Racial disparities do not explain TKR failure, with risk factors such as non-osteoarthritis TKR indication and low surgeon volume playing a role [43]. Metal hypersensitivity is a known cause of unsatisfactory TKR outcome, especially in patients undergoing revision surgery, although a clear correlation with symptomatic knee after surgery is not fully established [44]. To address the limitations in current treatments, researchers focus on engineering to develop advanced tissue construct/OC substitutes for regeneration with matching mechanical stability that of native OC unit/cartilage and bone. However, many of the developed OC constructs satisfied all the functional and mechanical properties that of the native OC unit in the *in vitro* experimental conditions, but failed to recapitulate the same in the *in vivo* conditions. So it is the need of the hour to design OC constructs with at par performance in both *in vitro* and *in vivo* experimental set-ups at constant physiological, biological, and microenvironmental conditions. The various commercially available OC products for OC defect management are listed in Table 1.

Table 1. Commercially available products for OC defect management.

Commercially available OC TE product	Components	Key Features	Advantages	Disadvantages	Reference
TruFit® (Smith & Nephew)	Poly DL-lactide-co-glycolide, Calcium sulfate, Polyglycolide fibers, Surfactant	Cylindrical implant	The material degrades in approximately 4–8 months	Not intended to provide structural support during the healing process	[45,46]
Collagraft® (Nuecoll Inc.)	Collagen, hydroxyapatite/tricalcium phosphate (HA/TCP) granules	Purified type I bovine collagen, commercially available as sterile strips (45 x 10 x 3 mm) rehydrated just prior to use, approved for use in the US and Japan	For the treatment of acute long bone fractures and traumatic osseous defects with bone marrow and rigid fixation	*In vivo* conditions only validate subchondral or bone support not validating cartilage regeneration	[47–50]
ChondroMimetic™ (TiGenix NV)	Collagen, GAG, Calcium phosphate.	The plug consists of a chondral layer with collagen and GAG and an osseous layer with collagen, GAG, and calcium phosphate	Showed to support the simultaneous natural repair mechanism of both articular cartilage and bone having defect range of≤ 12 mm diameter and ≤ 8 mm depth	Only applicable to small chondral and subchondral lesions and clinical results are poor for larger lesions	[51]
MaioRegen® (Med&Care) (collagen-based 3D scaffold)	Collagen, Magnesium enriched-HA	Using de-antigenated type I equine collagen	Good clinical outcome with complete graft integration in 78.3% of patients		[52]

Table 1. *Cont.*

Commercially available OC TE product	Components	Key Features	Advantages	Disadvantages	Reference
BST-Cargel® (Piramal Life Sciences)	Chitosan, Glycerophosphate, Autologous blood	Injectable hydrogel	This product has proved to be efficient in the initiation and amplification of the intrinsic wound healing processes of subchondral bone, as well as of the cartilage repair		[53–57]
Gelrin C	Polyethylene glycol diacrylate (PEG-DA), Fibrinogen	Biodegradable implant using denatured fibrinogen	Exposure to ultraviolet light converts the liquid into a soft, elastomeric hydrogel implant		[58,59]
CaReS (Cartilage Regeneration System)	Collagen, autologous cartilage cells	CaReS-OneStep is a cell-free matrix available	Support the cartilage regeneration	Only for cartilage regeneration and difficulty in getting autologous cartilage cells	[60]
BioPoly RS Knee System (by BioPoly LLC)	Ultra-high-molecular-weight polyethylene, hyaluronic acid	Femoral condyle resurfacing device	The device is designed to permit arthroscopic-assisted implantation to be quick and straightforward	Restricted to cartilage regeneration only	[61]

Table 1. *Cont.*

Commercially available OC TE product	Components	Key Features	Advantages	Disadvantages	Reference
SaluCartilage™ (SaluMedica)	Polyvinyl alcohol	Biocompatible and hydrophilic cylindrical device	This material mimics human cartilage in terms of water proportions and has been evaluated as a synthetic surface for the replacement of damaged cartilage	The hydrogel showed an inadequate connection to the bone and a risk of dislocation	[62]
TruGraft™ (Osteobiologics)	Poly(lactic-co-glycolic) acid (PLGA)		Support osteoblast proliferation and differentiation, high alkaline phosphatase activity, and deposition of a mineralized matrix used in OC repair		
Agili-C™ (CartiHeal)	Calcium carbonate, Aragonite, Hyaluronic acid	Calcium carbonate for the bone region, and aragonite and hyaluronic acid for the cartilage part	The implant shows a structure similar to natural bone with high pore interconnectivity essential for blood vessels, and the hyaluronic acid helps the ECM of the cartilage to be maintained with their proper characteristics		[63,64]
HYAFF®11 (Fidia Advanced Biopolymers)	It is composed of purified hyaluronan esterified in its glucuronic acid group with distinct types of alcohols	A biodegradable scaffold is used for the repair of chondral and OC lesions.	The advantage of having good cell adhesiveness even without coating and surface conditioning		[65,66]

2.3. OC constructs design considerations for implantation

One of the challenging factors in developing OC construct is the size and shape of the graft. The developed graft should be implantable in the defect site with self-molding ability *i.e.*, to be able to change the shape according to the size of the small as well as large OC lesions. The ideal material should be biocompatible, and non-toxic, along with sufficient mechanical strength to support the load bearing of both cartilage and bone in the OC unit [67]. Considering the size and shape of the implant for the OC unit, it is very significant that the integration between cartilage and bone along with articular surface contour should occur [68,69]. The articular surface of joints is typically curved and matched to the opposing joint surface. Restoring the native contour and curvature real time during repair is essential to prevent issues such as joint instability, abnormal loading, and decreased range of motion that could occur in long run [70–72]. Another important is the feature is that a load-bearing implant must satisfy all the essential parameters for providing support and strength to the host tissue. Thus, the repaired tissue must be able to withstand the mechanical forces without undergoing excessive wear or degradation [73,74]. In view of these factors, biomaterials like hydrogels and their composites with suitable mechanical stability gained more attention due to the ease of preparing zonal gradients for regenerating different layers of cartilage and aiding mineralisation for the underlying bone. Most of the commercially available OC constructs have cylindrical shapes, some others have rectangular shapes, and a limited number are available in liquid formulation (eg. hydrogels) that could be directly injected into the defect site. The types of commercially available OC constructs are summarized in Figure 2.

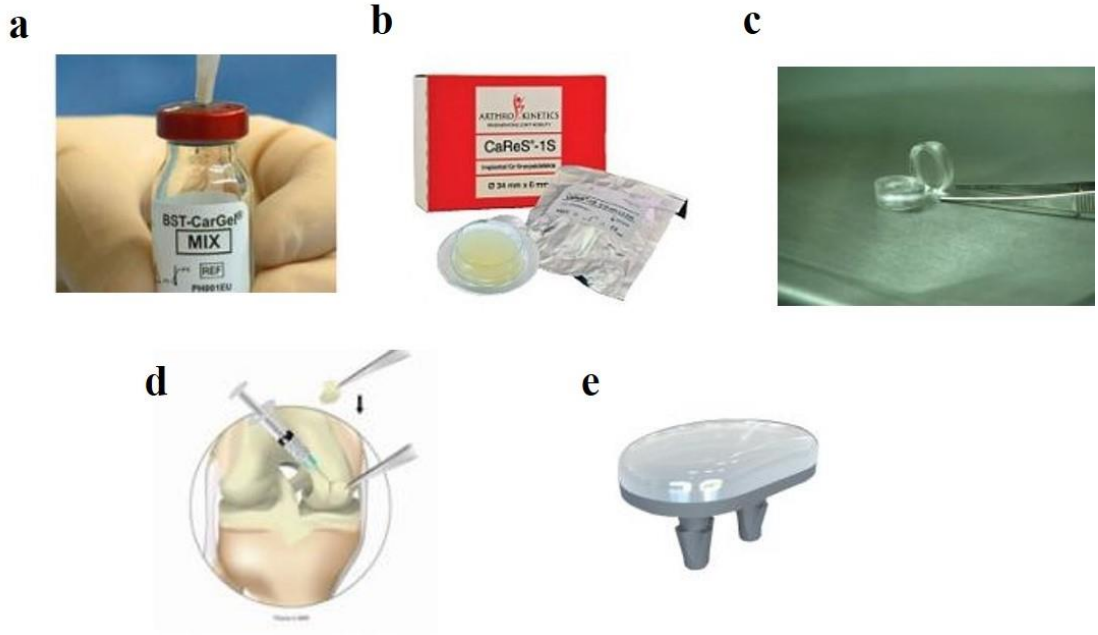

Figure 2. Commercially available OC constructs. (a) BST-Cargel (b) caReS cartilage-regeneration system (c) Gelrin C (d) Chondrocelect (e) BioPoly-rs-knee-system.

Mechanically robust, non-resorbable hydrogels have emerged as promising candidates for the permanent replacement of damaged cartilage tissue. These materials are designed to

mimic the structural and functional properties of native cartilage, offering a potential solution to the challenges associated with cartilage regeneration. Recent studies have focused on developing hydrogels with high moduli and hydration levels to replicate the unique mechanical behavior of cartilage. For instance, composite hydrogel systems incorporating a lubrication layer and a load-bearing layer have demonstrated exceptional compression modulus, creep recovery, and resistance to swelling [75,76]. Moreover, the incorporation of bioactive molecules, such as icariin, into poly(vinyl alcohol) (PVA)—based hydrogels has shown promise in promoting chondrocyte activity and cartilage repair [76]. To further enhance the performance of these hydrogels, research has explored the development of tunable architecture and mechanical properties. Dual crosslinked gelling systems, as described by Yu *et al.* (2022), have exhibited excellent osteogenic potential, suggesting their potential for bone cartilage interface applications [77]. Additionally, the incorporation of bioactive molecules like kartogenin into hydrogel composites has demonstrated the ability to create favourable microenvironments for cartilage regeneration, promoting cell growth, adhesion, and differentiation [78]. These advancements highlight the potential of mechanically robust, non-resorbable hydrogels as viable alternatives to biological grafting for the treatment of cartilage defects.

3. Biological approaches to restoring the OC interface

Recent studies on OC tissue restoration are mainly targeted to the complete regeneration of hyaline cartilage and the subchondral bone. Repairing the damaged articular cartilage back to its functionally normal state has been a major challenge for OC tissue engineering. Currently, the treatment methods such as bone marrow augmentation and stimulation mosaicplasty [79], microfracture [80], and autologous chondrocyte implantation [81] have been used for patients to relieve pain and associated difficulties. However, these are challenging scenarios including the limitations like availability of donor sites, the required size and shape of the OC autograft, and the dedifferentiation of chondrocytes during passaging in culture [23]. The succeeding section will precisely discuss the existing challenges in the currently used treatment sapproaches.

3.1. Bone marrow stimulation and augmentation

Vascularization is essential to heal damaged mesenchymal tissue, [82] whereas in chondral defect, poor vascularization due to the lack of vascular, lymphatic, and nervous systems lead to a decreased rate of healing at the site of defect. The recent trends in cartilage regenerative research focuses on the stimulation of bone marrow progenitor cells that are only able to proliferate to the underlying bone plate [83]. Whereas, the management approach with multiple boreholes and fraying of the surface layer of the cortical bone is not feasible for arthritic patients. Only the complete removal of the sclerotic surface could promote healing of the lesion [79,84]**.** Stedman's Microfracture technique, in which repair of cartilage *via* bone marrow stimulation has the disadvantage of calcified cartilage layer formation [85]. The modified microfracture technology for defects smaller than 1cm which is called the nano

drilling method is becoming more popular today, showing initial clinical improvement post surgery but with an accelerated decline in clinical outcome scores and a higher failure rate during long-term follow-up [85–87].

3.2. OC autograft transfer

OC autograft transfer delivers viable, mature hyaline cartilage–bone units into chondral defects. The systematic review by Richeter *et al.*, (2016) found that ~90% of patients who underwent OC autograft transfer had good or excellent outcomes up to 10 years post surgery [26]. The autograft for this purpose was taken from areas of lower contact pressures on the weight-bearing articular surfaces of the knee [88,89]. It involves the harvesting of 'plugs' from regions of the distal femur that bear low loads (such as the intercondylar notch or medial or lateral trochlea) and promises a higher chance of successful donor graft incorporation and less risk of immune-mediated graft rejection. This method has more application in young and active patients with more load-bearing activities in the early postoperative period, *i.e.* nearly 6-8 months after surgery [90]. However, donor site morbidity and the availability of autologous grafts are the major limitations faced during OC autograft transplantation.

3.3. OC allograft transplantation

The bone marrow augmentation and stimulation techniques and OC autograft transfer have been reported to be unproductive or impracticable for lesions >2 cm^2 [91,92]. Also, the repair of fibrocartilage using bone marrow augmentation and stimulation techniques yield physiological and biomechanical results mediocre to the normal native structure of articular cartilage. Perhaps in young and active patients, cell-based cartilage repair like autologous chondrocyte implantation remains a viable option for severe OC defects even though it necessitates two separate procedures and a prolonged recovery [90].

In an OC allograft transfer a fully thickened, viable articular cartilage is implanted, however, it is a single-stage technique that evades donor site morbidity, permitting the resurfacing of large defects, and produces a more natural, matching contour of the native recipient surface anatomy [93]. Recent studies based on OC allograft transfer reveal that there was improvement when comparing patient pre-surgical scores and patient-reported outcome scores, in knee chondral repair [94]. This technique is highly useful in overcoming extensive subchondral edema, unshouldered lesions, and restoration of bone loss [95].

3.4. Matrix induced -autologous chondrocyte implantation (MACI)

Autologous chondrocyte implantation (ACI) is a surgical technique for fully thickened cartilage lesions in knee joints. A small piece of normal cartilage at the site of the lesion is removed and cultured *in vitro* to enhance the number of cells and is re-implanted to the defect site. ChondroCelect® is the first commercially available cell-based product that successfully completed the entire development track from research to final product for knee cartilage

regeneration. This implant consists of chondrocytes derived from the patient's own cartilage surgically implanted, to induce the synthesis of hyaline cartilage at the tide mark of bone and cartilage to restore the native joint structure and functions [96]. In the last decade, a case series by Peterson *et al.*, 2010 disclosed that meniscal injuries occurring before ACI, or a history of bone marrow procedure before the MACI implantation do not affect the final results of ACI. However, the bipolar lesions at the site of defect and age of the host are the factors that interfere with the outcome [97]. Extended studies have revealed that some limitations which include delamination, dislodgment of the retained periosteal flap, hypertrophy of the periosteum, degeneration or failure of the cartilage repair, *etc.* occur after ACI procedure [98,99]. There are several modifications, which have been introduced to improve the quality of the ACI technique and they are considered as first, second, and third generation of ACI. When the first generation of ACI use suspended autologous cultured chondrocytes in combination with a periosteal patch, the second generation ACI techniques use other membranes (a collagen type I/III membrane) to retain autologous chondrocytes in the cartilage defect, whereas a cell-loaded membranes/ carriers/scaffolds are applied arthroscopically in the third generation MACI [100]. Even though the method of ACI improved the functional outcome, a small percentage of patients still needed revision surgeries [101]. Initially, MACI was limited to knee ACI and was gradually tried in other regions to treat localised full thickened cartilage defects [102].

The MACI technology is advanced and reduces the surgical complexity as it could be completed in minimum procedure time. Fibrin adhesive has also been used in MACI to facilitate chondrocyte migration from the membrane base to the healing tissue. Several positive outcome after the clinical application of the MACI implant in the animal and human knee have been reported [100,103–106]. The MACI technique replaced the need to suture the graft into the cartilage defect, and can be applied by arthroscopic technique, and decreases the stimulus for vasculogenic hypertrophy [107,108]. Cell-based repair of articular cartilage using autologous chondrocyte implantation has been demonstrated in the hip joint [109] recently.

Preclinical data characterizing cartilage healing are limited to short-term studies in rabbits, and sheep models and little information is available about the survival and efficacy of the MACI for cartilage repair. The equine model study by Nixon *et al.*, 2017 reveals that MACI appeared to improve cartilage healing in a critical-sized defect compared with collagen matrix alone [105]. The main limitation related to the use of ACI and MACI is that the implantation requires two surgical procedures for the patients, which could increase the morbidity of the treatment as well as the socioeconomic costs. If at all possible, a complete cartilage repair could be targeted in a solitary stage that accomplishes the goals of restoring hyaline-like repair tissue with durable and long-term functional quality.

4. Challenges in the choice and design of scaffolds for OC regeneration

Ideal biomaterials to be used as scaffolds for OC tissue regeneration should possess properties like biocompatibility, biodegradability, high porosity, compressibility, non-cytotoxicity, non-antigenicity, flexibility/elasticity, osteo-conductivity, and suitability

for chondrocyte cell attachment proliferation and differentiation [110]. The scaffolds should mimic the physico-chemical properties of native ECM in the OC tissue (both cartilage and subchondral bone), be able to provide mechanical support, and biochemical cues, and promote cell-matrix interaction for initiating the tissue regeneration process [111,112]. Due to the poor healing and limited regenerative capacity of the OC unit, chondral damage is considered irreversible, with limited functional restoration. According to the International Cartilage Repair Society (ICRS) criteria, partial thickness chondral damage is unable to heal itself as the subchondral bone presents a barrier between the defect and bone marrow. Whereas, in the case of full thickness condition the chondral defect is in direct contact with pluripotent mesenchymal stem cells. In the spontaneous healing process that occurs, the newly formed fibrocartilage fills the gap of the defect and acts as a part of hyaline cartilage. This newly developed fibrocartilage is poor in mechanical properties in comparison with native structure [113].

4.1. Material for OC tissue engineering

It's worth noting that ongoing research aims to optimize the biomaterials and fabrication techniques, focusing to improve the functional integration between the cartilage and bone components and promote long-term tissue regeneration. Overcoming the limitations of biomaterials for OC tissue engineering is an active area of research. The type of biomaterial used to prepare scaffolds for OC tissue engineering are listed in Table 2.

Table 2. Type of biomaterials used/using currently for synthesis of OC unit.

Sl. No.	Biomaterials used/employed currently for the synthesis of OC unit	Advantage	Disadvantage	Reference
1	Natural Polymers (e.g., Collagen, Fibrin,)	Biocompatible, mimics the natural extracellular matrix (ECM), promotes cell attachment, and can facilitate tissue regeneration	Limited mechanical strength, potential for degradation over time, and lack of control over material properties	[114,115]
2	Synthetic Polymers (e.g., Poly(lactic acid) (PLA), Poly(glycolic acid) (PGA), Poly(caprolactone) (PCL), poly(D,L-lactide-co-glycolide) (PLG))	Tailorable mechanical properties, biodegradable, and can provide structural support during tissue regeneration	Lack of inherent bioactivity, potential for inflammation or immune response, and slower tissue integration compared to natural materials	[116,117]
3	Hydrogels (e.g., Hyaluronic acid, Alginate, Gelatin)	High water content, good biocompatibility, and ability to mimic the native cartilage ECM. Can provide a suitable environment for cell encapsulation and tissue growth	Limited mechanical properties, difficulty in achieving load-bearing capacity, and potential for swelling or degradation over time	[118–120]

Table 2. *Cont.*

Sl. No.	Biomaterials used/employed currently for the synthesis of OC unit	Advantage	Disadvantage	Reference
4	Resorbable Hydrogels	Biocompatible, injectable, the physical and chemical properties of the hydrogel tailored to specific clinical needs, support cell function and tissue formation	Limited initial mechanical strength, may require additional support structures	[121–123]
5	Ceramic-Based Scaffolds (e.g., Hydroxyapatite, Tricalcium phosphate)	Biocompatible, mimics the mineral phase of bone and can provide structural support. Facilitate bone ingrowth and integration	Brittle nature, limited ability to mimic cartilage properties, and potential for stress shielding	[124–126]
6	Composite Scaffolds	Combination of different biomaterials to mimic the OC interface. Allows for tailoring of mechanical and biological properties	Complex fabrication processes, the potential for material mismatch at the interface, and challenges in achieving seamless integration	[127–131]
7	Decellularized Extracellular Matrix (ECM)	Retains the natural ECM composition and architecture, supports cell adhesion and tissue regeneration, and provides bioactive cues	Limited availability, potential for immune response, and challenges in achieving consistent decellularization and sterilization	[132–136]
8	3D Printing/Bioprinting	Enables precise control over scaffold architecture, can incorporate multiple materials, and offers customization for patient-specific needs	Limited range of biomaterials suitable for printing, challenges in achieving proper mechanical properties, and long-term stability	[116,137,138]

4.1.1. Decellularised cartilage

Recently, native ECM tissue-based materials with acellular component are in demand as they provide structural support, and enhance stem cell recruitment, and differentiation without any external inducible factors. Sutherland *et al.*, in their decellularised cartilage-based study provide evidence of osteogenesis and chondrogenesis *in vitro* [139]. The decellularised ECM (dECM) are fabricated in different methods, with whole tissue decellularisation, which can be easily fabricated without any technical trouble and could be lyophilised through decellularizing and recellularising of dense tissues. The powdered dECM in the freeze-dryer method could be used to mold scaffolds with adjustable geometry but have only poor

mechanical properties as compared to the whole tissue scaffolds. Recent studies on dECM-based materials in combination with hydrogels, polymeric solutions for 3D patterned printing, and electrospinning came up as hope in chondroinductive tissue regeneration in the OC unit [140,141].

4.1.2. Gradient biphasic/triphasic scaffolds

A biomimetic gradient biphasic/triphasic scaffold must have a seamlessly integrated layer structure, suitable pore size, and excellent mechanical properties. Though tissue engineering fabrication and the implementation of bi-phasic scaffolds is a successful journey, the recapitulation of the depth-dependent features of native tissue remains a challenge. Additionally, the major limitations of engineered constructs are non-efficient nutrient transport and matrix accumulation which hinder regenerative tissue maturation within the central core of large constructs [142].

In the OC defect, the designed bi-phasic scaffold should initiate regeneration of both cartilage and subchondral bone segments. The scaffold appeared permissive to bone and cartilage tissue growth and penetration, ensuring the diffusion of nutrients and oxygen, as evident from neo-angiogenesis within a month [143]. The bi-phasic scaffold can be synthesised independently by different processes, further in which the individual layer could be combined [144]. According to Liu *et al.*, the novel bilayer OC graft consists of organic compound type I collagen incorporated chondral scaffold layer for the chondral regeneration and bioactive magnesium-doped hydroxyapatite (Mg/HA) crystals co-precipitated with the organic component for the subchondral layer [145]. The gradient triphasic scaffolds are particularly suited for the regeneration of cells according to their zonal discrimination. Many triphasic scaffolds are chondral scaffolds designed to reproduce the stratified structure and zonal characteristics of the cartilaginous region, while including the cell properties, phenotypes, alignment, zone-specific growth factors, matrix compositions, collagen fiber orientations, and mechanical properties [146]. In another study, Fu *et al.*, successfully fabricated a reproducible triphasic scaffold with inherent tissue functional properties and depth-dependent cellular organization by co-culture of mesenchymal cells and chondrocytes. This scaffold components included porous hollow fibers and cotton threads to augment nutrient transport. They concluded that the addition of cotton thread increases the matrix accumulation in the central core and change local modulus at the deep layer similar to that of native tissue, thus raising a real-world promise for the biomimetic repair of focal chondral defects [146].

Wang *et al.* demonstrated the use of a triphasic methylpropenylated gelatin hydrogel scaffold for OC defect repair, integrating chondroitin sulfate and hydroxyapatite to enhance chondrogenic and osteogenic capabilities [147]. Yu *et al.* reported the fabrication of an anisotropic hydrogel based on a decellularized extracellular matrix, employing the use of controlled diffusion to create gradient structures for cartilage injury repair. [148]. Gradient microgel suspensions can influence cell behavior and differentiation within porous scaffolds, and tuning of matrix formulation can steer divergent differentiation outcomes [149]. Weigel *et al.* presented a method to fabricate freestanding multimaterial sheets using

aspiration-based alignment of microgels, enabling spatially controlled functionality in polymer materials [150]. Camacho *et al.* introduced a solvent-cast 3D printing strategy for peptide-functionalized polymers to achieve surface functionalization in a single step, enabling spatially controlled biochemical cues for enhanced tissue regeneration [151]. The fabrication of reinforced biphasic scaffolds made from polyvinyl alcohol (PVA), gelatin, and polycaprolactone (PCL) optimised the scaffold's mechanical strength, thermal stability, and bio-functionality, indicating suitability for maxillofacial surgery applications [152].

4.1.3. Biomimetic multiphasic scaffolds

There exist stringent requirements for biomimetic scaffolds in terms of OC tissue regeneration as they must recreate the features of a functional OC unit *i.e.*, biochemical, biomechanical, and biological features of the cartilage and subchondral bone [143]. The biomimetic scaffolds might mimic and simulate the composition of the natural extracellular matrix to repair OC defects [145].

Innovative 3-D printing developed *via* additive manufacturing technique or layer-by-layer manufacturing technique has come into existence to overcome the limitations of conventional scaffold manufacturing. This type of layer-by-layer manufacturing technique uses customized designing methods for the construction of 3-D layered scaffolds. Through such customized scaffold designing, it is possible to produce constructs that have suitable pore size, and mechanical properties and are capable of providing favourable microenvironment for the growth of cells specific to each layer within the interface. There are different types of additive manufacturing techniques to develop scaffolds with desired anatomical shapes [19,67]. The leading limitations of 3D bio-printing are that its structural integrity and mechanical properties will be different in the *in vivo* applications and the designing of scaffold for load-bearing tissues will be very difficult. Hence, hybrid 3-D printing technology evolved to overcome these limitations.

The zonal differentiation of the ECM component in the OC unit requires the synthesis of biomimetic ECM with varying mechanical strength, with ability to support the chondrocyte in each zone according to its function. According to this zonal differentiation, a 3-D bio-print for OC tissue must provide the same or similar properties as that of the native ECM. Hybrid 3-D bio-printing with multiple layers of different combinations of biomaterials can provide matching mechanical properties, pore size, and interconnectivity for the distribution and proliferation of chondrocytes within the construct/scaffold [153]. A diagrammatic representation of a 3-D bio-print for OC construct development is shown in Figure 3.

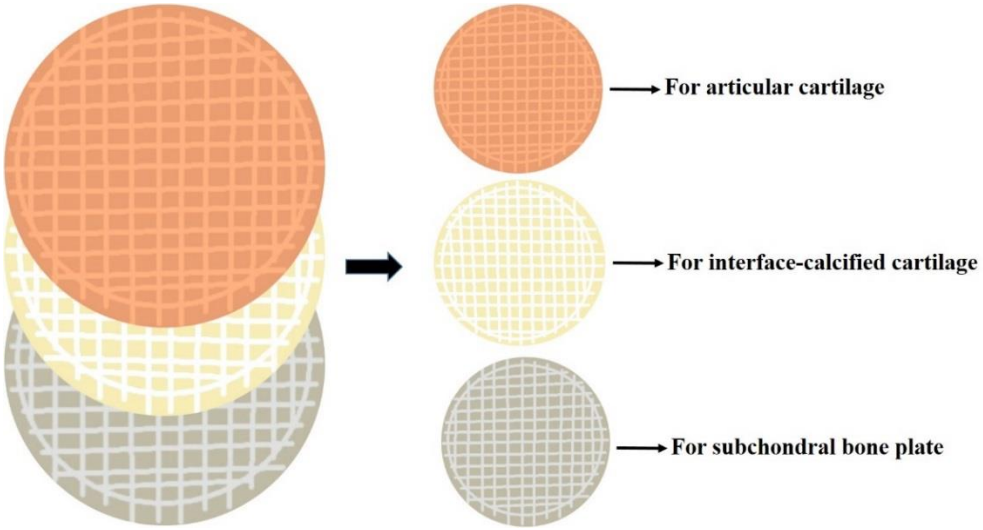

Figure 3. Diagrammatic representation of 3-D bio-print for OC construct development.

Current research in tissue engineering has focused on biomimetic multiphasic scaffolds with spatially controlled material properties to enhance tissue regeneration outcomes. Studies have highlighted the use of innovative scaffold designs, such as triply periodic minimal surfaces (TPMSs) [154], and the development of multifunctional core-shell particles for sequential ion release in bone engineering scaffolds [155]. Biomimetic hydrogels have also emerged as promising materials, offering tunable mechanical and biological properties for tissue repair and regeneration applications [156]. By mimicking the native tissue microenvironment and integrating bioactive substances, these scaffolds aim to improve cell adhesion, tissue integration, and overall therapeutic efficacy. The incorporation of spatially controlled material properties in these scaffolds represent a significant advancement in the field of tissue engineering, paving the way for more effective and tailored approaches to tissue regeneration [157].

5. Cell sources

5.1. Stem cells in OC tissue engineering

Due to the poor healing and limited regenerative capacity, chondral damage in the OC unit is considered irreversible with partial regeneration. Mesenchymal stem cells (MSC) are one of the best cell choices able to differentiate into multiple lineages such as chondral, bone, muscular, and tendon tissue. The widely used MSCs are adipose-derived MSC (ADMSC) and bone marrow-derived MSC (BDMSC) which are isolated from adipose tissue and bone marrow respectively and able to differentiate into osteoblasts, adipocytes, and chondrocytes [82].

Investigation by Kim *et al.*, on seeding human ADMSC on a transforming growth factor (TGF)-β3 encapsulated polylactide-co-caprolactone (PLCL) scaffold (supercritical carbon dioxide (CO2)-1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) co-solvent system) revealed that scaffolds by a co-solvent system exhibited distinct improvement in the compressive E-modulus and deposition of extracellular matrix [158]. Another study by Zhang *et al.*, introduced an approach to promote cartilage formation by ADMSCs seeded polylactic-co-glycolic acid

(PLGA) scaffold exposed to dynamic compression in combination with exogenous SOX-9 treatment [159]. ADMSC chondrocyte co-culture-based study by Wang *et al.*, has revealed that in the presence of ECM components, robust articular cartilage matrix deposition and increased compressive moduli were attained [160]. A bilayered nanopatterned construct seeded with predifferentiated ADMSCs yielded a stratified bilayered hydrogel construct with improved repair quality of cartilage defects [161].

Then approaching to the bone marrow-derived stem cell studies, both bone marrow concentrate (BMC) and BDMSCs were used as cell sources. In the case of BMC, a concentrate graft derived from bone marrow consisting of a heterogeneous population of cells including MSCs [162] was used. BDMSC and BMC are widely used in one-step arthroscopic techniques, with BMC as the preferred source of choice. The main advantage of using BMC directly over BDMSC is that it could be directly used for implantation technique without the need for an extensive laboratory preparatory phase [163]. Hernigou *et al.*, in their BDMSCs-based comparative study in osteoarthritic patients revealed that the method of implantation of BDMSCs in subchondral bone is more effective than the intra-articular injection of the same dose of BDMSCs in postponing total knee arthroscopy [164]. All these MSC-based OC tissue regeneration studies require a standardised and validated method of obtaining large quantities of zone-specific chondrocytes derived from MSCs/BDMSCs-based tissue engineering approaches.

6. Recreating the microenvironment and translational challenges

As mentioned earlier, OC defects are considered the leading cause of disability worldwide, as spontaneous regeneration in this region is restricted due to the inaccessibility to progenitor cells and limited blood supply [165]. OC tissue engineering aims to regenerate functional tissue, mimicking the anatomical and physiological properties of injured cartilage and its subchondral bone. An OC tissue coculture system bilayered scaffold seeded with coculture of ATDC5 (chondrogenic cell line) and MC3T3-E1 (osteoblast cell line) cells in a dual-chamber perfusion bioreactor was described. The authors have studied the system through both *in vitro* co-culture of cartilage and bone cells, and *in silico* computational modelling of the microenvironment inside a micro-CT scanned during perfusion system. This system was shown to have desired microenvironment for OC tissue engineering and it can potentially be used as an inexpensive tool for testing newly developing pharmaceutical products for OC defects [165]. The two important tools that are used here for recreating the OC microenvironment for tissue engineering purpose, specifically enhanced the natural healing process are the bilayered scaffold and the bioreactor. Apart from the bi-phasic and multi-layered scaffolds, what is the contribution of a bioreactor for OC tissue remodelling purpose? This question raises new thoughts for the development and designing of bioreactors which are capable of providing a differential microenvironment for the growth and development of both cartilage and bone tissue segment separately.

Transport of nutrients and gas as well as the removal of waste is one of the other important consideration when designing a good bioreactor. One limiting condition is the amount of gas (oxygen) supplied and the amount reaching to cell. Gruenloh *et al.*, in their *in vitro* experiment demonstrated that the senescence of human embryonic stem cells is reduced

in the low oxygen (3%) or hypoxic condition, as well as the mobility of cells, were much higher at 5% CO_2 and ambient O_2 (normoxic condition) [166]. Yasui *et al.*, also observed that low oxygen conditions promote chondrogenesis in human synovial-derived mesenchymal stem cells in their *in vitro* experiments [167]. Thus, the cells of cartilage need a lower concentration of oxygen for their entire regeneration processes and that of the bone need a high concentration of oxygen for the same. While taking account of these matters, a controlled supply of oxygen is necessary for the regeneration of OC units in a bioreactor [168]. In the superficial zone, cartilage needs 7% of oxygen whereas in the deep zone it needs only 1%, a prevailing hypoxic condition is crucial along with other necessary factors for the regeneration [169]. Cartilage being avascular in nature, a good integration of OC unit with host system is a difficult task and would only be possible by providing a good microenvironment to keep the quality of regenerated OC unit similar to that of the native state.

Loss of regenerative cells through cell death after transplantation is the other challenging problem. As per Zhang *et al.*, and Robey *et al.*, almost half the population of transplanted cells die *via* inflammation, and apoptosis within 5 days after implantation, mainly due to the harsh host environmental conditions, [170,171]. Cellular senescence of transplanted cells such as mesenchymal stem cells and autologous chondrocytes occur due to the deprivation of anchorage-dependent cellular adhesion to the ECM. To conquer this cellular senescence after transplantation, it is better to incorporate certain moieties like RGD into the scaffold to enhance the interaction of cell adhesion molecules aiding in cell adhesion [172,173]. Whereas the senescence induced by the inflammatory response could be vanquished by using a scaffold that has anti-inflammatory properties [174]. Incorporating the anti-inflammatory and antioxidant molecules might enhance cellular proliferation and reduce apoptosis, cellular senescence, and inflammatory response after integration [175].

Recollecting on different arenas of OC tissue regeneration and repair, the crucial area on the clinical side is the translation challenge during OC graft transfer. Other than the challenges mentioned in the previous sections, the main clinical problem faced during transplantation surgery is the probability of acquiring cartilage damage from donor to recipient during integration. This damaged donor cartilage makes the recipient OC unit restore poorly, ultimately leading to transplantation failure. Another aspect to consider is the mismatching of the topology of the recipient joint with the graft making it unfit and leading to infection. The pain and associated bleeding after transplantation surgery is a challenging clinical complication because of donor site morbidity [176]. According to the view of surgeons, transplantation surgeries are difficult and require a congruence of multiple factors along with post-critical care for a successful outcome.

Host demographics like age, gender, and physical condition also play a major role in determining the response and integration of the implanted OC unit into host tissue. The rate of recovery after surgery for patients differ and could result in pain, discomfort, and swelling. Frank *et al.*, in their comparative study, reveal that the two sets of study population below the age of 40 and above the age of 40 have equally recovered after transplantation surgery. However, the rate of recovery in the aspects of recovery from pain, the extent of daily activities, and physical activities are more in the population below the age of 40 compared to the other group [177]. Recent clinical trials in the OC units regeneration are listed in Table 3.

Table 3. Recent clinical trials in the OC regeneration (details adapted from clinical trial.gov)

Sl.No.	Condition or disease	Clinical trials ongoing	Biomaterial used	Site and type of procedure	Study type	Primary outcome measure	Related References
1	Patient Satisfaction Graft Failure Osteo Arthritis Knee	Autologous Semitendinosus Tendon Graft as Meniscal Transplant - a Clinical Pilot Study	semitendinosus tendon	meniscal transplant in osteoarthritis -Surgical technique	Observational	Failure [Time Frame: 2 years] Surgical failure of transplant is defined as meniscus symptoms (joint line tenderness, swelling, locking, or positive McMurray) resulting in a need for re-arthroscopy and subtotal or total resection of the transplant.	[178–180]
2	Acute Knee Cartilage Injury/ Tear of Articular Cartilage of Knee	Evaluation of an Acellular OC Graft for Cartilage Lesions ("EAGLE") European Post Market Study	BioMatrix CRD™ biphasic scaffold contains type I collagen cartilage phase and β-tricalcium-phosphate (80 %) with polylactic acid (PLA) (20 %) for subchondral bone	All patients will receive BioMatrix CRD to repair an articular cartilage lesion or OC defect	Observational	Rate of implant failure resulting in device removal and/or further surgical intervention due to a device-related complication	
3	Degenerative Lesion of Articular Cartilage of Knee	Randomized Controlled Trial of Microfracture Versus Adipose-Derived Stem Cells for the Treatment of Isolated Articular Cartilage Defects	adipose-derived stem cells and collagen scaffold	Cartilage degradation /adipose-derived stem cells Application and Microfracture	Interventional	Health Scores on the KOOS Questionnaire [Time Frame: Completed at baseline, 6 months, 12 months, and 24 months post-operatively.] The Knee Osteoarthritis Outcome Score (KOOS), a standard outcome questionnaire for the assessment of health-related quality of life, will be completed.	[181–189]
4	Cartilage Damage Cartilage Disease	All Autologous Cartilage Regeneration in the Treatment of the Knee Cartilage Defects: Pilot Study	healthy cartilage and the autologous platelet concentrate	Cartilage damage/ A one-step technique in which the healthy cartilage harvested is fragmented directly *in situ* and then mixed with the autologous platelet concentrate and directly injected into the cartilage defect.	Interventional	Change in knee functionality assessed by KOOS [Time Frame: (before treatment, 6, 12, and 24 months postoperative]	[81,190–192]
5	Cartilage Damage	Randomized Controlled Trial Comparing Clinical, Outcomes of Instant MSC Product Accompanying Autologous Chondron Transplantation (IMPACT) for Focal Articular Cartilage Lesions of the Knee to Conservative Treatment	Autologous recycled chondrons (chondrocytes surrounded by pericellular matrix) with MSCs and mixed in Tisseel®(fibrinogen and thrombin concentrate)	Cartilage damage-Grade III or IV cartilage lesions of the knee ranging in size 2-8 cm^2/the autologous defect-derived chondrons will be combined with allogeneic cryopreserved and thawed MSCs to enhance cartilage formation	Phase 3-Interventional	Clinical change on a scale of 0-100 [Time Frame: At baseline, 3, 6 and 9 months] KOOS-questionnaire (Knee injury and Osteoarthritis Outcome Score, 100 indicating no symptoms and 0 indicating extreme symptoms)	[193–195]

Table 3. *Cont.*

Sl.No.	Condition or disease	Clinical trials ongoing	Biomaterial used	Site and type of procedure	Study type	Primary outcome measure	Related References
6	Articular Cartilage Lesion of the Femoral Condyle	Prospective, Randomised, Open Label, Multicentre Phase-III Clinical Trial to Compare the Efficacy and Safety of the Treatment With the Autologous Chondrocyte Transplantation Product co.don chondrosphere (ACT3D-CS) With Microfracture in Subjects With Cartilage Defects of the Knee With a Defect Size Between 1 and 4 cm2	co.don chondrosphere®, a three-dimensional autologous chondrocyte transplantation product (ACT3D-CS)	Microfracture-Articular Cartilage Lesion of the Femoral Condyle/the Autologous Chondrocyte Transplantation Product co.Don Chondrosphere (ACT3D-CS) With Microfracture in Subjects With Cartilage Defects of the Knee With a Defect Size Between 1 and 4 cm2	Phase 3-Interventional	Change of overall KOOS (Knee Injury and Osteoarthritis Outcome Score)from baseline (Day 0)to final assessment compared between ACT3D-CS (co. don chondrosphere) and MF (microfracture)	
7	Articular Cartilage Lesion of the Femoral Condyle	A Comparative Clinical Trial for the Repair of Chondral Knee Defects: Transplantation of Autologous Cultured Chondrocytes *vs.* Autologous Mesenchymal Stem Cells Derived From Adipose Tissue	adipose tissue-derived stem cells and cultured autologous chondrocytes	Articular Cartilage Lesion of the Femoral Condyle-implantation	Phase 2-Interventional	Hyaline cartilage production for chondral knee lesions repair [Time Frame: 18 months]	[81,196,197]
8	Foreign-Body Reaction Inflammation Effusion (L) Knee Knee Pain Swelling	Instant MSC Product Accompanying Autologous Chondron Transplantation (IMPACT): Safety and Feasibility of a Single-stage Procedure for Focal Cartilage Lesions of the Knee	chondrons (chondrocytes with their pericellular matrix) and MSCs with fibrin carrier	focal articular cartilage lesions of the knee/one-step surgical procedure	Phase 2 Interventional	Safety: Adverse Events [Time Frame: 18 months] Adverse events rate	[198–200]
9	Osteochondritis Dissecans	Repair of Articular OC Defect	autologous chondrocyte-laden and biphasic cylindrical plug (DL-poly-lactide-co-glycolide, with its lower body impregnated with -tricalcium phosphate as the osseous phase)	symptomatic isolated osteochondritis at the femoral condyle was treated by replacing the pathological tissue with a biphasic cylindrical plug *via* the surgical method	Interventional	Knee Injury and Osteoarthritis Outcome Score [Time Frame: 1 Year]	

7. OC reconstruction for osteoarthritic conditions

Cartilage plays a crucial role in maintaining the homeostasis of synovial joints *via* uninterrupted synthesis and degradation of the cartilage niche. During the synthetic phase, chondrocytes continuously produce ECM. In the second phase, the enzyme produced by the chondrocytes (matrix metalloproteinase- MMPs) digests the matrix so that the synthetic step of ECM is inhibited, leading to cartilage erosion [201]. The MMPs, cytokines, and chemical mediators such as nitric oxide (NO), prostaglandins, interleukin-1b (IL-1b), tumor necrosis factor-a (TNFa), IL-6, and IL-8 are elevated in the inflamed synovium due to the action of hypertrophic chondrocyte in the pathogenesis of OA [202]. The loss of joint flexibility due to limited movement and load bearing is the leading cause of structural and functional impairment of articular cartilage.

The pathophysiology of OA is that it affects the joint tissue even though the real cause is yet unknown. It may be due to biochemical, enzymatic, genetic, and biomechanical origin or their combination leading to changes, including the loss of typical structure and function of cartilage and subchondral bone. The narrowing of joints is a characteristic change during the disease progression. Repetitive impulsive loading increases bone formation associated with relative bone stiffening during the initial stages, followed by articular cartilage degeneration [203]. Recent studies in OA animal models and clinical samples have revealed that there exist location-specific and stage-specific pathological changes in OA development [204]. The requisites for an ideal OC biomimetic unit are made complex by the observation that there exist top-down and bottom-up calcification processes and the mineral pattern formed and deposited varies from hyper-mineralised stiffer carbonated hydroxyapatite in early stages to hypo-mineralised softer HAP. Further to this, is the expected scaffold functionality in the persisting inflammatory and degenerative hypoxic microenvironment demands the need for drug delivery scaffolds releasing anti-inflammatory molecules/radicals and stimulatory growth factors for cartilage regeneration. Hence, newer intelligent and smart biomaterial scaffolds are the need of the hour, which could detect and respond according to the changing microenvironment within the host body and could balance the mineral laydown along with endogenic cartilage progenitor homing capacity. Also, the patient-specific pathological milieu such as in OA and RA (Rheumatoid Arthritis) should be taken into account for the design of a precise and personalied OC scaffold.

8. Conclusion

Articular cartilage is a complex tissue characterized by limited regenerative capacity, reliant on diffusion for nutrient exchange, and possessing unique mechanical properties. The subchondral bone plays a crucial role in cartilage metabolism, yet its presence complicates tissue regeneration efforts in Osteoarthritis. Reproducing the intricate structure and function of the native OC unit remains a significant challenge. Current treatment options, including total knee replacement, often fall short of providing long-term sustained solutions. To address this unmet clinical need, there is a growing focus on developing innovative biomaterials and

scaffolds capable of mimicking the native OC unit. While various materials have been investigated, the achievement of optimal clinical outcomes requires careful consideration of factors such as size, shape, mechanical properties, biocompatibility, and the ability to support zonal regeneration. Hydrogels, in particular, show promise as regenerative biomaterials for designing resorbable matrices due to their tunable properties and potential to create biomimetic structures. Cell-based therapies, especially those utilizing MSCs, offer additional opportunities for OC regeneration. However, challenges related to cell sourcing, scaffold-cell interactions, and optimum bioreactor conditions need to be addressed. Moreover, translating promising preclinical findings into successful clinical applications requires careful consideration of factors such as cell survival, scaffold integration, and long-term tissue function. Future research should focus on developing biomaterials with enhanced bioactivity and mechanical properties, optimised cell delivery and differentiation strategies and standardized bioreactors environment in creating functional OC constructs. Ultimately, a comprehensive understanding of the complex interplay between cartilage, bone, and the surrounding microenvironment is essential for developing effective therapies to restore and maintain joint function. Effective OC unit regeneration holds immense potential to improve joint function outcomes specifically in pathological scenarios of Osteoarthritis patients.

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Conflicts of interests

The authors declare that there are no conflicts of interest.

Authors' contribution

Jalaja Aswathy contributed to the investigation, data curation, and writing of the original draft. Josna Joseph was involved in the investigation, data curation, and writing, specifically in the review and editing stages. Annie Abraham provided support in the resources, conceptualization, validation, and formal analysis, and also contributed to the writing through review and editing, as well as to visualization and supervision.

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