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Review

POTENTIAL STRATEGIES FOR EFFECTIVE UTILIZATION OF COSTAL CARTILAGE IN ARTICULAR CARTILAGE INJURY REPAIR

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Abstract

Background: Joint diseases are one of the leading causes of global disability. Various methods of cartilage repair, including microfracture, mosaic chondroplasty, and autologous chondrocyte transplantation, have been actively studied. Currently, the use of autologous articular cartilage yields the most favorable outcomes. However, the requirement for harvesting healthy articular cartilage poses significant limitations, prompting research into alternative sources such as autologous costal cartilage. Recent studies on animal models and clinical trials have demonstrated that costal cartilage can serve as a viable alternative, offering similar mechanical properties and promising clinical outcomes. Nevertheless, challenges such as poor graft integration, uncontrolled cell differentiation, incomplete morphological and mechanical tissue matching, and donor site morbidity remain. **Results**: This review summarizes the current research on the use of costal cartilage for the treatment of articular surface defects and proposes various literature-based strategies to mitigate these issues and enhance the protocols for costal cartilage transplantation. Costal cartilage application in clinical settings requires the development of standardized protocols for transplantation, personalized treatment strategies, optimized cultivation protocols and long-term follow-up to enhance overall success rates. **Conclusions:** These improvements will enable broader application of costal cartilage, leading to consistently better clinical outcomes in the treatment of joint cartilage injuries.

Keywords: Mosaicplasty, chondroplasty, articular cartilage, costal cartilage, tissue engineering.

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Introduction

According to statistics, local cartilage injuries of the joints account for 30 to 60 % of all joint pathologies and lead to a deterioration in quality of life and disability among the population [1]. Cartilage itself has limited regenerative capacity due to its avascular and hypocellular structure [2]. Currently, extensive cartilage injuries, including those associated with aging, are practically untreated in clinical practice. Joint replacement is the only alternative, which often fails to fully restore motor functions and requires revision surgery within 10–15 years.

There are several surgical approaches to the restoration of the articular surface (Fig. 1). For small lesions (<2 cm^2), the chondroplasty procedure is employed. This involves the arthroscopic removal of loose and unstable cartilage and the smoothing of the surface. To stimulate chondrogenesis and cartilage regeneration, the microfracture technique can be used. In this procedure, physicians create subchondral bone perforation (microfracture). However, microfracturing can lead to the formation of fibrous tissues in the area of the joint surface defect [3], and clinical trial results are quite inconsistent and generally unsatisfactory [4,5].

A new advancement in microfracture technology is the procedure known as autologous matrix-induced chondrogenesis (AMIC). In this approach, physicians also perform microfracturing, but they cover the defect with a collagen membrane, which is either sutured in place or fixed with fibrin glue. According to systematic reviews, AMIC has shown good clinical outcomes in terms of pain relief and joint mobility, with minimal side effects [6,7]. A similar technology involves the use of scaffolds to fill the defect, including artificial collagen sponges and decellularized cartilage. In this procedure, the entire surface of the defect is cleared down to the level of the subchondral bone, and the scaffold is then implanted into the site. However, experiments on laboratory animals show no significant differ-

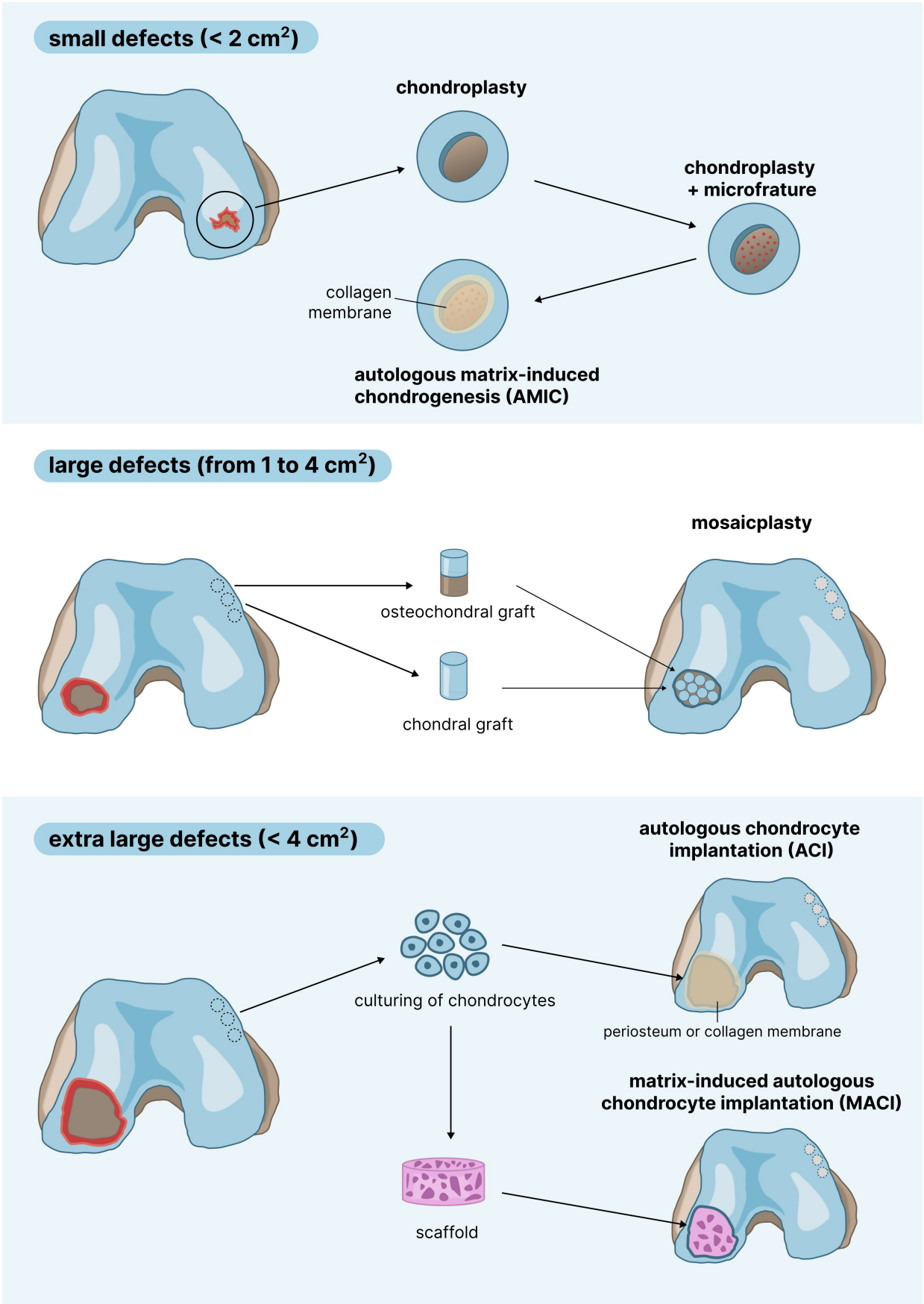

Fig. 1. Main surgical approaches to the restoration of articular cartilage injuries. Image was created with https://www.figma.com.

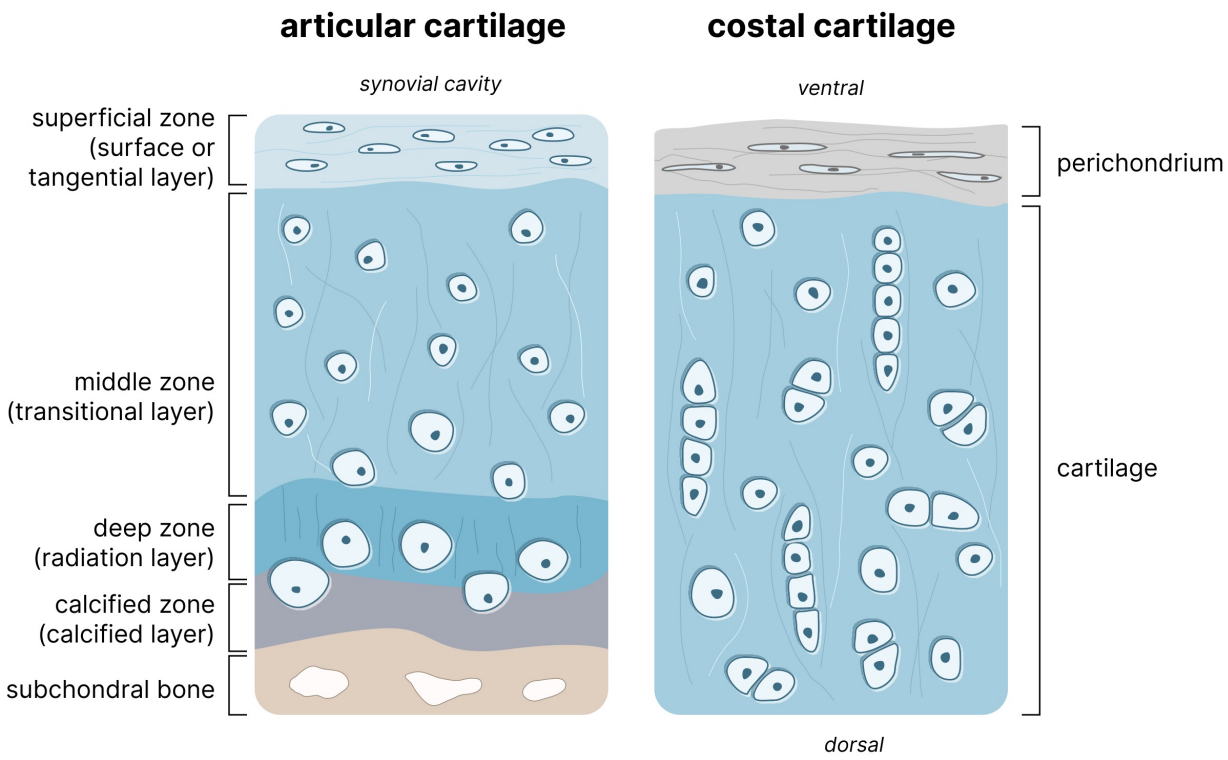

Fig. 2. Comparison of the histological structure of articular (left) and costal (right) cartilage. Image was created with https://www.figma.com.

ences compared to controls [8], and clinical outcomes are comparable to microfracture [9].

Another relatively effective and inexpensive method for repairing large defects (from 1 to 4 cm^2) is mosaicplasty (mosaic chondroplasty), where fragments of autologous intact joint cartilage are usually taken from non-weight-bearing surfaces and transplanted into the defect. These fragments may consist solely of cartilage (chondral graft) or include subchondral bone (osteochondral graft). However, the effectiveness of this technique greatly depends on the patient's age and the availability of undamaged areas of the required size, making the procedure inaccessible to many patients [10].

In developed countries, autologous chondrocyte transplantation techniques are actively used for large (<4 cm^2) defects. The first of them, autologous chondrocyte implantation (ACI) method was reported in 1994 [11] and remains the most used surgical technique [12]. For this procedure, a cartilage fragment is harvested from non-weight-bearing areas, individual cells are isolated from it, cultured, and then transplanted back into the defect in the patient. Since the first report on the technology, 35,000 ACI procedures were performed worldwide by 2010. However, currently, there is no requirement to report the procedure to national and international registries, making it difficult to determine the statistics of ACI procedures [13]. Despite the reported improvements in biomechanical and functional outcomes after ACI, the low level of evidence does not allow for well-founded conclusions regarding the results of ACI [14]. Also ACI does not show complete restoration of native cartilage structure [15]. Additionally, the rate of reoperations within 5 years is 10.3 % [16]. Research is actively going on to develop new cellular technologies to address this problem, but currently, autologous chondrocytes show the best results [17].

The next step in ACI was the development of matrix-induced autologous chondrocyte implantation (MACI) technology [18]. After the autologous chondrocytes expansion within 4 weeks, cells are not immediately injected into the joint but cultured on the collagen membrane for 3 days. During the surgery, a membrane with cells is placed in the defect area so that the cells face the bone [19]. Nevertheless, ACI and MACI have several significant drawbacks. First, the necessity for two surgeries (collection of autologous chondrocytes and transplantation) is traumatic for the patient. Secondly, chondrocytes dedifferentiate into fibroblast-like cells during expansion in monolayer culture [20]. Subsequently, this leads to the inability of dedifferentiated chondrocytes to form hyaline cartilage. And finally, the currently available technologies are quite expensive and don't allow to restore the articular cartilage's native structure.

Given the above, it is important to search for alternative sources of cartilage for both mosaicplasty and chon-

Table 1. Results of clinical application of mosaicoplasty of articular cartilage using costal graft.

Reference	Patients	Surgery	Follow-up period	Result	Complications
[47]	5 patients (men, 18–52 years-old)	Reconstruction of proximal interphalangeal joint using CCG or COG	10 months – 9.5 years	Increased range of motion	2 joints—necrosis of the CCG transplant
[54]	2 patients (men, 24 and 25 years-old)	COG transplantation for capitulum humeri treatment	2 years	Increased range of motion Satisfactory union of the implanted graft	Not reported
[46]	116 patients (97 women, 19 men, 47–82 years-old)	Partial trapeziectomy and autotransplantation of CCG in patients with trapeziometacarpal arthritis	Mean 5, 6 years	Improved grip strength, resumption of professional activities. Pain reduction Cartilage viability	Pleural tear without pneumothorax, 5 surgeries for graft removal 11 cases of graft ossification, and 12 cases of adjacent area ossification. Areas of bone metaplasia and calcification.
[46]	18 patients (16 men, 2 women, 47–82 years-old)	Removal of the proximal part of the scaphoid and autotransplantation of CCG in patients with radioscaphoid osteoarthritis	4, 3 years	Increased range of motion No exacerbation of osteoarthritis. Consolidation observed in 17 cases, no signs of necrosis after thirteen months.	Algodystrophy and graft dislocation
[48]	29 patients (27 men, 2 women, 14–68 years old)	Reconstruction of finger joints defects using COG	4 months–5 years	Increased range of motion Pain reduction	Not reported
[51]	7 patients (4 men, 3 women, 18–74 years-old)	Reconstruction of the radial epiphysis correlated using COG	2 years	Increased functional wrist score Pain reduction	Lysis of the proximal graft [52]
[55]	26 patients (men, 13–16 years-old and 1 patient 43 years-old)	Reconstruction of defects of the humerus head using cylindrical COG	Over 2 years	Graft osteointegration, revascularization, and congruity of the reconstructed articular surface. Significant improvement in elbow joint movement in both flexion and extension.	One patient experienced postoperative pneumothorax, five patients underwent an additional minor surgery and subsequently returned to their previous activities
[52]	18 patients (26 –62 years old)	Replace the proximal pole of the scaphoid	6 months –10 years	Preserved radial and ulnar deviation	Potential for osteoarthritis progression
[52]	4 patients (32–51 years-old)	Lunate excision with COG transplantation	3–36 months	Improved flexion-extension and grip strength	Not reported
[56]	22 patients (12–16 years-old)	Reconstruction of the capitellum using COG	12–77 months	Functional improvement Pain reduction No osteoarthritis	4 patients—additional surgery because of free body (2), restricted range of motion and cartilage avulsion
[37]	1 patient (15-year-old man)	Autologous CCG transplantation into a defect in the medial edge of the patella	2 months	From the second month post-surgery, the patient gradually bore weight on the affected leg and actively participated in physiotherapy.	Not reported

Table 1. Continued.

Reference	Patients	Surgery	Follow-up period	Result	Complications
[43]	55 patients (28 boys, 27 girls, 0.6–17.3 years -old)	TMJ reconstruction with CCGs	10 years	A positive correlation was established between ankylosis and subsequent complications. A higher risk of complications was observed in patients with acquired defects compared to congenital ones.	32.7 % ankylosis 16.4 % excessive growth 12.7 % pneumothorax 34.5 % temporo-zygomatic facial nerve palsy 10.9 %/1.8 % graft site/donor site infection Pain TMJ dislocations
[59]	1 patient (36-year-old man)	Reconstruction of the coronoid process using COG	30 months	Consolidation Restoration of elbow joint congruity, mobility Absence of pain.	Mild pain was observed only with repeated heavy lifting Osteoarthritic changes
[57]	72 patients (71 men and 1 women, 11–25 years-old)	Reconstruction of humeral capitellum using COG	36–147 months	Improvement in elbow extension/flexion Surface integrity	Donor-site pain persisted only 3 to 4 days after surgery Additional surgeries (ligament reconstruction, arthroscopic removal of loose bodies and Kirschner-wire removal)
[49]	23 patients (19 men and 4 women, 18–55 years-old)	Total finger joint arthroplasty using COG	77 months	Improvement in active finger extension/flexion	Not reported
[50]	21 patients (men, mean age 26 years)	Reconstruction of the proximal pole of the scaphoid using COG	29 months	Significant improvements in active wrist movements, grip strength	1 patient has undergone excisi of the scaphoid and fourcorner fusion, 4 patients have shown progression of post-traumatic osteoarthritic changes in the wrist joint, 4 patients exhibited progressive ossification
[42]	1 patient (15-year-old man)	Alloplastic TMJ reconstruction using CCG transplantation	5 years	Significant improvement in the maximum incisal opening	Costal chondral grafts failed to integrate, leading to bilateral ankylosis and subsequent bilateral endoprosthesis
[45]	4 patients (48-year-old woman, two 48-year-old men, 17-year-old man)	TMJ condyle reconstruction using CCG	10 years, 4.5 years, 6 months, 2 months, respectively	Restoration of normal mandibular excursion and protrusion Absence of TMJ pain.	Development of Frey's syndrome, complaints of pain and swelling in the left TMJ, audible TMJ sound Minor donor site complications Ankylosis
[38]	20 patients (8 women, 12 men, age 31.02 ± 7.19 years)	Use of autologous CCG for treating osteochondral lesions of the femoral head	12 months	Increased range of motion Pain reduction Complete graft osteointegration in all cases by 12 months. Biochemical components of the graft matched those of the recipient's hyaline cartilage.	No complications observed, side effects included temporary wound complications (in 2 patients), itching (in 1 patient), and ankle pain (in 1 patient)

drocytes for ACI and MACI. Allogeneic transplantation is proposed for this purpose, which increases the risk of immune rejection and is also associated with donor cartilage damage, or the use of hyaline cartilage from other organs.

In this regard, costal cartilage attracts attention, as it is hyaline, similar to articular cartilage and possesses analogous structure, composition, and mechanical properties (Fig. 2). In the study by Farinelli *et al.* [21], the possibility

Table 1. Continued.

Reference	Patients	Surgery	Follow-up period	Result	Complications
[39]	1 patient (49-year-old woman)	CCG transplantation for osteochondral lesions of the talus	4 years	Osteoarthritis development prevention Pain reduction The graft formed a smooth articular surface within 2 years and fused with the talus bone by 4 years.	Not reported
[40]	5 patients (men, age 36.6 ± 11.1 years)	Autologous COG transplantation for osteochondral lesions of the talus	12 months	Improved joint mobility Graft integration, defect filling with tissue. Pain reduction A substantial amount of hyaline cartilage matrix and chondrocytes	Not reported
[53]	1 patient (20-year-old woman)	Complete resection and reconstruction using a costal osteochondral graft in a patient with a giant cell tumor in the proximal phalanx of the metacarpophalangeal joint	3 years	Improvements in grasp and pinch strength, range of motion of the metacarpophalangeal joint, proximal interphalangeal, and distal interphalangeal joints	Not reported
[58]	1 patient (25-year-old man)	Humeral head reconstruction using COG in patients with an elbow injury	1 month	Increased range of motion in flexion-extension. Initial signs of consolidation, complete skin healing	Not reported

CCGs, costal chondral grafts; COG, costal osteochondral graft; TMJ, temporomandibular joint.

of using costal chondral grafts (CCGs) for the restoration of joint cartilage defects was substantiated through histochemical, immunohistochemical, and ultrastructural analyses. The hyaline cartilage of synovial joints is characterized by a unique microstructure that provides a high compressive load during joint movement. Articular cartilage is characterized by the absence of type I collagen, the presence of type II collagen, and the chondrocyte marker Sox9 (sex-determining region Y protein (SRY)-Box Transcription Factor 9). Articular cartilage consists of three zones: in the superficial zone, chondrocytes are oriented parallel to the joint surface, while in the middle and deep zones, chondrocytes are typically arranged columnarly, parallel to collagen fibers [21]. Costal cartilage also has a hyaline nature and corresponding markers and is covered by a thin, vascularized perichondrium layer. Three layers were also found in the costal cartilage, distinguished based on chondrocyte orientation. The outer layer is characterized by flattened chondrocytes oriented parallelly. In the middle and deep zones, columnarly oriented chondrocytes were observed, aligned parallel to collagen fibers and perpendicular to the perichondrium [21]. The orientation of chondrocytes, matrix composition, and arrangement of collagen fibers indicate that costal chondral grafts can withstand typical joint loads, making costal cartilage a successful option for joint cartilage reconstruction, although it is worth noting slight differences in mechanical properties: rib cartilage is more rigid in compression and soft in tension [22].

Thus, costal cartilage can serve as a source of grafts for mosaicplasty, a source of extracellular matrix (ECM) for creating scaffolds, and a source of cells for transplantation. There are certain risks and drawbacks in using costal cartilage for reconstructing articular cartilage defects, and in this review, we have attempted to systematize existing data on its application and propose experimentally substantiated solutions to the identified problems.

Mosaicplasty Using Costal Cartilage

The process of mosaicplasty was first proposed in the work by Hangody & Kárpáti [23]. During an arthroscopic procedure, resection of the damaged cartilage is performed. Subsequently, osteochondral autografts are harvested from

non-weight-bearing areas of the knee joint and transformed into several cylindrical osteochondral plugs, which are then implanted into the defect site [23]. This surgery is mainly performed on patients with cartilage lesions in the knee joint, particularly in the areas of the femoral condyles and patella, as well as the tibial plateau and elbow joint [24]. The bone component of the graft is necessary for better integration of the transplant, as mature cartilage tissue has a poor tendency to fuse with the recipient's cartilage [25]. The advantages of this operation include a single-stage procedure, a short rehabilitation period, and adaptability to the defect geometry [23].

Several studies have highlighted the advantages of costal chondral grafts (CCGs), including the abundance of material, ease of creating a three-dimensional (3D) framework, resistance to resorption and deformation, as well as a low frequency of unfavorable outcomes [26–30]. Similarly to the articular cartilage transplants, a costal graft can be harvested along with a portion of the bone (costal osteochondral graft (COG)). The results of its application may vary for joints with different loads, so we will further consider outcomes and potential limitations for different joints separately.

Building on the advantages of costal grafts, including their material abundance and resistance to resorption, the next section will delve into the application of mosaicplasty, both in animal models and human clinical studies.

Animal Studies

Knee Joint

Du *et al*. [31] investigated the possibility of restoring knee joint defects in rabbits using mosaicplasty with CCG. Segmented costal cartilage was transplanted into bone-cartilage defects in the femoral groove. After 12 weeks, there were no clear boundaries between the grafts and peripheral articular cartilage, an increase in macroscopic International Cartilage Repair Society (ICRS) scores was observed, and there were no signs of inflammation or necrosis. Integration of the costal chondral graft was noted both laterally and inferiorly, and immunostaining revealed similar staining intensity for type II collagen in the graft compared to articular cartilage. However, the authors note insufficient integration of CCG and native articular cartilage, although graft loss was not observed in the work [31].

In another study, the integration mechanism of CCG was investigated using an osteochondral defect model in the trochlear groove of mice. In the control group without a transplant, the Catwalk system test showed a reduction in the footprint, indicating weight shift and knee disability, whereas in the CCG group, joint function was restored. Micro computed tomography (micro-CT) showed a congruent articular surface and cartilage continuity, indicating good osteointegration. These data were confirmed by histochemical analysis: after 8 weeks, the transplant fused with articular cartilage, and subchondral bone tissue grew into the transplant with the formation of new bone. The use of transgenic mice demonstrated osteogenic differentiation of cells in the transplanted graft, accompanied by the ingrowth of blood vessels. However, the study lasted only 8 weeks, and during this time, complete replacement of the transplanted graft with subchondral bone was not observed [32].

Temporomandibular Joint (TMJ)

Damage of the TMJ affects 34 % of the population, necessitating experimental research of new treatment approaches using animal models [33]. During graft transplantation into a joint, facial symmetry may be affected, and to prevent this, it is crucial to determine the optimal size of the COGs hyaline cartilaginous cap. In the study by Peltomäki *et al*. [34], changes in the mandible have been examined after replacing the condyle with COG containing a short or long cartilage end in adult and growing marmoset monkeys. Radiological studies have shown that all transplants have good osteointegration and fit well in the articular fossa. However, the authors conclude that an excess of cartilage may lead to jaw deviation to the non-operated side in growing animals, whereas no such effect has been observed in adults [34]. Unfortunately, the number of animals in the study has been insufficient for statistically significant results, but it appears that the shape and size of the graft are important for further rehabilitation.

It is known that replacing the mandibular condyles with CCGs in childhood results in facial asymmetry, which may be associated with the faster growth of the reconstructed condyle compared to the non-operated side [35]. Therefore, it is important to conduct an assessment of the growth potential of the transplant. In a TMJ reconstruction model in rabbits, the most intense graft growth has been observed in growing animals (40 %), whereas in adults it has been lower (20 %), with the graft increasing in width rather than length. A statistically significant improvement in bite and jaw movement has been observed in growing rabbits. It is worth noting that there has been partial to complete loss of the graft in the rest of the cases; extensive fibrosis or bone fusion has also been observed in some cases. Additionally, in some animals, calcification of the cartilaginous part of the graft, thoracic cavity perforation, and rupture of the pleural membrane have occurred [36].

Animal studies on the use of costal grafts for joint repair have demonstrated promising results. CCG/COG mosaicplasty resulted in significant improvements in cartilage repair and functional restoration, although in some cases, complete integration with native cartilage was insufficient. Given these results from animal studies, the next section will explore clinical investigations into the application of grafts in different joints, focusing on their efficacy, safety, and potential complications in human subjects.

Clinical Studies

Joints of the Lower Limb

One of the first CCG transplantation surgeries on a patient knee joint has been performed in 2017. The graft, along with the perichondrium, has been harvested and transplanted into a defect on the patella, where holes have been pre-drilled similar to the microfracture technique. Unfortunately, the patient's condition after the surgery has not been assessed in this study [37]. It is worth noting that the microfracture technique before CCG transplantation is often used because it enhances graft integration due to bone marrow mesenchymal stromal cells.

In another more recent study, autologous costal cartilage has been transplanted to restore the congruence of the femoral head in 20 patients. Follow-up at 12 months has shown improvement according to the Harris hip score, EuroQol visual analogue scale, and University of California at Los Angeles (UCLA) physical activity participation score, with no significant deterioration at 36 months. CT scans have indicated complete osteointegration of the transplant, and the median relaxation time of the implanted CCG in T2 mapping has been close to that of articular cartilage, indicating structural similarity [38].

It is currently unclear whether CCG effectively restores osteochondral lesions of the talus. A case of reconstructing osteochondral lesions of the talus with CCG in a single surgery has been described. No donor site complications have been observed, and the patient could perform the full range of ankle movements without pain. There have been no signs of progressing ankle osteoarthritis; the transplant has formed a smooth joint surface within 2 years, and after 4 years, it has fused with the talus [39]. In a similar study, autologous COG has been used for osteochondral lesions of the talus. Prospective evaluation over 12 months post-surgery has shown statistically significant improvements in numeric rating score (NRS) for pain when walking, Tegner score, American Orthopedic Foot & Ankle Society (AOFAS) score, Foot and Ankle Ability Measure (FAAM) score, and magnetic resonance observation of cartilage repair tissue (MOCART) score. Additionally, after 12 months, complete defect filling, good integration, and signal similar to native cartilage have been observed, biopsy has shown the presence of chondrocytes and hyaline matrix [40].

Thus, clinical results generally demonstrate the effectiveness of using CCG or COG for treating cartilage injuries of the lower limb joints, which experience considerable physical load. Interestingly, the aforementioned studies have not reported graft dislodgement and integration problems, which are typical for classical mosaicplasty or rib graft transplantation studies in animals.

Temporomandibular Joint

CCGs are widely used in TMJ reconstruction due to several advantages, including growth potential, which is crucial in pediatric maxillofacial surgery [36,41]. However, inadequate understanding of the graft's reaction to the TMJ environment, including unpredictable growth and resorption, has led to complications in some cases [41]. A case of bilateral ankylosis (bone fusion) in a patient with an immature skeleton after CCG transplantation has been reported, requiring TMJ reconstruction with a non-growing implant [42]. In a retrospective 10-year study of 55 pediatric patients undergoing TMJ reconstruction with CCGs, 58.2 % of patients have experienced at least one complication, the most common being ankylosis (32.7 %) and excessive growth (16.4 %). Other complications included pneumothorax (12.7 %), facial nerve paralysis (34.5 %), pain, and TMJ dislocations. A positive correlation has been established between ankylosis and subsequent complications, including recurrent ankylosis. A higher risk of complications has also been observed in patients with acquired defects rather than congenital ones. There has been no significant correlation between complications and factors such as previous surgeries, bilateral surgeries, or intermaxillary fixation [43].

A systematic review has evaluated the long-term growth potential of CCG in patients with TMJ ankylosis and hemifacial microsomia (underdeveloped lower half of the face) with a minimum follow-up of 5 years. Among the 96 surgeries performed, optimal growth has been observed in 54 cases, excessive growth in 7, no growth in 1, graft resorption in 21, reankylosis in 8, and sequestration in 3 cases. Despite most favorable outcomes, the reviewed case series in the literature are considered to have a low level of evidence. Therefore, randomized clinical trials are required for adequate assessment [44].

In contrast, TMJ reconstruction in adult patients has shown more successful outcomes, although the study involved only 4 patients. The study has demonstrated the return of mandibular excursion and protrusion, as well as the absence of TMJ pain, ankylosis, and donor site complications [45]. This type of surgery is also suitable for patients diagnosed with submandibular space abscess and acute purulent osteomyelitis of the condyle [45].

Thus, TMJ reconstruction using CCG can potentially be successful in adults, but the high incidence of complications in pediatric applications requires further study and methodological improvement.

Joints of the Upper Limb

The CCG and COG techniques can be used to replace large parts of hand joints. In a large study by Tropet *et al.* [46], since 1992, 116 patients with trapezio-metacarpal arthritis have undergone surgery where the trapezium was partially removed and replaced with CCG. The follow-up with an average duration of 5.6 years has shown the absence of pain in 84 % of cases, a 45.3 % improvement in grip strength, and resumption of professional activities on average after 2.9 months. Magnetic resonance imaging (MRI)

of 39 patients has shown no graft wear, and CT has revealed 11 cases of graft ossification and 12 cases of adjacent area ossification. Nine biopsies have revealed viable cartilage, increased connective tissue, neovascularization, areas of bone metaplasia, and less frequently, calcification. Additionally, 18 patients with radioscaphoid osteoarthritis have undergone COG transplantation. With an average follow-up of 4.3 years, two complications have been identified, including algodystrophy and graft dislocation; in the remaining patients, consolidation has been shown in all cases within 3 months, with no exacerbation of osteoarthritis or necrosis [46]. In another study, it was demonstrated that COG transplantation is optimal for the reconstruction of the proximal interphalangeal joint, as necrosis of the graft was observed in cases of CCG transplantation [47]. Later studies on the reconstruction of various finger joints using COG showed excellent results in terms of range of motion, with no complications reported [48,49].

COG can also be used for the replacement of the scaphoid. Cases of COG reconstruction of the proximal scaphoid pole in 21 patients with proximal scaphoid nonunions with fragmentation have been described. With an average follow-up of 29 months, significant improvements in active wrist movements, grip strength, Disabilities of the Arm, Shoulder and Hand Scores (QuickDASH), and Patient-Rated Wrist Evaluation (PRWE) have been observed, and fusion has occurred in all patients. However, 4 patients have shown progression of post-traumatic osteoarthritic changes in the wrist joint, and 1 patient has undergone repeat surgery due to an initial low-quality graft with ossification. Progressive graft ossification has been observed in 14 patients [50]. Similar results were obtained by other researchers in a sample of 18 patients, although no complications were reported in their cases [51,52].

An interesting operation creating a part of the proximal phalanx with the metacarpophalangeal (MCP) joint from COG for subsequent transplantation in a patient after bone fragment removal due to a giant cell tumor has also been described. Results have shown improvements in grasp and pinch strength, range of motion of the MCP joint, proximal interphalangeal, and distal interphalangeal joints, with no recurrence after 1 year of follow-up [53].

Cylindrical COG has also been used to treat humeral capitellum cartilage defects. A small study involving two patients showed increased range of motion and good graft integration two years after treating osteochondritis dissecans of the capitulum humeri [54]. In a follow-up study of 26 patients, X-rays have shown graft osteointegration, MRI with T1-weighting has shown revascularization, and MRI with T2-weighting has shown the congruity of the reconstructed articular surface. All patients have shown functional improvement, assessed using the clinical rating system of Timmerman and Andrews. Minor surgical interventions included screw removal, loose body removal, and shaving of protruding cartilage [55]. Two studies on young athletes also showed good clinical results, allowing patients to return to physical activity [56,57].

A case has been described of a patient with an elbow injury, where humeral head reconstruction using COG, consisting of one-third cartilage and two-thirds bone, has been performed. The bone part of the graft has been used to reconstruct the lateral column of the humerus, and the cartilage part has allowed the reconstruction of the articular side of the humerus. X-rays have shown the beginning of consolidation after one month of follow-up, and the range of motion has been 35° during flexion-extension [58].

COG has also been used for coronoid process reconstruction in a patient with an anteromedial coronoid fracture. Fusion has been observed 24 months after surgery, with CT and MRI showing congruency of the elbow joint, an increased range of motion, and the patient reported no pain and was able to return to work, although slight osteoarthritic changes were observed on radiographs [59]. Similarly, COG can be used to treat injuries of the radial epiphysis: a study involving 7 patients showed improved joint functionality without significant complications [51].

Thus, COG plays a significant role in the reconstruction of upper limb joints, particularly in the wrist and elbow areas, allowing the reconstruction of entire lost fragments. Typical complications include ossification, graft loss and osteoarthritis, less frequently persistent or increased pain syndrome.

Clinical studies have demonstrated the effectiveness of costal grafts in the treatment of cartilage injuries across various joints (Table 1, Ref. [37–40,42,43,45–59]). In the lower limb, CCGs have shown promising results, particularly in femoral head restoration, with complete osteointegration observed in several cases. For the TMJ, CCG transplantation shows potential in adults, but complications in pediatric applications, such as ankylosis and excessive growth, require further research. In upper limb joints, CCG and COG have been successfully used to reconstruct joint defects, though some complications like graft ossification and osteoarthritis have been reported. However, despite these positive outcomes, there are significant limitations and side effects associated with CCG and COG transplantation, necessitating the exploration of potential approaches to overcome these challenges.

Current Approaches to Overcoming Limitations

Costal chondral grafts have several advantages. These include ease of extraction, restoration of functional load-bearing capacity, and high biocompatibility. However, there are potential issues such as poor graft integration, ossification, osteoarthritis, donor site pain and difficulty of use on growing children.

Limitations of Existing Studies

Many of the aforementioned studies have such limitations as a small number of cases, gender bias, short follow-

up periods, and the absence of control groups. Future research should involve large-scale controlled studies as well as long-term follow-ups.

Quality of the Costal Graft Material

The low quality of CCG can be due to rib calcification, necessitating a preoperative evaluation of the bone and cartilage parts of the rib using CT [60]. During surgery, the graft should be trimmed to match the size and shape of the defect, and cartilage survival can be enhanced by drilling the bone part of the graft [40]. Another issue is the fragility of the graft. The likelihood of fracture of the COG can be reduced by decreasing the length of the cartilaginous cap, thereby enhancing the mechanical stability of the osteocartilaginous junction. Additionally, to avoid fractures at the bone-cartilage interface and to increase structural integrity, a small part of the periosteum or perichondrium around the junction is preserved [61]. Another study has identified the heterogeneity of the mechanical properties of different areas of costal cartilage, which can also be practically utilized. The middle area of the costal cartilage has shown the highest modulus of elasticity and hardness values compared to the distal and proximal segments [62].

Graft Integration

The integration of costal chondral grafts can be improved by transplanting them into the defect along with the perichondrium. The surrounding costal cartilage perichondrium is a layer of vascularized dense connective tissue formed by an outer fibrous and inner cambial layer. Both layers contain collagen types I and IV, while type II collagen and Sox9 are absent [21]. Dou *et al*. [63] utilized transgenic rats with ubiquitously expressed enhanced green fluorescent protein (GFP) to investigate the role of periosteal and perichondrial transplant cells in joint healing. Both the periosteum and perichondrium were directed cambially towards the joint space. In the case of the perichondrial transplant, the chondrocyte marker Sox9 was already observed on the third day and maintained throughout the experiment. Type II collagen and proteoglycans were detected in the transplanted tissue after two weeks and remained until the end of the experiment. Furthermore, on day 112, cells positive for both GFP and osteoblastic marker osteocalcin were found in the bone beneath the transplant, indicating the potential involvement of perichondrial cells in bone remodeling and differentiation into osteoblasts. Despite the presence of chondrocyte markers, transplantation of the periosteum resulted in the maintenance of collagen type I alpha 1 chain (*Col1a1*) expression and a fibrocartilaginous appearance of the transplant. Thickness of the periosteal transplant consistently decreased, unlike perichondrial transplants. These findings suggest the ability of perichondrial cells to acquire a phenotype characteristic of articular cartilage cells while forming native hyaline cartilage [63].

It was shown that the costal cartilage perichondrium contains a pool of stem cells that produce new chondrocytes involved in tissue renewal [64], which could potentially be used to improve the integration of transplanted grafts. For example, in nasal septum reconstruction, costal cartilage fragments were wrapped in the costal perichondrium before transplantation, leading to complete defect filling in 78 % of patients [30]. Moreover, the microcirculatory network of the perichondrium can address some limitations of the osteocartilaginous graft, such as cartilage resorption and loss of its anatomical function. Hardy *et al*. [65] have described a technique for obtaining a vascularized chondrocostal graft. Radiographs and CT scans have shown that the perichondrium of the obtained grafts was richly vascularized by superior and inferior intercostal branches in all specimens.

Pathologies of the Donor Area

Donor site complications include pleural tear, pneumothorax, pleural effusion, atelectasis, empyema, pneumonia, and occasional fractures. In cases where multiple grafts are required, harvesting from alternate ribs is recommended to reduce donor site pain [41]. Pleural tears, pneumothorax, and pleuritis can be prevented or minimized through careful dissection of the periosteum, and for large pleural tears, a thoracotomy tube is applied. Hematomas and seromas are prevented by closing the harvest site in a layered fashion; treatment includes drainage. Damage to the intercostal neurovascular bundle can be avoided by maintaining a subperiosteal dissection plane and placing the incision over the midbody or superior aspect of the rib [61].

A mouse model has established a correlation between the amount of repair and the surface area/volume ratio, suggesting that the regeneration rate increases with a small resected area surrounded by abundant perichondrial tissue [64]. Therefore, to prevent donor site complications, a minimally invasive method for harvesting small pieces of costal cartilage requiring an incision of less than 1.5 cm, compared to the traditional 10 cm, can be used. In a study involving 35 patients, there were no complications, infections, deformities, and donor site pain was minimal, although one patient had pneumothorax [66].

A method for preventing chest wall asymmetry can be the transplantation of a free dermofat graft (FDFG) into the perichondrial socket at the costal cartilage harvest site. In a study involving 76 patients, 38 underwent FDFG transplantation, while 38 were in the control group. Three months post-surgery, chest CT scans and three-dimensional (3D) colormap quantification showed significantly less asymmetry in the FDFG group compared to the control group [67]. To prevent local depression and asymmetry of the bilateral thoracic height, xenogenic decellularized pig costal cartilage was used to fill the costal cartilage defect after graft harvesting. An *in vitro* study showed no cytotoxic effects of decellularized costal cartilage on chondrocytes, with cell vi-

ability exceeding 90 %. CT scans showed a greater amount of newly formed cylindrical-shaped tissue in the decellularized cartilage group compared to the control. Regenerated tissues in the decellularized costal cartilage group exhibited typical lacunar structures, positive cartilage ECM staining, calcified nodules, and fibrous tissue, and were characterized by increased expression of *Sox9,* aggrecan (*Acan*), collagen type II alpha 1 chain (*Col2a1*), and osteogenic Runt-related transcription factor 2 (*Runx2*) [68].

Despite encouraging reports on the potential of the perichondrium to improve CCG integration, it is recommended to leave part of the perichondrium at the donor site to preserve the structural integrity of this area [61]. This is confirmed by studies in mice. In the group with costal cartilage removed along with the perichondrium, no regeneration occurred even after 9 months, whereas in the group where only costal cartilage was removed, new tissue formation occurred within 1–2 months. The newly formed tissue was stained with Alcian blue, contained clustered chondrocytes, and had an abundant hypertrophic profile. Moreover, implantation of labeled tdTomato perichondrium led to the formation of ectopic cartilage with tdTomato-positive cells, confirming their origin from the perichondrium [64].

TMJ Reconstruction in Growing Children

TMJ reconstruction was first described in 1920 and has been actively applied in clinical practice, with potential problems being most studied, including unpredictable growth, bone resorption, and recurrent ankylosis [41]. Furthermore, the optimal thickness of the cartilage part of the graft that promotes facial symmetry restoration in growing children without subsequent complications has not yet been established [36]. Using grafts with varying cartilage thickness in combination with long-term follow-up will help optimize this approach. Preoperative virtual analysis, surgical simulation design, and intraoperative resection and reconstruction assisted by digital methods can be conducted to determine optimal resection and reconstruction methods. For TMJ reconstruction, an optimal approach has been determined for each patient using 3D reconstruction of the skull, mandible, major blood vessels, and nerves, followed by surgical modeling. Accurate localization of the defect and its relation to other structures contributes to safer and more effective surgical reconstruction [69].

Thus, it can be concluded that a unified protocol for the transplantation of CCG and COG for the reconstruction of various joints is required. Such a protocol should apparently include methods to reduce donor site complications and stimulate healing using the perichondrium or decellularized scaffolds. Additionally, the perichondrium can be used to improve graft integration, and the development of computer modeling methods will allow for predicting the precise sizes and shapes of grafts to enhance reconstruction outcomes.

Scaffolds from Decellularized Costal Cartilage

Experimental Studies

Due to the existing limitations of autologous costal chondral grafts, decellularized costal cartilage can serve as an alternative. This material retains highly conserved ECM proteins while avoiding rejection reactions by removing the cellular component [70]. Moreover, decellularized xenogeneic costal cartilage can be successfully utilized for rib reconstruction after the patient's own ribs have been harvested for joint surface restoration [68].

A cost-effective and reproducible protocol for obtaining decellularized sheep costal cartilage has been developed. It consists of cycles of freezing/thawing, trypsin digestion, and incubation in hyperosmolar and hypoosmolar saline solutions. The resulting scaffold preserved the architecture of hyaline cartilage, showed an absence of chondrocytes, a significant reduction in nuclei, and a 20-fold decrease in deoxyribonucleic acid (DNA) content compared to untreated costal cartilage [71].

In an *in vivo* experiment, it has been shown that a xenograft composed of decellularized costal cartilage ECM, fibrin glue, and human adipose-derived stem/stromal cells (hASCs), when subcutaneously implanted, maintained 98.97 % ± 17.35 of its original volume after 3 months. In contrast, the xenograft made of hASC-glue degraded within a month, indicating the importance of ECM in volume maintenance. Furthermore, the combination of fibrin glue and decellularized costal cartilage promoted chondrogenesis of hASCs *in vivo* without *in vitro* induction. Co-localization of hASCs labeled with fluorescent nanodiamonds, collagen II, and aggrecan was observed, along with stronger staining with Alcian blue and Masson's trichrome compared to the ECM-glue group [72].

As alternative grafts for rhinoplasty, sodium deoxycholate-based decellularized costal cartilage (SDCC) and combination method-based decellularized costal cartilage (CDCC), where the ionic detergent was replaced with trypsin, have been obtained and characterized. SDCC and CDCC have shown good biocompatibility and are non-toxic to chondrocytes. However, in the CDCC group, compared to the SDCC group, immunohistochemical and biochemical analyses have revealed higher glycosaminoglycans (GAG) content, significantly higher Young's modulus, and stress at fracture. Moreover, after implantation into the rabbit nose, degradation in the central area with a large invasion of inflammatory cells around the graft was observed in the SDCC group after 6 months. The thickness of the SDCC graft was 53 % of the preoperative thickness, while the CDCC graft thickness was 94 %, with fewer inflammatory cells and higher GAG content [70].

To preserve the properties of hyaline cartilage and morphology after implantation, a decellularized allogeneic cartilage paste (DACP) using human costal cartilage mixed with a crosslinked hyaluronic acid-carboxymethyl cellulose

carrier has been developed. *In vitro* studies of DACP have shown high cell viability, migration, and proliferation, as well as increased expression of collagen II and aggrecan. In a rabbit knee joint defect model, treatment with microfracture combined with DACP implantation, compared to microfracture alone, has led to uniform defect filling with regenerative tissue, similar to native tissue in GAG deposition, higher collagen II content, higher ICRS scores, and lower collagen I deposition [73].

In one study, a bioengineered ear was constructed using decellularized sheep costal cartilage placed within a 3D-printed external auricular scaffold. Implantation of the ear scaffolds did not cause complications within 3 and 6 months. Fibrous tissue infiltrated the scaffolds, and vascularization was observed within capsules at 3 and 6 months [74].

A major limitation of the decellularized scaffold is the incomplete removal of detergents, which can exert strong cytotoxic effects on cell cultures and host cells post-implantation. Intensive washing of decellularized scaffolds can help reduce the number of residual contaminants, thereby improving biocompatibility [75]. Additionally, the use of xenogeneic material poses risks due to the presence of porcine retroviruses and serious immunological barriers, facing regulatory and financial challenges [76]. Numerous methods are currently being investigated to overcome these difficulties, such as modifying decellularization protocols, optimizing sterilization protocols, and masking or removing antigens [77].

Current Approaches to Overcoming Limitations

To integrate xenogeneic decellularized scaffolds into translational research, a crucial task is the elimination of immunogenicity of the material. Xenografts contain immunogenic regions, including galactose-α-1,3-galactose, N-glycolylneuraminic acid, and Sd^a carbohydrate antigen, as well as non-conservative collagen regions. Additionally, aggressive decellularization methods release damage-associated molecular patterns (DAMPs), including DNA, reactive oxygen species, and fragmented ECM molecules, which activate the immune system and cause graft rejection. Therefore, an effective decellularization method that removes antigens while preserving the native ECM structure is key to preventing transplant rejection [77].

Various processing methods are employed to reduce the immunogenicity of decellularized matrices. Selective antigen removal involves eliminating specific antigens, such as α-gal, using α-galactosidase. The solubilization-based antigen removal method is necessary to remove soluble proteins and prevent intermolecular disulfide bridge formation by using reducing agents and salt. During the decellularization process, structural changes in the ECM can occur, leading to the exposure of hidden antigens that increase immunogenicity and reduce mechanical properties. To address these issues, crosslinking with chemical agents (e.g., glutaraldehyde), natural agents (e.g., chondroitin sulfate, genipin), physical crosslinking through UV irradiation, and dehydrothermal treatment are applied [77]. Additionally, coating scaffolds with albumin is a relatively inexpensive and straightforward method to reduce the immune response [78].

It is known that the process of removing cells and cellular antigens is associated with changes in the material's mechanical properties. This can be overcome by collagen cross-linking or combining it with various polymers [79,80]. Adding single-wall carbon nanotubes to decellularized articular cartilage increased the scaffold's mechanical characteristics without affecting compatibility [81].

Coating decellularized cartilage with Silk-Elastin-Like Proteins hydrogel has demonstrated an increase in mechanical properties during movement. However, it is important to note that the cells seeded onto the matrix did not migrate inward, a common observation when using native articular cartilage [82]. In this regard, the combination of electrospun gelatin-polycaprolactone nanofibers and decellularized cartilage extracellular matrix appears to be more promising. This combination has been shown to improve scaffold biocompatibility, accelerate chondrocyte maturation, and restore surface congruity when transplanted into a defect [83]. Similar results have been obtained in studies using scaffolds based on decellularized cartilage integrated with poly(lactic-co-glycolic acid) fibers within a citric acid-modified chitosan hydrogel [84].

Overall, various biomaterials can be used in combination with decellularized rib cartilage to improve its biocompatibility and integration with adjacent tissue. Besides different decellularization methods affecting the immune response and using crosslinking agents, various hydrogel microparticles carrying chitosan, gelatin, alginate, hyaluronic acid, heparin, fibrin, chondroitin sulfate, and other natural and synthetic components can be introduced into the scaffold [85]. Scaffold treatments with platelet-rich plasma or platelet-derived growth factor (PDGF)-BB also prove effective [85,86]. Recent studies propose new methods for incorporating chondroitin sulfate into scaffolds or combining it with a gelatin-hyaluronic acid hydrogel, resulting in improved biocompatibility and cell differentiation [87,88].

Thus, decellularized rib cartilage can be a promising scaffold for creating tissue-engineered constructs (TECs) as it retains all biologically active components, while artificial scaffolds face challenges in replicating the properties of native cartilage [89]. Costal cartilage is already used in the reconstruction of the nose, ear, and articular cartilage, but further research is required to optimize decellularization protocols and post-decellularization techniques to reduce immune response and enhance biocompatibility.

Autologous Costal Chondrocyte Transplantation

Autologous chondrocyte transplantation (ACI and MACI) is actively used for treating large defects in the articular surface. A major limitation of these technologies is the necessity to harvest healthy cartilage tissue for cell isolation and expansion, which results in additional trauma and is not feasible for elderly patients. Costal cartilage can also be used for autologous chondrocyte transplantation: costal cartilage shows a high cell yield (12,340 $\pm$ 1536 $\times$ 10^6 cells/g), high GAG and collagen content. For comparison, the femoral head contains 5.121 $\pm$ 0.494 $\times$ 10^6 cells/g, whereas the knee cartilage contains 4.665 $\pm$ 0.458 $\times$ 10^6 cells/g. Costal chondrocytes grow well in culture, retain chondrogenic potential, and overall can serve as a good alternative to articular chondrocytes (further discussed by [60,62]).

Nevertheless, the issue of chondrocyte dedifferentiation in culture has been noted for both articular and costal chondrocytes [20,90]. This effect occurs with prolonged cultivation in monolayer culture and leads to the loss of the original chondrocyte phenotype, causing them to dedifferentiate into fibroblast-like cells. Subsequently, this leads to the inability of dedifferentiated chondrocytes to form hyaline cartilage.

Nevertheless, the use of costal chondrocytes for autologous transplantation is not yet an established method and active research is ongoing. Below, we will review the results of animal studies and clinical trials of this technology.

Animal Studies

In a study on rabbits, bone-cartilage defects have been repaired using allogeneic scaffold-free bioengineered pellets derived from costal chondrocytes. While untreated defects were filled with fibrocartilaginous tissue, the group with costal chondrocyte pellets has demonstrated the formation of tissue integrated with bone, rich in proteoglycans and type II collagen. However, it should be noted that the transplanted pellets did not differentiate into bone in the subchondral region, and by week 16, the thickness of the formed cartilage exceeded that of the intact cartilage [91].

In another study on rats, tissue-engineered constructs (TECs) created from costal chondrocytes have been developed as scaffold-free cell sheets. Interestingly, the authors deviated from using the standard chondrogenic differentiation medium containing transforming growth factor β3 (TGFβ3) and used cell expansion medium with the addition of L-Ascorbic acid 2-phosphate trisodium salt, significantly reducing the cost of the procedure [92]. Overall, the density and three-dimensional structure are crucial for the chondrogenic differentiation of chondrocytes, while the addition of growth factors is used to accelerate the process, increase extracellular matrix content, and prevent hypertrophy [93]. On day 14 TECs grown with ascorbic acid addition have shown greater construct thickness, more extensive staining for type II collagen, and higher GAG content. Quantitative polymerase chain reaction (qPCR) results have indicated increased expression of *Col2a1, Acan*, and *Sox9* genes in TECs with ascorbic acid, although there was also an increased expression of the hypertrophy marker collagen type X alpha 1 chain (*Col10a1*). In both groups, type I collagen expression was quite high, which is undesirable for hyaline cartilage formation. *In vivo* studies on a rat knee cartilage defect model have shown integration of TECs with native cartilage, greater hardness and modulus of elasticity in constructs with ascorbic acid, and maintained high levels of GAG, type II collagen, and aggrecan in the matrix after 12 weeks of implantation [92].

However, it should be noted that the mechanical properties of various tissue-engineered cartilage do not always match native cartilage. In study of Huwe *et al.* [22], the cultivation of neocartilage in non-adherent agarose wells with the addition of factors such as TGFβ1, chondroitinase ABC (c-ABC), lysyl oxidase-like 2 (LOXL2), copper sulfate, and hydroxylysine has resulted in tissue with a higher cell count and stronger staining for proteoglycans compared to native medial condyle articular cartilage. However, the mechanical properties were reduced, and the calculated functionality index was 55 % of the functional properties of native articular cartilage [22].

Therefore, replacing autologous articular chondrocytes with costal chondrocytes could be a promising technique. Nonetheless, the dedifferentiation of chondrocytes during expansion, leading to the formation of fibrocartilage, and the incomplete match of the resulting tissue in morphology and mechanical properties pose potential risks. Consequently, cell culture protocols require improvement.

Clinical Studies

In clinical practice, chondrocyte-derived pellet-type autologous chondrocyte implantation (CCP-ACI) has been used for treating full-thickness knee cartilage defects. A fragment of costal cartilage was harvested from the patient, cells were isolated and expanded in culture for several days. During cultivation, costal chondrocytes gradually acquired a dedifferentiated phenotype characterized by fibroblast-like morphology and type I collagen expression. However, after pellet formation, immunohistochemical analysis has shown a high amount of type II collagen and aggrecan in the center of the pellet and a weak presence of type I collagen in the outer layer. A 5-year follow-up has shown that in 4 out of 6 patients, the graft thickness corresponded to the normal cartilage structure, although no qualitative analysis of its composition was conducted [94].

In another prospective randomized study, the efficacy of CCP-ACI was compared with microfracture in treating defects in 30 patients. Forty-eight weeks after surgery, the MOCART score, which evaluates defect restoration, integration, subchondral plate integrity, and subchondral bone, and synovitis degree, has shown a statistically sig-

Table 2. Results of clinical application of autologous costal chondrocyte transplantation of articular cartilage damage treatment.

Reference	Patients	Surgery	Follow-up period	Result	Complications
[94]	7 patients (3 women, 4 men, 27–48 years-old)	(CCP-ACI) for treating knee cartilage lesions.	5 years	Increased range of motion Pain reduction Three patients had complete defect filling after 5 years, two patients had hypertrophy of the restored tissue after 2 years, which persisted in one patient after 5 years. Synovitis disappeared in two patients.	One patient experienced an ipsilateral patella fracture No specific adverse reactions, including immune reactions, osteogenesis, or tumorigenesis, were observed
[95,96]	CCP-ACI: 20 patients (14 men, 6 women, 41.5 ± 13.0 years-old) Microfracture: 10 patients (3 men, 7 women, 47.2 ± 10.8 years-old)	CCP-ACI and microfracture in treating knee cartilage defects	48 weeks	Increased range of motion Pain reduction Complete defect restoration was observed in 20 % of cases in the CCP-ACI group, and full integration in 85 %.	Postprocedural hematoma and postoperative adhesion were observed in 2 subjects in the CCP-ACI

CCP-ACI, Chondrocyte-derived pellet-type autologous chondrocyte implantation

nificant increase compared to preoperative scores in both groups and significantly higher values in the CCP-ACI group. Complete defect restoration was observed in 20 % of cases in the CCP-ACI group, and full integration in 85 %. Radiographic examination revealed no deformities or abnormalities in either group [95]. Five years post-operation, MOCART and Lysholm scores and KOOS (Knee Injury and Osteoarthritis Outcome Score) in the CCP-ACI group were significantly higher than in the microfracture group. MRI conducted one year and five years post-CCP-ACI has revealed statistically significant improvement in structural integration with native cartilage compared to microfracture [96].

Overall, clinical results generally show positive outcomes for patients (Table 2, Ref. [94–96]). However, it is important to note isolated cases of poor graft integration, incomplete defect surface restoration, and the absence of qualitative analysis of the newly formed tissue in the defect.

Current Approaches to Overcoming Limitations

As described above, the use of costal chondrocytes instead of articular chondrocytes for transplantation has generally shown good results but has several drawbacks, such as cell dedifferentiation, incomplete integration, and a qualitative mismatch of tissue in the defect. It should be noted that similar drawbacks are present in almost all cell-based technologies for treating articular cartilage injury [17].

To overcome the cell dedifferentiation problem for articular chondrocytes, Kwon *et al.* [97] have proposed a complex cell culture protocol. For cell expansion, they used a medium supplemented with a cocktail of growth factors: TGFβ1, fibroblast growth factor 2 (FGF2), and platelet-derived growth factor (PDGF). This was followed by an aggregate rejuvenation stage, where cells were cultured in a medium with a different set of factors: TGFβ1, growth differentiation factor 5 (GDF5), and bone morphogenetic protein 2 (BMP2) for 7 days. In the third step, neocartilage was obtained using the self-assembling process, with the sequential addition of TGFβ1, c-ABC, and LOXL2. This protocol has preserved the chondrogenic potential of the cells up to passage 11, allowing for a reduction in the amount of tissue required for their isolation. In the formed neocartilage, type I collagen was virtually absent, and the amount of proteoglycans and type II collagen was comparable to native cartilage. Additionally, the use of growth factor cocktails significantly increased the mechanical characteristics, and the authors have managed to obtain tissue-engineered constructs with a Young's modulus of about 2 MPa [97]. Although the authors did not directly compare the mechanical properties of their neocartilage with native cartilage, the values are comparable with those obtained in another study: 1.03 ± 0.48 MPa for human articular cartilage [98].

Recently, many studies have focused on the role of mechanical stimuli in articular cartilage engineering [99, 100]. For cultivating tissue-engineered constructs, conditions that apply cyclic hydrostatic pressure (5–10 MPa) and fluid-induced shear (FIS) stress (0.05–0.21 Pa) are preferable [100]. TECs derived from minipig costal chondrocytes have shown increased mechanical characteristics and GAG and collagen content when cultured in specialized FIS stress devices [101]. In a study on ovine costal chondrocytes, cultivating a three-dimensional aggregate culture under a mechanical load of 5.0 kPa has slightly improved the mechani-

cal characteristics of the resulting constructs, although it did not significantly affect the qualitative composition [102]. It should be noted that while constant hydrostatic pressure can have an effect, cyclic pressure is more physiological [100].

Additionally, hypoxia is a physiological norm for articular cartilage: oxygen levels in the articular cartilage are 5–10 % at the surface and less than 1 % in the deep layers [103]. Indeed, culturing chondrocytes in three-dimensional alginate beads under hypoxia has led to increased deposition of glycosaminoglycans, type II collagen, and expression of *Col2a1* [104,105]. Similar results have been obtained for cartilage progenitor cells (CPCs) in a 3D system of gelatin methacryloyl microspheres. Under hypoxia, there was a higher number of cells and greater expression of chondrogenic markers such as glycosaminoglycans, collagen II, *Gdf5,* proteoglycan 4 *(Prg4), Sox9* compared to normoxia. Additionally, hypoxic CPC microspheres demonstrated prochondrogenic and anti-catabolic effects in *in vitro* and *in vivo* osteoarthritis models [106]. Interestingly, these hypoxic effects are observed in healthy cells but not in chondrocytes derived from osteoarthritic cartilage [107].

However, with increasing TEC thickness, uneven cell phenotypes and insufficient redifferentiation or cell death in the center are observed [108]. As an alternative, micropellets consisting of approximately 166 articular chondrocytes can be used, which are then combined into larger TECs. Combined with hypoxia (2 % O_2), micropellets have shown significantly higher synthesis of GAG, aggrecan expression, and type II collagen compared to normoxic micro- and macropellets, as well as macropellets in hypoxia [108].

A key regulator of gene expression under hypoxia is hypoxia-inducible factor (HIF). It has been shown that exposure to 5 % hypoxia and 20 % stretching at a frequency of 0.5 Hz in human articular chondrocyte cultures increases the expression of aggrecan and *HIF-1*α. Reducing expression of aggrecan and *HIF-1*α expression using short interfering ribonucleic acid (siRNA) significantly decreased aggrecan expression, reflecting a possible regulatory mechanism under hypoxic conditions [109]. Another potential mechanism for chondrocyte adaptation to hypoxia involves hemoglobin (HB) subunits B and A, forming the hemoglobin body (Hedy), whose expression is stimulated under hypoxia. Mice with inducible knockout of the *Hbb* gene exhibited massive chondrocyte death under hypoxia, suggesting that Hedy may be essential for chondrocyte survival in a hypoxic environment [110]. Thus, the combination of hypoxia and three-dimensional cultivation, which supports the maintenance of the chondrocyte phenotype, may be a promising direction in cartilage tissue engineering.

Gene editing technologies can enhance the efficacy of cell therapy by increasing the production of ECM. For this purpose, chondrocytes undergo genetic manipulations *in vitro*, after which they are injected into the patient. The delivery of certain transgenes, such as Sox9, TGFβ1, BMP2, insulin-like growth factor 1 (IGF1), and BMP7, stimulates the secretion of type II collagen and proteoglycans [111]. Knockout of the cell cycle inhibitor p21 in human chondrocytes has also led to increased synthesis of glycosaminoglycans in 3D cultures and greater matrix production in colonies [112].

Gene editing can also be used to reduce inflammatory responses. For example, knockout of TGF-β activated kinase 1 (TAK1) prevented the activation of the nuclear factor (NF)-κB signaling pathway and reduced the expression of pro-inflammatory interleukin (IL) 1β, IL6, and tumor necrosis factor (TNF)α, as well as matrix metalloproteinase 13 (MMP13) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS). This also increased the amount of glycosaminoglycans in 3D culture [113]. Modifying the activity of the catabolic enzyme MMP13 using clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR associated protein 9 (Cas9) in human chondrocytes led to increased production of type II collagen [114].

It is worth noting that the use of costal chondrocytes in various hydrogels can be employed for denser defect filling and overcoming the integration problem. Moreover, such techniques can be used independently or in combination with mosaicplasty using COG or CCG. In one study, rabbits were subcutaneously injected with commercial fibrin glue mixed with chondrocytes from various sources, including costal chondrocytes, and cartilage formation was observed [115]. Another study has shown that constructs of fibrin gel and costal chondrocytes, although having average biomechanical properties, were more stable *in vitro* compared to ear or articular chondrocytes [116]. Additionally, 3D bioprinting technologies using inks containing chondrocytes are actively being developed. The most promising scaffolds for imitating natural architecture are those created through extrusion bioprinting using bioinks that contain cells and biocompatible materials. Additionally, functionally graded scaffolds represent a novel approach, allowing for the mimicry of spatial biochemical and functional organization differences within the tissue [117]. This method can also be used for printing costal cartilage at graft harvesting sites [118].

Thus, existing methods for obtaining tissue-engineered constructs from costal cartilage can be improved by using various growth factors and placing the constructs in more physiological culture conditions. An important step in this direction could be the development of bioreactors where TECs are cultured under hypoxic conditions and exposed to cyclic hydrostatic pressure and shear stress.

Conclusions

Given the significant anatomical and physiological similarities, costal cartilage can be utilized in the treat-

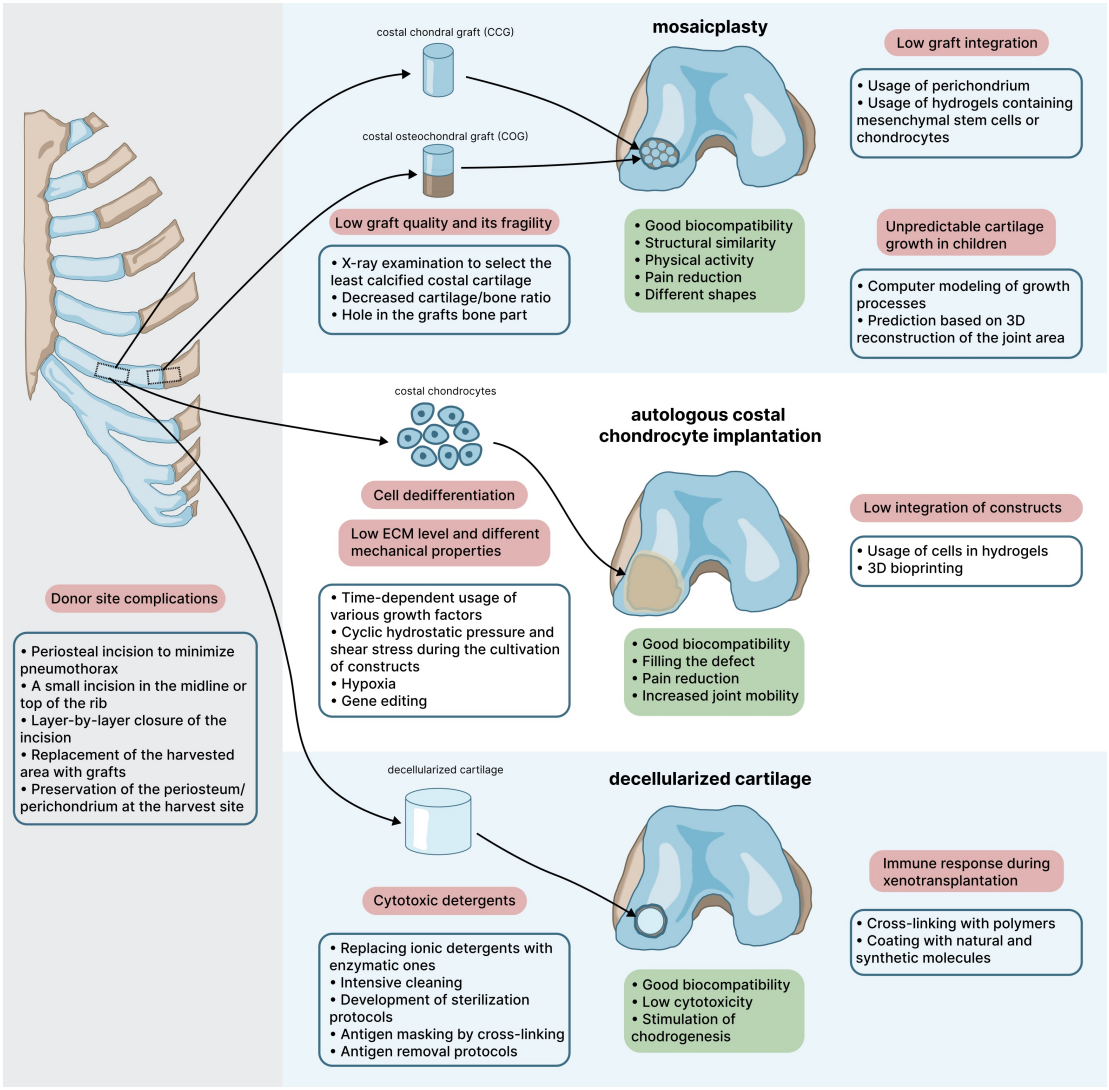

Fig. 3. Existing advantages (green box) and disadvantages (red box) of using costal cartilage for articular cartilage reconstruction, along with potential methods for improvement (highlighted in a box). 3D, three-dimensional. Image was created with https://www.figma.com.

ment of joint cartilage injuries. It can serve as a source of chondral or osteochondral grafts for transplantation, as well as components like ECM for scaffold creation or cells for creating tissue-engineered constructs. The application of costal cartilage in experimental animals and clinical practice has generally shown satisfactory results, but there are several drawbacks.

Firstly, the graft transplantation technique requires the development of a standardized protocol for reconstructing various joints to minimize surgical complexity and risks while optimizing success rates. This protocol may include the use of perichondrium or cell-based hydrogels to improve graft integration. The development of computer modeling methods will allow for accurate prediction of graft size and cartilage/bone ratio.

Secondly, personalized treatment strategies should be tailored to patient characteristics such as age, lesion severity, and joint function to select the optimal grafts and scaffold materials. Such individualized approaches can enhance the success rates and functional outcomes of the procedures. For instance, younger patients or those with less severe lesions may benefit from different graft materials or cell-based therapies compared to older patients or those with more advanced joint damage.

Thirdly, optimizing cultivation protocols for cell technologies and the creation of tissue-engineered constructs is essential, leveraging the similarities between costal and articular chondrocytes. For scaffold fabrication, it is important to optimize decellularization protocols and reduce immune response in xenogeneic transplantation.

Additionally, the donor site also deserves special attention, as a significant number of complications are associated with it. The operation should follow a specific protocol to avoid pneumothorax, and something should be placed at

the donor site to stimulate regeneration, such as perichondrium, scaffolds, tissue-engineered constructs, or a combination of these methods.

Long-term follow-up procedures are crucial to evaluate the efficacy, safety, and impact on patients' quality of life. These follow-ups should include assessments of graft integration, joint function, pain levels, and overall patient satisfaction over extended periods. Standardized metrics and imaging techniques should be employed to provide consistent and reliable data.

Thus, we have attempted to outline potential research directions for using costal cartilage in articular cartilage tissue regeneration (Fig. 3). Further research and protocol improvement will lead to a minimally invasive and effective method for treating articular cartilage defects, which will be highly demanded in clinical practice. Personalized treatment strategies and long-term follow-up evaluations will further ensure the success and sustainability of these interventions.

List of Abbreviations

Acan, aggrecan; ACI, autologous chondrocyte implantation; ADAMTS, a disintegrin and metalloproteinase with thrombospondin motifs; AMIC, autologous matrix-induced chondrogenesis; AOFAS, American Orthopedic Foot & Ankle Society; BMP, bone morphogenetic protein; c-ABC, chondroitinase ABC; Cas9, clustered regularly interspaced short palindromic repeats associated protein 9; CCGs, costal chondral grafts; CCP-ACI, chondrocyte-derived pellet-type autologous chondrocyte implantation; CDCC, combination method-based decellularized costal cartilage; COG, costal osteochondral graft; *Col1a1*, collagen type I alpha 1 chain; *Col2a1*, collagen type II alpha 1 chain; *Col10a1*, collagen type X alpha 1 chain; CPCs, cartilage progenitor cells; CRISPR, clustered regularly interspaced short palindromic repeats; CT, computed tomography; DACP, decellularized allogeneic cartilage paste; DAMPs, damage-associated molecular patterns; DNA, deoxyribonucleic acid; ECM, extracellular matrix; FAAM, Foot and Ankle Ability Measure; FDFG, free dermofat graft; FGF2, fibroblast growth factor 2; FIS, fluid-induced shear; GAG, glycosaminoglycans; GDF5, growth differentiation factor 5; GFP, green fluorescent protein; hASCs, human adipose-derived stem/stromal cells; HB, hemoglobin; Hedy, hemoglobin body; HIF, hypoxia-inducible factor; ICRS, International Cartilage Repair Society; IGF1, insulin-like growth factor 1; IL, interleukin; KOOS, Knee Injury and Osteoarthritis Outcome Score; LOXL2, lysyl oxidase-like 2; MACI, matrix-induced autologous chondrocyte implantation; MCP, metacarpophalangeal; MMP13, matrix metalloproteinase 13; MOCART, magnetic resonance observation of cartilage repair tissue; MRI, magnetic resonance imaging; PDGF, platelet-derived growth factor; *Prg4*, proteoglycan 4; PRWE, Patient-Rated Wrist Evaluation; qPCR, quantitative polymerase chain reaction; QuickDASH, Disabilities of the Arm, Shoulder and Hand Scores; *Runx2*, Runt-related transcription factor 2; SDCC, sodium deoxycholate-based decellularized costal cartilage; Sox9, sex-determining region Y protein (SRY)-Box Transcription Factor 9; TAK1, transforming growth factor β activated kinase 1; TECs, tissue-engineered constructs; TGFβ3, transforming growth factor β3; TMJ, temporomandibular joint; UCLA, University of California at Los Angeles; 3D, three-dimensional.

Availability of Data and Materials

Not applicable.

Author Contributions

SAS, ADK and PST contributed to the design of this work. SAS and ZAM analyzed the data. SAS drafted the work. ADK and ZAM prepared illustrations. ADK and PST revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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