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Construction of three-dimensional cartilage autograft and evaluation of the superiority of interperichondrial implantation

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ABSTRACT

Aims: This study aimed to develop a three-dimensional (3D) cartilage autograft using diced cartilage and fibrin tissue glue and to compare the outcomes of interperichondrial implantation versus subcutaneous implantation in terms of graft viability, biomechanical properties, and histopathological characteristics.

Methods: Eleven albino rabbits underwent auricular cartilage harvesting, with a 3×2 cm segment dissected bilaterally. After dicing, the cartilage fragments were combined with fibrin tissue glue and molded into two 3D dorsal nasal grafts. One graft was implanted into the interperichondrial pocket of the right ear, and the other was placed subcutaneously in the right dorsal region. Two control sites were created: subcutaneous fibrin-only implantation on the left dorsal region and an empty interperichondrial pocket on the left ear. The rabbits were sacrificed at eight weeks, and the grafts were evaluated macroscopically, physically, and histopathologically.

Results: Two animals were excluded due to graft loss from flap necrosis. In the remaining rabbits, the interperichondrial group exhibited superior shape retention, less volume loss, and higher elasticity compared to the subcutaneous group ($p<0.05$). Histopathological assessment showed significantly greater chondrocyte viability ($p<0.05$) and new cartilage formation ($p<0.05$) in the interperichondrial group, coupled with lower vascularization ($p<0.05$) and reduced fibrosis ($p<0.05$). By contrast, the subcutaneous group exhibited prominent vascularization, dense fibrous encapsulation, and more pronounced shape and volume loss. No significant intergroup differences were observed for fibrin residue or ossification ($p>0.05$). The control grafts (fibrin-only and empty interperichondrial sites) demonstrated no cartilage formation.

Conclusion: Diced cartilage grafts combined with fibrin tissue glue are better supported in the interperichondrial environment than in the subcutaneous tissue. Interperichondrial implantation not only preserves graft shape and volume but also enhances chondrocyte viability and cartilage regeneration, emphasizing its potential as a clinically valuable strategy in reconstructive cartilage grafting.

Keywords: Cartilage engineering, diced cartilage, fibrin glue, interperichondrial implantation, subcutaneous implantation, perichondrium, rabbit model, cartilage regeneration

INTRODUCTION

Cartilage defects represent a significant clinical challenge due to the tissue's limited regenerative capacity and the high incidence of degenerative joint diseases worldwide.[1] Autologous cartilage grafting is often preferred in clinical practice to restore functional tissue, as it reduces immunological complications and leverages the patient's inherent biological properties.[2] Among available techniques, diced or minced cartilage grafts have gained popularity for various reconstructive purposes including defect filling, contour correction, and augmentation.[3]

Although three-dimensional (3D) cartilage constructs can be produced by isolating chondrocytes and culturing them in biocompatible polymer scaffolds, such approaches are time-consuming, labor-intensive, and costly, requiring specialized laboratory facilities.[4,5] These practical barriers can limit the widespread clinical application of engineered cartilage tissues.[6,7] To overcome these challenges, replacing isolated chondrocytes with diced or minced cartilage fragments and utilizing readily available bio-polymers, such as fibrin tissue glue, could streamline the generation of 3D cartilage grafts, making the process more feasible and cost-effective.[8,9]

Since cartilage has a very limited ability to regenerate, additional biological support may be needed to preserve graft viability and strength. The perichondrium, an envelope of dense connective tissue surrounding cartilage, contains progenitor cells and supports vascularization at the interface, which can

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be crucial for graft survival.[10,11] Consequently, implanting 3D cartilage constructs interperichondrially-i.e., between layers of perichondrium-has been proposed as a method to enhance nutrient diffusion, mechanical stabilization, and overall tissue remodelling.[12-14]

In this study, we aimed to explore an alternative approach to 3D cartilage grafting by utilizing diced cartilage instead of chondrocytes. To achieve this, we selected a rabbit model and employed fibrin tissue glue as a biopolymer scaffold to enhance graft cohesion and integration. Given the limited regenerative capacity of cartilage, we hypothesized that perichondrial support would be critical for maintaining graft viability and structural integrity. Therefore, we compared the outcomes of interperichondrial implantation and subcutaneous implantation in terms of graft survival, biomechanical properties, and histopathological characteristics. By systematically evaluating these grafts through visual, physical, and histological assessments, we aimed to determine the superiority of interperichondrial implantation and provide insights into optimizing clinical cartilage grafting techniques.

METHODS

This experimental study was conducted at the Department of Plastic and Reconstructive Surgery, Trakya University Faculty of Medicine, using 11 albino rabbits. The experimental protocol was approved by the Trakya University Faculty of Medicine Ethics Committee (Date: 06.02.2003, Decision No: 03). All procedures were carried out in accordance with the ethical rules and the principles. Histopathological examinations were carried out at the Department of Pathology, Trakya University Faculty of Medicine.

Surgical Procedure

Anesthesia was induced using 2% xylazine hydrochloride (Rompun, Bayer, Leverkusen, Germany) at 0.5 ml/kg and 10% ketamine hydrochloride (Ketalar, Pfizer) at 0.5 ml/kg. A 1/3 segment of each auricular cartilage (3×2 cm in size) was excised bilaterally following perichondrial dissection and preserved in 0.9% saline solution. Interperichondrial implantation sites were prepared in the same regions.

The harvested cartilage grafts were diced and combined with fibrin tissue glue (Tisseel, Baxter, Austria) to form two three-dimensional dorsal nasal grafts. A two-part mold made of polysiloxane (Zetaplus, Zhermack, Italy) was used to shape the grafts (Figure 1).

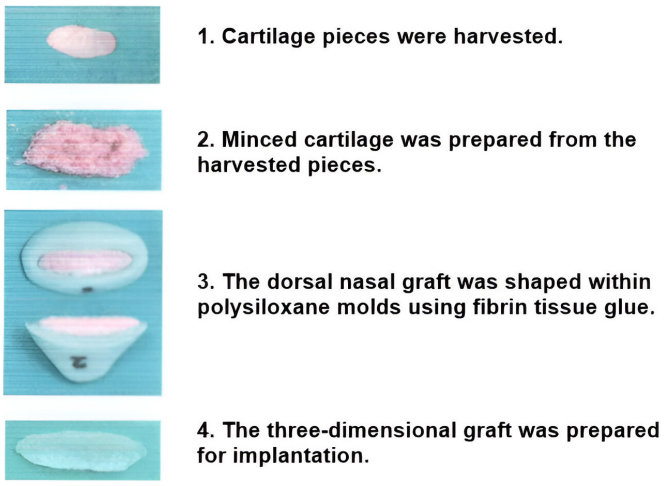

Figure 1. Construction of the three-dimensional cartilage graft

Graft Groups

The first graft was placed in the interperichondrial area of the right ear (interperichondrial graft group) (Figure 2), while the second graft was placed in the subcutaneous area of the right dorsal region (subcutaneous graft group).

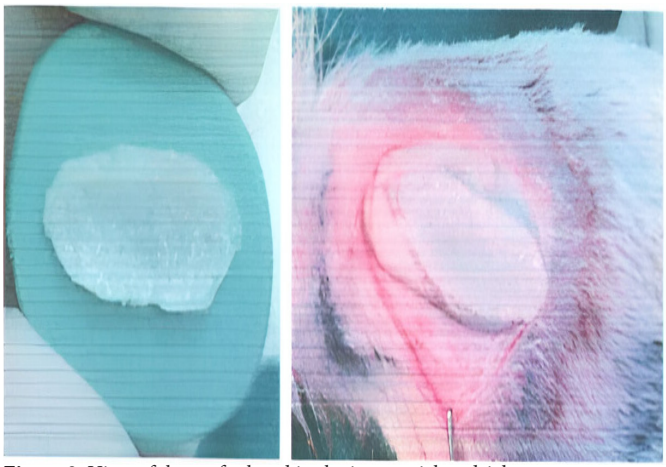

Figure 2. View of the graft placed in the interperichondrial area

In the left dorsal region, a shaped fibrin tissue adhesive without diced cartilage was placed into the subcutaneous area, while the interperichondrial area of the left ear was left empty. These two regions served as control groups (Figure 3).

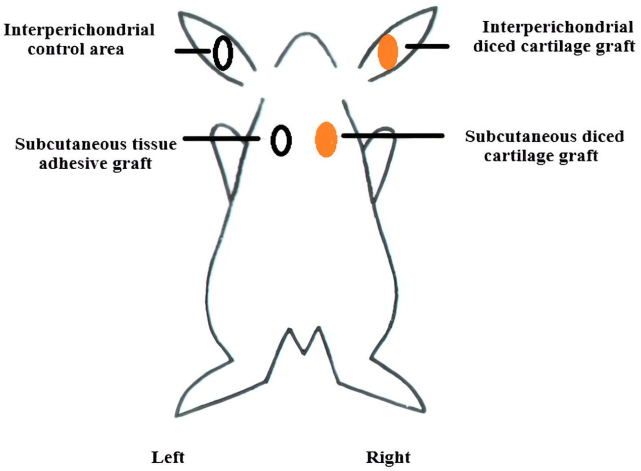

Figure 3. Implantation area of cartilage grafts and control groups

Sample Collection

The rabbits were sacrificed 8 weeks postoperatively, and the placed cartilage structures were retrieved for evaluation. The harvested samples were assessed based on visual, physical, and histopathological criteria. Shape and volume loss percentages were determined by two independent observers. Elasticity measurements were conducted and compared between the two groups. Interobserver agreement was assessed, followed by a direct comparison of the interperichondrial and subcutaneous implantation groups.

Retrieved specimens were fixed in 10% formalin for 24 hours. Sections were stained with hematoxylin-eosin (H&E) for general histological evaluation. Masson's trichrome staining was used to assess fibrotic tissue formation. Samples were examined under a light microscope, and six parameters were analyzed: viability, new cartilage formation, residual fibrin tissue glue, vascularization, fibrosis, and ossification.

Statistical Analysis

All data were analyzed using Minitab Release 13 software package version (Minitab Inc. State College, PA, USA). The Wilcoxon signed-rank test and Kappa test were employed to evaluate inter-observer differences, while the Mann-Whitney U test and Chi-square analysis were used for intergroup comparisons. Significance was accepted at $p<0.05$ (*) for all statistical analyses.

RESULTS

All rabbits gained weight throughout the study and exhibited no signs of distress findings. However, in two rabbits, graft extrusion was observed in the auricular region due to flap necrosis during the first week, leading to graft loss. These cases were excluded from the study.

Macroscopic examination of the retrieved samples revealed distinct differences between the interperichondrial and subcutaneous grafts. The structures obtained from the interperichondrial space were white in color and lacked a surrounding capsule, whereas the grafts retrieved from the subcutaneous region appeared white-blue and were encapsulated by a thin fibrous membrane, which made them easily separable from the surrounding tissues. In the control groups, the fibrin tissue glue placed in the left dorsal subcutaneous region was completely resorbed by the 8th week, and no cartilage formation was observed. Similarly, in the interperichondrial control sites of the left ear, no cartilage formation was detected in any of the animals by the end of the study period (Figure 4).

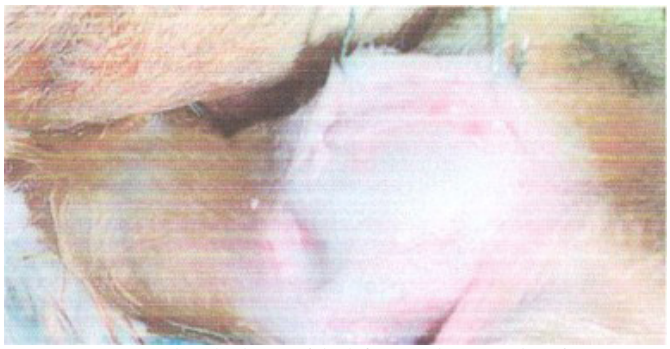

Figure 4. Interperichondrial area of the left ear without cartilage formation

When comparing the macroscopic morphology of the interperichondrial and subcutaneous graft groups, the interperichondrial graft group exhibited better structural organization and greater preservation of shape and volume (Figure 5). Conversely, the grafts retrieved from the subcutaneous region appeared more fibrotic and fragile, with noticeable shape and volume loss (Figure 6). Elasticity was also reduced in the subcutaneous graft group compared to the interperichondrial graft group. Statistical analysis confirmed significant differences between the two groups in terms of volume loss, shape loss, and elasticity ($p<0.05$ for all) (Table 1). Interobserver analysis showed no significant discrepancies in the evaluation of these parameters.

Histopathological assessment further demonstrated that chondrocyte viability was higher in the interperichondrial graft group compared to the subcutaneous graft group ($p=0.014$) (Table 2). Moreover, the interperichondrial graft group exhibited lower vascularization ($p=0.014$) and fibrosis ($p=0.001$), but greater new cartilage formation (p-0.002)

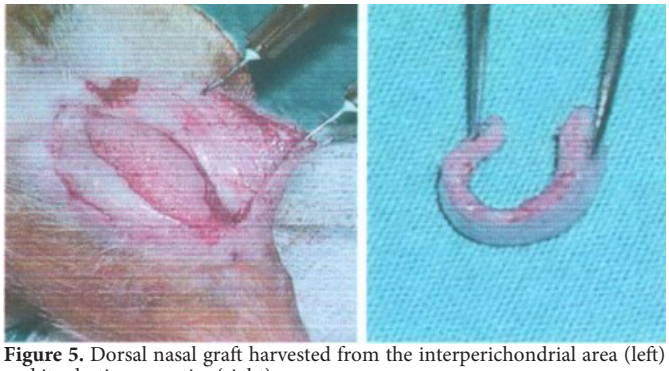

Figure 5. Dorsal nasal graft harvested from the interperichondrial area (left) and its elastic properties (right)

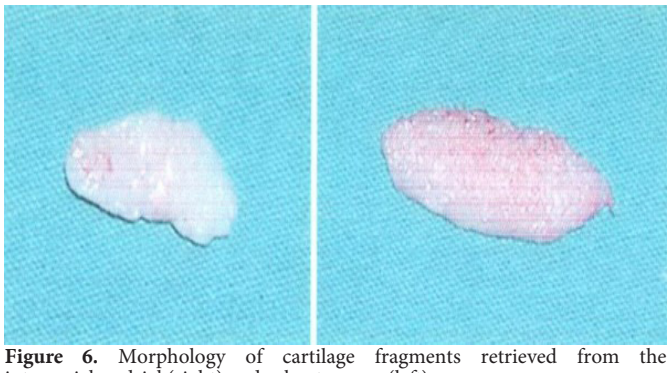

Figure 6. Morphology of cartilage fragments retrieved from the interperichondrial (right) and subcutaneous (left) areas

Table 1. Visual and physical evaluation of the obtained structures

Graft area	Subject	Observer	Volume loss (%)	Shape loss (%)	Elasticity
Interperichondrial	1	1	8	8	+++
		2	7	7	+++
	2	1	8	7	+++
		2	6	5	++++
	3	1	5	8	++++
		2	5	5	++++
	4	1	8	7	+++
		2	7	3	++++
	5	1	4	4	++++
		2	4	5	++++
	6	1	5	5	++++
		2	4	3	++++
	7	1	7	5	+++
		2	6	5	+++
	8	1	9	8	++++
		2	4	3	+++
	9	1	5	3	++++
		2	9	8	+++
Subcutaneous	1	1	20	30	+++
		2	16	20	+++
	2	1	30	40	++
		2	8	15	+++
	3	1	7	10	+++
		2	12	20	+++
	4	1	19	32	++
		2	22	36	++
	5	1	12	20	+++
		2	18	30	+++
	6	1	15	35	++
		2	19	28	+++
	7	1	20	40	+++
		2	8	15	++
	8	1	15	32	+++
		2	7	10	+++
	9	1	8	15	+++
		2	22	35	++

Table 2. Histopathological evaluation of the obtained structures

Graft area	Subject	Viability	Fibrin tissue glue residue	Vascularity	New cartilage formation	Fibrosis	Ossification
Interperichondrial	1	Good	No	Good	Good	Low	No
	2	Good	No	Good	Moderate	Low	No
	3	Good	No	Moderate	Good	Low	No
	4	Moderate	No	Good	Moderate	Low	No
	5	Good	No	Moderate	Good	Low	No
	6	Good	No	Low	Good	Orta	No
	7	Moderate	No	Good	Moderate	Orta	No
	8	Good	No	Moderate	Good	Low	No
	9	Good	No	Good	Good	Low	No
Subcutaneous	1	Moderate	No	Good	Low	Severe	No
	2	Low	No	Good	yok	Severe	No
	3	Moderate	No	Good	Low	Moderate	No
	4	Moderate	No	Good	Low	Severe	No
	5	Good	No	Good	Moderate	Moderate	No
	6	Moderate	No	Moderate	Low	Severe	No
	7	Moderate	No	No	Low	Severe	No
	8	Moderate	No	Low	Low	Severe	Yes
	9	Low	Yes	Moderate	No	Moderate	Yes

(Figure 7, Table 2), whereas the subcutaneous graft group showed increased vascularization and dense fibrosis (Figure 8, Table 2). However, no significant differences were noted between the groups in terms of fibrin tissue glue residue and ossification (p>0.05) (Table 2).

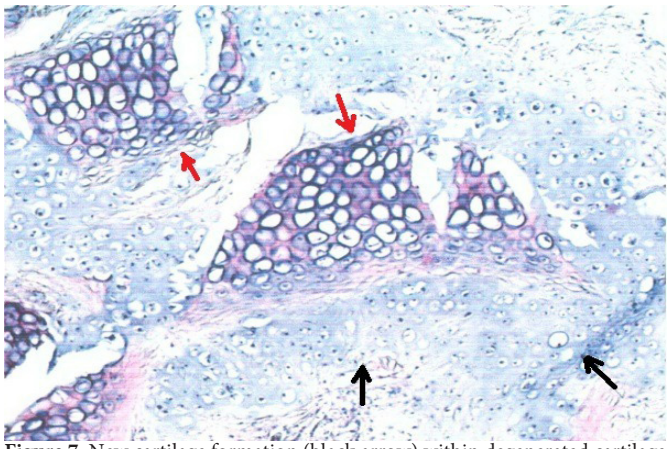

Figure 7. New cartilage formation (black arrow) within degenerated cartilage fragments (red arrow) (Hematoxylin-Eosin, x50)

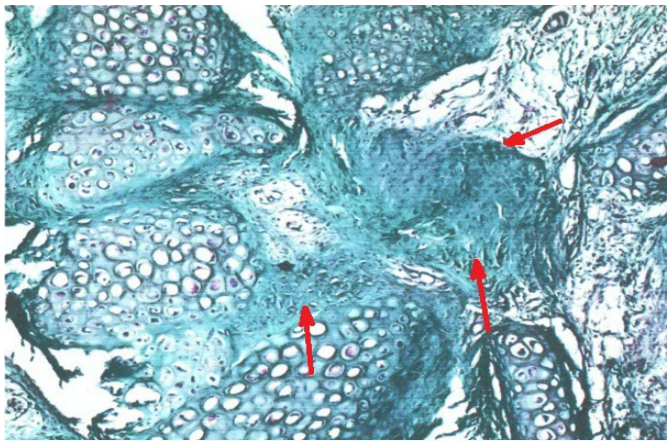

Figure 8. Formation of abundant connective tissue (red arrow) observed among degenerated cartilage fragments (Masson's Trichrome Staining, x50)

DISCUSSION

The findings of this study highlight the importance of the perichondrial environment in promoting the viability and structural integrity of 3D cartilage grafts composed of diced cartilage and fibrin tissue glue. Our results showed that interperichondrial implantation yielded superior macroscopic and histological outcomes compared to subcutaneous placement, suggesting that the unique biological and mechanical features of the perichondrium play a pivotal role in cartilage regeneration.

An ideal cartilage structure can be engineered by culturing chondrocytes within synthetic or biological polymer scaffolds, a technique widely explored in tissue engineering literature.[15,16] However, this method is both time-consuming and costly, requiring specialized laboratory facilities and extensive processing. Additionally, the amount of viable tissue obtained is often insufficient for clinical use, and these constructs are prone to volume loss over time, limiting their long-term effectiveness.[17,18] Due to these drawbacks, engineered cartilage is not readily available for immediate intraoperative application, making its routine use in surgical procedures challenging.[19]

The perichondrium has long been recognized as an essential component for cartilage repair, attributable to its reservoir of progenitor cells, local growth factors, and the capacity to support vascularization at the graft-host interface.[20] However, its precise mechanism of fostering cartilage tissue engineering remains an active area of investigation. In the interperichondrial environment, diced cartilage fragments appear to benefit from an enhanced chondrogenic niche, as evidenced by higher chondrocyte viability, less fibrosis, and greater new cartilage formation in our study. These observations align with previous reports indicating that perichondrial grafting or enveloping may help maintain the chondrogenic phenotype and facilitate tissue remodelling.[21-24]

Conversely, the subcutaneous environment offers a comparatively higher vascular density and reduced mechanical support, often leading to fibrotic encapsulation of grafted tissues.[25] In our study, the subcutaneous grafts exhibited greater shape and volume loss as well as higher vascularization and fibrosis, findings that mirror clinical challenges encountered when cartilage grafts are placed in non-perichondrial sites.[4,26] Excessive vascular ingrowth has been associated with a propensity for fibrocartilage formation or even ossification in certain contexts, potentially compromising the long-term functional properties of the implant.[1] Although we did not observe significant ossification in our subcutaneous grafts, the increased fibrotic response likely impairs biomechanical resilience, diminishing the potential for durable cartilage repair.

In histopathological assessment, seeing a chromatin-containing nucleus in living cartilage cells indicates viability.[27] While necrotic areas may be present within the newly generated graft from diced cartilage due to inadequate nourishment, the remaining viable chondrocytes possess strong proliferative abilities and a marked capacity for new cartilage formation.[28] Additionally, growth factors secreted from the perichondrial surface, including epidermal growth factor, fibroblast growth factor, and insulin-like growth factors, play a crucial role in new cartilage formation.[23,29] We demonstrated that cartilage grafts obtained from the interperichondrial space more closely resemble native cartilage in terms of visual, physical, and histopathological characteristics. Previous studies have also shown that the presence of the perichondrium significantly enhances graft survival and new cartilage formation.[30,31] In contrast, cartilage fragments lacking perichondrium tend to be fragile and exhibit significant chondrocyte loss. Notably, in grafts with perichondrial support, the healing process is characterized by new cartilage formation rather than fibrotic tissue development.[31] However, in highly vascular implantation sites, the presence of macrophages and partial graft resorption should be anticipated.[32]

In this study, vascularization was evaluated using H&E staining, which provides general insights into tissue morphology and blood vessel presence. However, immunohistochemical staining (IHC) with endothelial markers such as platelet endothelial cell adhesion molecule (PECAM-1), also referred to as cluster of differentiation 31 (CD31), vascular endothelial growth factor (VEGF), and alpha smooth muscle actin (α-SMA) offers a more detailed and quantitative assessment of vascularization.[33] Robust CD31 staining indicates the presence of mature microvessels infiltrating the graft, reflecting effective angiogenesis. In graft analyses, $CD34^+$ cells can denote angiogenic activity or immature vessels forming.[34] VEGF expression in the graft or surrounding tissue signifies an active drive for new vessel formation. It plays a primary role in initiating angiogenesis and can even promote vascular invasion into cartilage.[35] In graft histology, α-SMA positivity around capillaries indicates maturation and stabilization of neovessels by pericyte recruitment.[34,36] Collectively, these markers provide a detailed picture of graft revascularization. Using such markers in combination enhances the histological evaluation of cartilage graft viability and integration by quantifying microvessel density and the maturity of the vascular network.

Previously, synthetic polymers like polyglycolic acid/polylactic acid, calcium alginate, and polyethylene oxide were used to join small pieces of diced cartilage. However, these materials have drawbacks, including poor resorption, fibrosis formation, and immunogenicity concerns.[37,38] The use of fibrin tissue glue as a bio-scaffold proved advantageous for molding and stabilizing the diced cartilage fragments.[39] Similar to other scaffolds such as collagen matrices or hyaluronic acid derivatives, fibrin provides a provisional matrix conducive to cellular adhesion and nutrient exchange.[40,41] Nevertheless, it is ultimately resorbed, underscoring the importance of having a robust chondrogenic milieu-such as the interperichondrial space-for sustained graft survival and cartilage formation. Our control group findings, showing complete resorption of fibrin without cartilage formation in the absence of diced cartilage, further corroborate the necessity of a cartilage-derived cellular component and an appropriate biological niche.

Autologous 3D cartilage grafts support high chondrocyte viability and robust extracellular matrix production, which are crucial for long-term graft success. Studies constructing 3D cartilage (for example, packing diced cartilage into molds) report that the resulting graft retains living chondrocytes and abundant cartilage-specific matrix (collagen II, glycosaminoglycans), with mechanical properties akin to native tissue.[42] Cartilage grafts nurtured by perichondrium show significantly greater chondrocyte survival than those without. An experimental comparison demonstrated ~87% viable chondrocytes in grafts wrapped with perichondrium, versus only ~41% in grafts wrapped in a non-perichondrial material (fascia) under otherwise identical subcutaneous conditions.[26] In practical terms, a graft surrounded by perichondrium establishes a microcirculation faster, which is crucial for the survival of larger or three-dimensional cartilage pieces that rely on diffusion.[43] On the other hand, mechanical testing of engineered 3D cartilage implants (e.g., auricular grafts) has shown stiffness and flexibility comparable to native ear cartilage, indicating they can endure physiological stresses.[42] Grafts supported by perichondrium tend to retain their volume and mechanical strength over time.[44] Due to these factors, interperichondrial implantation is considered superior when feasible. In practice, surgeons may create a pocket between perichondrial layers or preserve the graft's native perichondrium and secure it in a vascular bed to capitalize on these benefits.

Limitations

This study has several limitations. First, our sample size was relatively small, and two grafts were lost in the early phase due to flap necrosis. Additionally, although the rabbit model is widely used in preclinical research due to its manageable size and cost-effectiveness, interspecies differences in immune response and regenerative capacity may influence the direct translation of these findings to human clinical practice. Future work could involve extending the follow-up period to assess long-term structural integrity and biomechanical performance of the constructs, as well as exploring adjunctive techniques, such as growth factor delivery or preconditioning of cartilage fragments, to further enhance graft outcomes.

CONCLUSION

Our study provides meaningful insights into the design of clinically translatable 3D cartilage grafts. By capitalizing on the favorable characteristics of diced cartilage fragments

and fibrin glue, and harnessing the biological potential of the perichondrium, we present a potentially more feasible and cost-effective alternative to traditional chondrocyte-based tissue engineering approaches. Interperichondrial implantation offers distinct advantages in preserving graft shape, volume, and chondrocyte viability, emphasizing its potential as a preferred strategy in clinical cartilage repair and reconstructive applications.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was carried out with the permission of the Trakya University Faculty of Medicine Ethics Committee (Date: 06.02.2003, Decision No: 03).

Informed Consent

Because the study was designed using an albino rabbit, no written informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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