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Collagen Type I, II and CD Markers Gene Expression of Articular Cartilage Repair Following Wedge Resection Trochleoplasty

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Abstract

Objectives: Articular cartilage injury poses a significant clinical challenge due to its limited intrinsic regenerative capacity. Wedge resection trochleoplasty is a common technique for correcting patellar instability, but the biological quality of the repaired cartilage remains unclear. This study aimed to investigate the gene expression patterns of collagen type I, II and CD markers (CD31 and CD45) in cartilage repair following wedge resection trochleoplasty in a rabbit model.

Materials and Methods: In this experimental study, 18 adult male New Zealand White rabbits underwent wedge resection trochleoplasty of the femoral trochlea. Animals were divided into three postoperative groups: 4, 8, and 16 weeks. Gene expression of COL1A1, COL2A1, CD45, and CD31 in the repair tissue was quantified using real-time polymerase chain reaction (PCR).

Results: Results showed that COL1A1 expression was significantly elevated at 4 weeks and then declined, but remained higher than baseline at all time points. In contrast, COL2A1 expression progressively and significantly increased up to 16 weeks. The COL2A1/COL1A1 ratio improved over time. Expression of both CD45 and CD31 peaked at 4 weeks and subsequently declined significantly.

Conclusions: Wedge-resection trochleoplasty promotes progressive cartilage remodeling over time, with the most pronounced chondrogenic response observed at 16 weeks. These findings may help guide interpretation of postoperative healing after trochlear reconstruction and provide a molecular benchmark for future translational studies.

Keywords: Trochleoplasty, Articular cartilage, Repair, Collagen type II, Collagen type I, CD31, CD45

Introduction

Articular cartilage injury remains a significant clinical challenge due to the tissue's limited intrinsic regenerative capacity (1). The avascular and aneural characteristics of articular cartilage limited cellular recruitment and matrix remodeling following injury, frequently resulting in incomplete repair characterized by fibrocartilaginous tissue rather than native hyaline cartilage (2). This limitation is particularly relevant in surgical procedures involving intentional disruption of the osteochondral unit, such as trochleoplasty for the correction of patellar luxation.

Wedge resection trochleoplasty is a widely utilized technique designed to deepen the femoral trochlear groove while preserving and repositioning the native osteochondral segment. Although this procedure is considered effective for restoring joint congruence and patellar stability, the biological quality of the repaired cartilage remains controversial (2,3). Macroscopic and histological improvements do not necessarily reflect the molecular composition or long-term functional integrity of the regenerated tissue (4). Therefore, evaluation of cartilage repair based solely on morphological criteria may overlook critical aspects of tissue quality.

The extracellular matrix composition of repaired cartilage is a key determinant of its biomechanical performance and durability. Hyaline cartilage is characterized by a matrix rich in type II collagen and aggrecan, whereas fibrocartilage predominantly contains type I collagen, conferring inferior compressive resistance and increased susceptibility to degeneration. The relative expression of collagen types I and II is therefore considered a central indicator of the quality and maturity of cartilage repair tissue (5,6).

In addition to matrix composition, cellular and inflammatory responses played a critical role in determining repair outcomes. CD markers such as CD31 and CD45 were commonly employed to assess neovascularization and inflammatory cell infiltration, respectively, both of which were associated with fibrovascular repair and impaired chondrogenic differentiation (7,8). Persistent vascular or inflammatory activity within the repair tissue may inhibit stable hyaline cartilage formation and promote fibrotic remodeling (9).

Despite the clinical relevance of wedge resection trochleoplasty, there is a paucity of experimental studies that systematically investigate the gene expression profile of cartilage repair following this procedure. In particular, the temporal expression patterns of collagen subtypes and CD-associated cellular markers during the healing

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Key Messages

- COL2A1 expression and the COL2A1/COL1A1 ratio increase over 16 weeks, indicating progressive chondrogenic differentiation after trochleoplasty.
- Persistent COL1A1 elevation and incomplete COL2A1 recovery confirm that repair tissue remains predominantly fibrocartilaginous, not true hyaline cartilage.
- Early peaks in CD45 and CD31 (inflammation/angiogenesis) resolve by 16 weeks, suggesting favorable resolution of acute vascular and inflammatory responses.

process remain poorly defined. Therefore, the aim of this study was to perform a detailed gene expression analysis of articular cartilage repair following wedge resection trochleoplasty in a rabbit model, with a specific focus on the expression of collagen type I and type II, as well as CD31 and CD45.

Materials and Methods

Sample Size Detection

Sample size was determined based on the exploratory nature of the study and on sample sizes commonly used in comparable rabbit cartilage repair experiments. Eighteen rabbits were randomly assigned to three postoperative time points (4, 8, and 16 weeks; n = 6 per group). The contralateral limb was used as an internal control for molecular analyses. Although a formal a priori power calculation was not performed, the sample size was considered sufficient to detect biologically meaningful differences in gene expression using a paired internal-control design.

Animals and Experimental Design

A total of 18 adult male New Zealand White rabbits (age: 5–6 months; weight: 2.5–3.0 kg) were used in this experimental study. Rabbits were randomly allocated into three postoperative evaluation groups: Group I, 4 weeks post-surgery (n = 6); Group II, 8 weeks post-surgery (n = 6); and Group III, 16 weeks post-surgery (n = 6). Only one knee joint per animal was subjected to surgery, while the contralateral limb served as an internal control for molecular analyses.

Surgical Procedure: Wedge Resection Trochleoplasty

All surgical procedures were performed under general anesthesia induced with an intramuscular injection of ketamine (35 mg/kg) and xylazine (5 mg/kg) (10). Under sterile conditions, a medial parapatellar approach was used to expose the femoral trochlea. A V-shaped osteochondral wedge including articular cartilage and subchondral bone was carefully removed from the trochlear groove using a microsurgical oscillating saw. The trochlear bed was deepened, and the wedge was recessed and reimplanted into its original position without internal fixation, relying on press-fit stability. The joint capsule and skin were closed in layers. Postoperative analgesia was provided using meloxicam (0.2 mg/kg, subcutaneous) for three consecutive days (10,11). Animals were allowed unrestricted cage activity postoperatively.

Tissue Harvesting

At the designated time points (4, 8, and 16 weeks), animals were euthanized using an overdose of sodium pentobarbital. The distal femur was harvested, and the repaired trochlear cartilage was carefully dissected. Cartilage samples were immediately snap-frozen in liquid nitrogen and stored at −80 °C until RNA extraction.

RNA Isolation and cDNA Synthesis

Only one knee joint per animal was subjected to surgery, while the contralateral limb served as an internal control for molecular analyses.

Total RNA was extracted from cartilage samples using TRIzol® reagent (Invitrogen, USA) according to the manufacturer's instructions. RNA concentration and purity were assessed spectrophotometrically by measuring absorbance at 260 and 280 nm. Samples with an A260/A280 ratio between 1.8 and 2.0 were considered acceptable.

One microgram of total RNA was reverse-transcribed into complementary DNA (cDNA) using a commercial reverse transcription kit (e.g., Thermo Fisher Scientific, USA) (12,13).

Quantitative Real-Time PCR (qRT-PCR)

Gene expression levels of Collagen type I (COL1A1), Collagen type II (COL2A1), CD31 (PECAM-1), and CD45 (PTPRC) were quantified using quantitative real-time PCR with SYBR Green chemistry (14). PCR reactions were performed in a final volume of 20 µL containing cDNA template, gene-specific primers, and SYBR Green master mix. Amplification was carried out under the following cycling conditions:

Initial denaturation at 95°C for 10 min 40 cycles of denaturation at 95°C for 15 s and annealing/extension at 60°C for 60 s. GAPDH was used as the housekeeping gene for normalization. Relative gene expression was calculated using the $2^{-\Delta\Delta Ct}$ method (15).

Primer sequences for COL1A1, COL2A1, PECAM-1 (CD31), PTPRC (CD45), and GAPDH are listed in Table 1. Primer specificity was verified by melt-curve analysis after amplification, and each assay produced a single distinct peak consistent with a specific amplicon. In addition, amplification efficiency was confirmed to be acceptable for comparative Ct analysis prior to use in the final experiments.

Statistical Analysis

Data are presented as mean ± standard deviation (SD). Statistical analyses were performed using SPSS software (version 20). One-way analysis of variance (ANOVA) followed by Tukey's post hoc test was used to compare

Table 1. Primer Sequences Used for qRT-PCR

Gene	Forward primer (5′→3′)	Reverse primer (5′→3′)	Product size (bp)
Collagen type I (COL1A1)	5′-CTG ACT GGA AGA GCG GAG AGT AC-3′	5′-CCA TGT CGC AGA AGA CCT TGA-3′	63
Collagen type II (COL2A1)	5′-TGG GTG TTC TAT TTA TTT ATT GTC TTC CT-3′	5′-GCG TTG GAC TCA CAC CAG TTA GT-3′	63
CD31 (PECAM-1)	5´GTGATAATTGCCGCCTTGAT-3´	5´GTTGGGATCTGACACGGTCT-3´	138
CD45 (PTPRC)	5′-TACT CTG CCT CCC GTT G-3′	5′-GCT GAG TGT CTG CGT GTC-3′	262
GAPDH (Housekeeping)	5′-ACT TTG TGA AGC TCA TTT CCT GGT A-3′	5′-GTG GTT TGA GGG CTC TTA CTC CTT-3′	107

gene expression levels among different time points. A P value < 0.05 was considered statistically significant.

Results

Gene Expression Analysis of Extracellular Matrix Markers

Quantitative real-time PCR analysis demonstrated a significant time-dependent alteration in the expression of extracellular matrix–related genes following wedge resection trochleoplasty (Figure 1, Table 2).

Expression of COL1A1 (collagen type I) was markedly elevated at 4 weeks post-surgery, indicating an early fibroblastic repair response. Although COL1A1 expression showed a gradual decline at 8 and 16 weeks, its levels at all time points remained significantly higher than baseline, suggesting persistent fibrocartilaginous characteristics of the repair tissue.

In contrast, COL2A1 (collagen type II) expression was minimal at 4 weeks, reflecting the absence of mature hyaline cartilage in the early repair phase. A significant upregulation was observed at 8 weeks, with a further pronounced increase at 16 weeks (P < 0.001), indicating progressive chondrogenic differentiation over time. Nevertheless, COL2A1 expression remained lower than that expected for native hyaline cartilage (Table 2).

Gene Expression of CD Markers

Gene expression was quantified relative to the contralateral internal control using the $2^{-\Delta\Delta Ct}$ method. Thus, the reported fold changes represent normalized postoperative expression levels relative to each animal's paired non-operated limb.

Analysis of inflammatory and angiogenic markers revealed a distinct temporal pattern during cartilage repair (Figure 2, Table 3).

Expression of CD45, a pan-leukocyte marker, was highest at 4 weeks, consistent with an active inflammatory response during the early repair phase. CD45 expression significantly decreased at 8 weeks and reached its lowest level at 16 weeks (P < 0.001), indicating progressive resolution of inflammation.

Similarly, CD31 (PECAM-1) expression, associated with angiogenesis and endothelial activity, was significantly

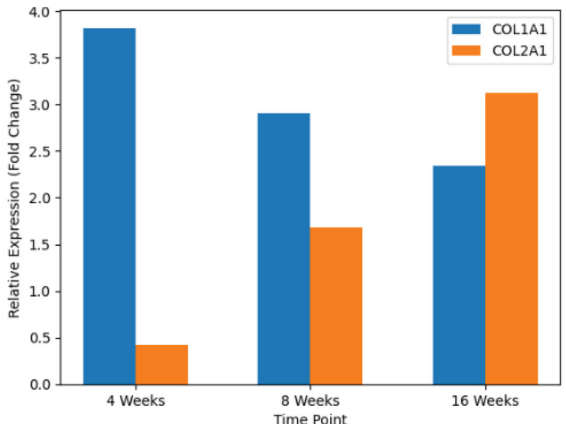

Figure 1. Relative Gene Expression of COL1A1 and COL2A1 in Repaired Trochlear Cartilage at 4, 8, and 16 Weeks Post-surgery.

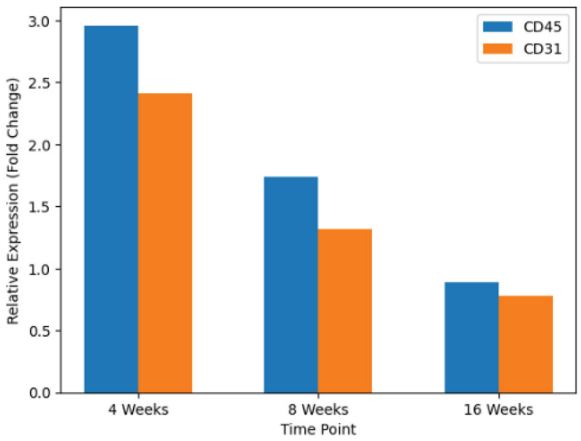

Figure 2. Temporal Changes in CD45 and CD31 Gene Expression Following Wedge Resection Trochleoplasty.

Table 2. Relative mRNA Expression of Collagen Type I and II

Gene	4 Weeks	8 Weeks	16 Weeks	*P* value
COL1A1	3.82 ± 0.61[a]	2.91 ± 0.48[b]	2.34 ± 0.39[c]	<0.001
COL2A1	0.42 ± 0.15[a]	1.68 ± 0.37[b]	3.12 ± 0.54[c]	<0.001

Values are expressed as fold change relative to control using the $2^{-\Delta\Delta Ct}$ method. Different superscript letters indicate statistically significant differences between groups (P < 0.05).

Table 3. Relative mRNA Expression of CD31 and CD45

Gene	4 Weeks	8 Weeks	16 Weeks	*P* value
CD45	2.96 ± 0.52[a]	1.74 ± 0.33[b]	0.89 ± 0.21[c]	<0.001
CD31	2.41 ± 0.44[a]	1.32 ± 0.29[b]	0.78 ± 0.18[c]	<0.001

Values are expressed as fold change relative to control using the $2^{-\Delta\Delta Ct}$ method. Different superscript letters indicate statistically significant differences between groups (P < 0.05).

Table 4. Ratio of Collagen- and CD-Related Expression Indices

Time point	COL2A1/COL1A1
4 weeks	0.11 ± 0.05[a]
8 weeks	0.58 ± 0.14[b]
16 weeks	1.33 ± 0.29[c]

elevated at 4 weeks. A marked reduction was observed at subsequent time points, suggesting regression of neovascularization as the repair tissue matured (Table 3).

Ratio of COL2A1 to COL1A1 Expression

To further characterize the phenotypic quality of the repair tissue, the COL2A1/COL1A1 expression ratio was calculated (Figure 3). The ratio was lowest at 4 weeks, reflecting a predominantly fibrous repair. A significant increase was observed at 8 weeks, with the highest ratio at 16 weeks ($P < 0.001$), indicating a gradual shift toward a hyaline-like cartilage phenotype, albeit incomplete (Table 4, Figure 3).

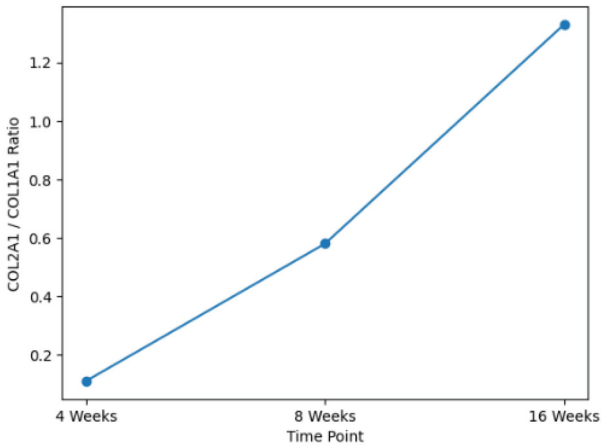

Figure 3. COL2A1/COL1A1 Ratio Demonstrating Progressive Chondrogenic Maturation of the Repair Tissue Over Time.

Discussion

The present study focused on temporal gene expression changes during trochlear repair and did not include direct histological or immunohistochemical quantification. Therefore, the molecular findings should be interpreted as evidence of matrix remodeling and chondrogenic progression rather than as a standalone histological endpoint. Nevertheless, the observed increase in COL2A1 and the concurrent reduction in the relative dominance of COL1A1 are consistent with a shift toward a more cartilage-like repair phenotype.

This study provides a comprehensive molecular characterization of articular cartilage repair following wedge resection trochleoplasty, with a specific focus on the temporal expression patterns of extracellular matrix–related genes (COL1A1 and COL2A1) and inflammatory and angiogenic markers (CD45 and CD31). The principal findings demonstrate that although the repair process progresses toward a more chondrogenic phenotype over time, as evidenced by increasing COL2A1 expression and a rising COL2A1/COL1A1 ratio, the reparative tissue remains predominantly fibrocartilaginous even at 16 weeks postoperatively (16). This molecular profile underscores the intrinsic limitations of cartilage regeneration following osteochondral injury and surgical manipulation (17).

One of the most striking observations in this study was the persistently elevated expression of COL1A1 throughout the healing period. Collagen type I is a hallmark of fibrous and fibrocartilaginous tissues and is typically associated with mechanically inferior repair tissue compared to native hyaline cartilage, which is rich in collagen type II (5,6). The high COL1A1 expression at 4 weeks reflects the early fibroblastic repair response commonly observed following full-thickness cartilage injury, driven by mesenchymal progenitor cell infiltration from the subchondral bone marrow (7). Although COL1A1 expression declined significantly by 16 weeks, it remained elevated relative to expected hyaline cartilage levels, indicating incomplete phenotypic restoration. Similar findings have been reported in rabbit and goat models of cartilage repair, where fibrocartilage persists as the dominant repair tissue despite apparent macroscopic improvement (17-19).

In contrast, COL2A1 expression exhibited a clear time-dependent increase, with the highest levels observed at 16 weeks. This upregulation suggests progressive chondrogenic differentiation within the repair tissue, potentially driven by mechanical loading and local biochemical cues within the recessed trochlear environment (20). However, the delayed and incomplete expression of COL2A1 indicates that true hyaline cartilage regeneration remains limited. These results are consistent with previous experimental studies demonstrating that although chondrocyte-like cells and type II collagen may emerge during later stages of repair, their distribution is often heterogeneous and insufficient to restore native cartilage architecture (20). The calculated COL2A1/COL1A1 ratio, which increased significantly over time, further supports the notion of partial phenotypic maturation rather than complete regeneration (2, 21).

The inflammatory and angiogenic response, as reflected by CD45 and CD31 gene expression, followed a distinct and biologically plausible trajectory. CD45 expression was highest at 4 weeks, corresponding to the acute inflammatory phase of repair, during which leukocyte infiltration and cytokine signaling play critical roles in debris clearance and tissue remodeling (8). The subsequent decline in CD45 expression at later time points suggests resolution of inflammation and transition toward a reparative phase. Persistent inflammation has been implicated in impaired cartilage regeneration and the progression of post-traumatic osteoarthritis (22);

therefore, the observed reduction in CD45 expression may represent a favorable aspect of the healing response following wedge resection trochleoplasty.

Similarly, CD31, an established marker of endothelial cells and neovascularization, exhibited a marked decline over time. While early angiogenesis was essential for subchondral bone remodeling and the delivery of reparative cells, sustained vascularization within cartilage repair tissue was generally regarded as detrimental to hyaline cartilage formation (23). The regression of CD31 expression observed in this study aligns with prior reports demonstrating that successful cartilage maturation is accompanied by vascular regression and restoration of an avascular cartilage phenotype (24). Nonetheless, the initial presence of angiogenic activity may also contribute to fibrocartilage formation, as vascular invasion is often associated with fibrous tissue deposition rather than stable hyaline cartilage (25).

When considered together, the gene expression patterns observed in this study closely mirror those reported in other full-thickness cartilage defect models and marrow-stimulation techniques, such as microfracture (26). In these models, early fibrocartilaginous repair predominates, followed by limited chondrogenic maturation that rarely achieves the biochemical and biomechanical properties of native cartilage. Importantly, wedge resection trochleoplasty differs from these techniques in that it aims to preserve and reposition native articular cartilage. However, our molecular data suggest that despite this theoretical advantage, the biological response still follows a largely fibrocartilaginous repair pathway. This finding provides a mechanistic explanation for clinical reports describing satisfactory short- to mid-term outcomes after trochleoplasty, alongside concerns regarding long-term degenerative changes (3,27).

The integration of these gene expression data with our previously reported macroscopic, histological, and immunohistochemical findings strengthens the overall interpretation of the repair process. While macroscopic appearance and structural integration improved substantially over time, molecular analysis revealed persistent deviations from the hyaline cartilage phenotype. This discordance highlights the limitations of relying solely on gross or histological assessments when evaluating cartilage repair outcomes and emphasizes the value of molecular analyses in elucidating tissue quality (4).

Limitations of the Study

A limitation of this study is the absence of an a priori formal power analysis. Although the sample size of six rabbits per time point is consistent with exploratory experimental studies and was supported by the use of contralateral internal controls, a larger cohort may be required to detect smaller effect sizes and to strengthen inferential power for subtle temporal differences.

Conclusions

The present study demonstrated that wedge resection trochleoplasty initiated a robust reparative response characterized by decreasing inflammation and angiogenesis and progressive, yet incomplete, chondrogenic differentiation. The persistent dominance of COL1A1 expression and the delayed upregulation of COL2A1 indicate that the repair tissue remains predominantly fibrocartilaginous. These findings suggest that while wedge resection trochleoplasty effectively restores joint congruence, it may not fully reestablish the durable biological properties of native hyaline cartilage, underscoring the need for adjunctive strategies to enhance cartilage regeneration.

Authors' Contribution

Conceptualization: Peyman Farrahi, Soroush Mohitmafi.
Data curation: Fariborz Moayer.
Formal analysis: Fariborz Moayer.
Funding acquisition: Fariborz Moayer.
Investigation: Peyman Farrahi, Soroush Mohitmafi.
Methodology: Peyman Farrahi, Soroush Mohitmafi.
Project administration: Soroush Mohitmafi.
Resources: Soroush Mohitmafi.
Software: Fariborz Moayer.
Supervision: Soroush Mohitmafi.
Validation: Soroush Mohitmafi.
Visualization: Soroush Mohitmafi.
Writing–original draft: Peyman Farrahi, Soroush Mohitmafi.
Writing–review & editing: Peyman Farrahi, Soroush Mohitmafi.

Conflict of Interests

Authors have no conflict of interest.

Ethical Issues

All experimental procedures were conducted in accordance with the guidelines for the care and use of laboratory animals and were approved by the Institutional Animal Care and Use Committee (IACUC) of Islamic Azad University, Karaj Branch (Approval No. IR.IAU.K.REC.1402.117).

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