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Posted Date: 23 March 2026

doi: 10.20944/preprints202603.1819.v1

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Abstract

Background/Objectives: Chondromalacia is the cartilage erosion on the articulating surfaces of the shoulder. Conventional care encompasses activity modification, physical therapy, NSAIDS, and the consideration of surgical methods. This study evaluates umbilical cord tissue allografts (UCTa) as an alternative intervention for chondromalacia in the glenohumeral joint, utilizing structural and functional properties to provide support and cushioning when standard care fails. **Methods**: From an observational repository, 115 patients with treatment-resistant chondromalacia of the shoulder were identified who received one to three applications of UCTa based on the severity of degeneration and reported pain. The data included patient-reported scales, the Numeric Pain Rating Scale, the Western Ontario and McMaster University Arthritis Index, and the Quality of Life Scale. The data was tested using the Wilcoxon signed rank, Kruskal-Wallis H, Mann-Whitney U, and Jonckheere-Terpstra tests. **Results:** The cohort averaged improvement in all categories, irrespective of the number of applications. No adverse events were reported. **Discussion:** Limitations included small sample size, recall bias, and the use of a non-specific scale. **Conclusions**: The results of this study expand the current literature of alternative noninvasive care for chondromalacia of the shoulder. The application of UCTa correlates with beneficial patient outcomes, and further studies with randomized controlled trials are merited in defining dosage and best practice procedures.

Keywords: chondromalacia; chondromalacia of the shoulder; intra-articular cartilage defects; umbilical cord tissue; umbilical cord tissue allografts; regenerative medicine

1. Introduction

Chondromalacia, the erosion of the cartilage on the articulating surfaces of the bone, results in the softening and subsequent tearing of the joint, specifically in joints with a high range of motion (Habusta, 2023). Due to its extensive range of motion, the glenohumeral (GH) joint in the shoulder is inherently unstable, leading to frequent injury and quicker degeneration (Cuéllar, 2017). Symptoms of cartilage defects in the glenohumeral joint of the shoulder include pain during and after sports activities, limited range of motion, and stiffness (Fiegen, 2021). Often, symptoms do not develop in the early stages of shoulder chondral defects, causing difficulty in prompt detection (Seidl, 2018). Degeneration of the GH joint is often associated with shoulder osteoarthritis (OA), a progressive narrowing of the GH joint that causes significant pain and functional disability (Thomas, 2016). Osteoarthritis is often characterized by the level of chondromalacia, with stage 1 encompassing early softening of the cartilage and stage 4 encompassing severe loss of joint space and osteophyte formation (George, 2008). Chondromalacia solely describes the cartilage degeneration in a joint, while

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OA can stem from various factors, including metabolic dysfunction, chronic inflammation, and neurological complications (Herrero-Beaumont, 2024). Degeneration of the GH joint without systemic factors is more likely found in men, older individuals, and those in occupations that involve collision sports or manual labor (Saltzman, 2017). Chondromalacia related to shoulder OA is commonly found in women due to their differences in joint anatomy, alignment, muscle strength, hormonal influences, obesity, and genetics. Additionally, degenerative changes in the GH joint are found in up to 17% of patients with shoulder pain (Ibounig, 2021). Comparatively, GH joint degeneration is thought to be uncommon due to the high occurrence of shoulder osteoarthritis (OA). Shoulder OA has been estimated to affect more than 28 million people in the United States (Stanborough, 2020). However, GH joint degeneration symptoms are still severe enough to have functional limitations and a decreased quality of life (Ibounig, 2021). Current standard-of-care options for patients suffering from glenohumeral joint defects include invasive and noninvasive interventions.

Operative approaches to glenohumeral joint defects depend on the condition of the patient's defect location, size, depth, and containment. Standard surgical options include palliative, reparative, restorative, and reconstructive surgeries (Saltzman, 2017). However, common surgical options carry risks and potential long-term complications. Recurrent shoulder instability, implant release, neurovascular injury, and late articular degeneration are possible challenges patients may experience post-operatively (Nascimento, 2017). According to a study by Nascimento (2017), the prevalence of postoperative arthritis in the long term ranges from 35% to 71% (Nascimento, 2017). Moreover, operative shoulder interventions can add to a patient's financial stress. Overall, perioperative and surgical costs for cartilage procedures ranged is from $7,258.51 to $16,016.70 USD (Zhang, 2015). The complications and economic impracticalities of shoulder articular cartilage operative procedures drive the need for continual development of noninvasive interventions. Standard noninvasive interventions for articular cartilage degeneration are commonly prescribed before surgical approaches are recommended, depending on the severity of injury. Standard-of-care practices aim to relieve symptoms through trials of activity modification, physical therapy, oral nonsteroidal anti-inflammatory medications (NSAIDs), and corticosteroid injections (Saltzman, 2015). While temporary relief can be achieved, the noninvasive practices target symptomatic relief and not the source of the issue. The need to develop alternative medicine to target the root cause of patient pain, shoulder articular cartilage degeneration, could revolutionize the standard of care interventions for patients.

Umbilical cord tissue (UCT), containing collagen fiber types I, II, III, and V, cytokines, proteoglycans, and various growth factors, is an additional noninvasive measure after failure to progress with current standard of care practices for shoulder articular cartilage degeneration (Gupta, 2020; Main, 2021). UCT functions as a support and cushioning that can replace the connective tissue in the articular cartilage of the glenohumeral joint. A study done by Lai (2024) achieved favorable results in applying UCT allografts (UCTa) to articular cartilage defects associated with hip osteoarthritis (OA), by promoting supplementation and support to the joint (Lai, 2024). Results showed an increase in range of motion and overall function, with a reduction in pain. Given its structural properties and its similarity to the composition of the articular cartilage, UCTa can be used homologously in various sites to advance the replacement, repair, and reconstruction of degenerating articular cartilage. In this observational case study, UCTa were applied to patients with glenohumeral joint cartilage degeneration to evaluate the durability and effectiveness of umbilical cord tissue as a potent alternative to the current standard of care interventions.

2. Materials and Methods

2.1. Study Design

The observational repository data have been collected following the guidelines of the Declaration of Helsinki, with approval from the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (IRCM-2022-311) since January 2022. Prior to application, all

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patients provided informed consent. All allografts used were the 150mg tissue product from Regenative Labs (Pensacola, FL), manufactured following the FDA's 361 guidelines for minimally manipulated human cell and tissue products. The details of the repository design and UCTa processing can be found in other published works derived from the database (Davis, 2022-knee; Lai, 2024-hip). Observer bias was minimized by having multiple observers at multiple clinical sites across the country. The cohort for this paper was narrowed down by identifying completed data sets for intraarticular shoulder applications only, excluding patients who also had rotator cuff-related defects or more than three applications. Participants were also excluded if they were lost to follow-up or if the data were outside the respective time range (± 15 days for 30-day follow-up, ± 30 days for 90-day, 120-day, 150-day, and 180-day follow-ups). One hundred fifteen patients met the criteria, and the final group sizes for patients with one, two, and three applications were 48, 31, and 35, respectively. No exclusions were made based on gender, age, body mass index (BMI), or level or initial score. Figure 1 displays a flow chart of this study's design.

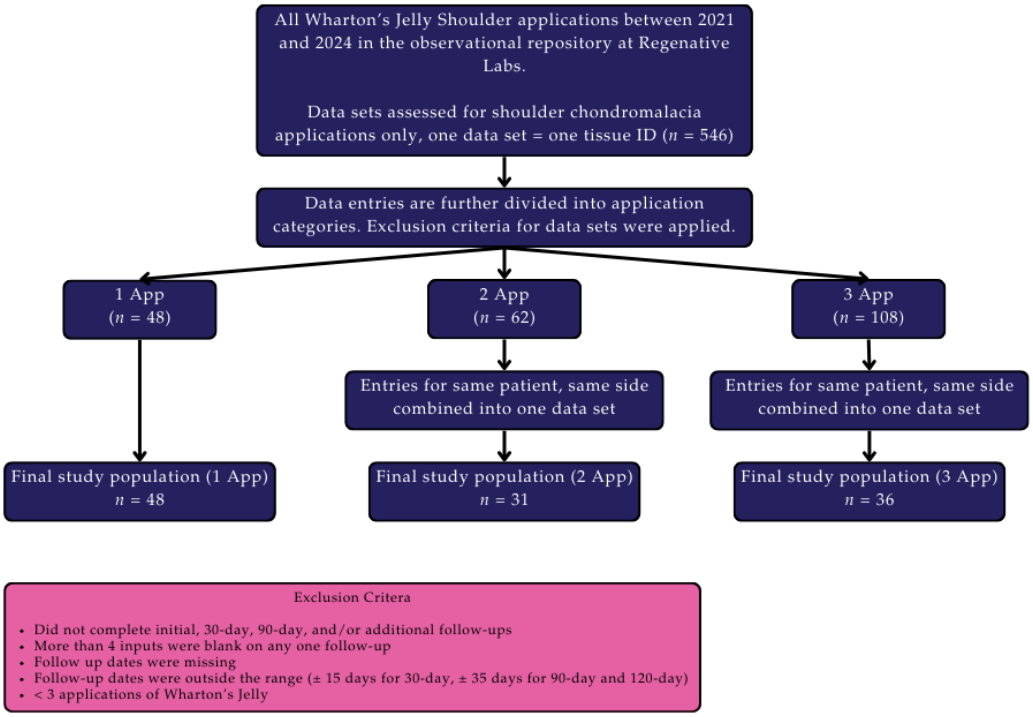

Figure 1. A flow chart of this study's design.

2.2. Study Population

A total of 115 patients were included in the participant group, consisting of 55 (48%) males, 58 (50%) females, and 2 (2%) patients with unreported sex. Based on the severity of the defect and the physician's discretion, 48 patients (25 males and 23 females) received a single application, 31 patients (12 males, 18 females, and 1 unreported) received two applications, and 36 patients (18 males, 17 females, and 1 unreported) received three applications. Throughout the analysis, the cohort was divided based on dosage. All patients receiving one application reported their final scores at the 90-day mark. In multi-application groups, final outcomes varied depending on when they received their second or third application, and data sets were defined as complete with one additional follow-up following their last UCTa application. In double application patients, 26 out of 31 patients reported final scores at the 120-day mark, and 5 patients reported final scores at the 90-day visit. In the triple application group, 22 out of 36 patients reported final scores at the 180-day mark, 7 reported scores at the 150-day mark, and 6 reported last scores at the 120-day visit. To account for the time variation, percentage improvement and total score difference were determined by utilizing the last data set provided, irrespective of the timeline. Several demographic factors were identified as potential

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confounders, including age, gender, and BMI, which may influence application response and reported outcomes. The mean age in the single, double, and triple application groups was 72, 73, and 72, respectively. The mean BMI in the single, double, and triple application groups was 29.15, 27.96, and 27.43, respectively. The patient demographics for each group are listed below (Table 1).

Table 1. Patient age, BMI, and gender by application amount.

Age Range	**1 app**	**2 app**	**3 app**	**Total**	**BMI Range**	**1 app**	**2 app**	**3 app**	**Total**
20-29	0	0	0	0	Underweight (<18.5)	1	0	2	3
30-39	0	0	1	1	Healthy weight (18.5-24.9)	5	1	3	9
40-49	1	0	0	1	Overweight (25.0-29.9)	12	3	15	30
50-59	0	0	0	0	Obese (>30.0)	13	3	7	23
60-69	14	6	10	30	NA	17	24	9	50
70-79	27	20	20	67	Mean BMI	29.15	27.96	27.43	
80-89	4	4	3	11	**Gender**	**1 app**	**2 app**	**3 app**	**total**
90-99	1	0	1	2	Male	25	12	18	55
NA	1	1	1	3	Female	23	18	17	58
Mean Age	72	73	72		NA	0	1	1	2

2.3. Intervention and Patient Care Procedures

Patients in this study presented visible cartilage degradation in the intraarticular space of the shoulder at Kellgren and Lawrence grade levels 3-4, limited range of motion, and shoulder instability. Patients had undergone at least 3 months of conservative care, including measures such as physical therapy, topical medication, NSAIDs, and activity modification. All patients in this group were eligible for surgery before umbilical cord tissue intervention based on the advanced grading of tissue deterioration and failed conservative care. X-ray and MRI imaging were used to determine the location and severity of structural tissue degeneration and damage to the surrounding tendons and ligaments. After failed standard conservative methods, the patients in this study opted to receive umbilical cord allografts to evade or delay surgical intervention. Patients were instructed to avoid the use of NSAIDs and oral steroid treatments for two weeks before application. Intra-articular applications of the allografts were administered to patients with tissue defects aligned with osteoarthritic degeneration. Sterile technique was used to prepare the application site, and a topical spray was used as an anesthetic. Following sterile technique, 2.0 ml of the 150mg Wharton's Jelly Allograft was drawn up into a 3 ml syringe and administered using anatomical landmarks and ultrasound to guide directly to the posterior side of the shoulder using a 25-gauge 1.5-inch needle. Following administration, the shoulder was passively moved through the full range of motion, and a sterile dressing was applied. Patients were instructed to minimize movement and strenuous activity, use ice packs in 15-20 minute intervals every 3-4 hours, support the arm with a pillow while resting, and remain hydrated while eating nutrient-rich foods for 72 hours following the procedure. Aftercare instructions were also to avoid the use of NSAIDs for at least 4 weeks following the procedure. Patients were instructed to gradually ease into using the shoulder by starting with mobility exercises like pendulum swings and shoulder rolls and working up to shoulder circles,

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resistance bands, and weights. At 3 months, patients were expected to resume regular activity. Follow-up appointments took place at the 30 and 90-day post-UCTa application mark, during which some patients received additional applications based on the severity of degeneration and the evaluation from their provider, duplicating the same sterile administration technique, and filled out the NPRS, WOMAC, and QOLS scales.

2.4. Data Analysis

The NPRS, WOMAC (Pain, Stiffness, Physical Function, and Total), and QOLS were used to measure patient-reported outcomes at initial and follow-up visits across all application groups. Although the WOMAC is not site-specific, clinical sites offering multiple musculoskeletal site applications used the WOMAC scale for all use sites for homogeneity of data entry. Descriptive statistics presented baseline characteristics (mean, standard deviation, median, and interquartile range [IQR]) in single, double, and triple application groups. No imputation was performed in statistical analyses, and all missing data sets were excluded. The threshold of significance was set to $p < 0.05$ in all statistical tests. The nonparametric Wilcoxon Signed-Rank test (WSRT) and Mann-Whitney U test were used to analyze changes in scores from the initial visit to follow-ups within and between groups. To control for Type I error within each outcome for the WSRT, Bonferroni correction was applied within each family of comparisons, and each dosage group was adjusted for its respective timeline. Similarly, pairwise comparisons in the Mann-Whitney test were adjusted using the Bonferroni correction ($\alpha = 0.05/3 = 0.017$). The correlation coefficient, r, was calculated for significant values in the WSRT and the Mann-Whitney to indicate effect size. In addition, a Mann-Whitney test was used to determine significant differences between patient sex. Further statistical analysis on patient sex was not performed due to the small sample size once stratified by dosage. Significant values are bolded in the tables below. Analyses were performed using SPSS Statistics (Version 31, IBM Corp, Armonk, NY).

In addition to significance testing, ranges were reported to describe the magnitude and variability of clinical improvement across the sample. The ranges were calculated using the minimum and maximum group-level mean change scores observed from the initial visit to the final follow-up within each dosage group. Outcome ranges were calculated only for the WOMAC scales (Pain, Stiffness, Functionality, and Total), as these outcomes retained sufficient complete follow-up data to reliably represent the observed span of improvement. NPRS and QOLS scores were not included in the effect-range analysis due to a higher proportion of missing final visit data, which could have introduced bias and artificially inflated variability in change in scores. Outcome ranges were treated as descriptive indices of the observed variability and were not analyzed inferentially, consistent with the non-normal distribution of the data. No hypothesis testing was performed on these values because the ranges describe the observed span of clinical improvement rather than population-level parameters.

3. Results

The cohort of 115 patients was divided into categories based on dosage frequency. A decrease in NPRS and WOMAC scores equates to improvement; inversely, an increase in QOLS scores equates to improvement. In the single application group, 32 out of 36 patients reported some level of improvement in NPRS from initial to 90-day visits, 36 out of 48 patients reported improvement in the WOMAC total, and 33 out of 48 reported improved QOLS scores. In the double application group, improvement was reported by 19 out of 29 patients for NPRS, 30 out of 31 for total WOMAC, and 18 out of 31 for QOLS. In the triple application group, 28 out of 33 in NPRS, 32 out of 35 for total WOMAC, and 26 out of 35 for QOLS, reported improvement. Table 1 presents the average percent improvement for all application categories. WOMAC scores in the multi-application groups fluctuated from visit to visit. Despite the variation, they displayed a total decline in scores from the initial date to the final follow-up. Variability in multi-application use was common, often driven by

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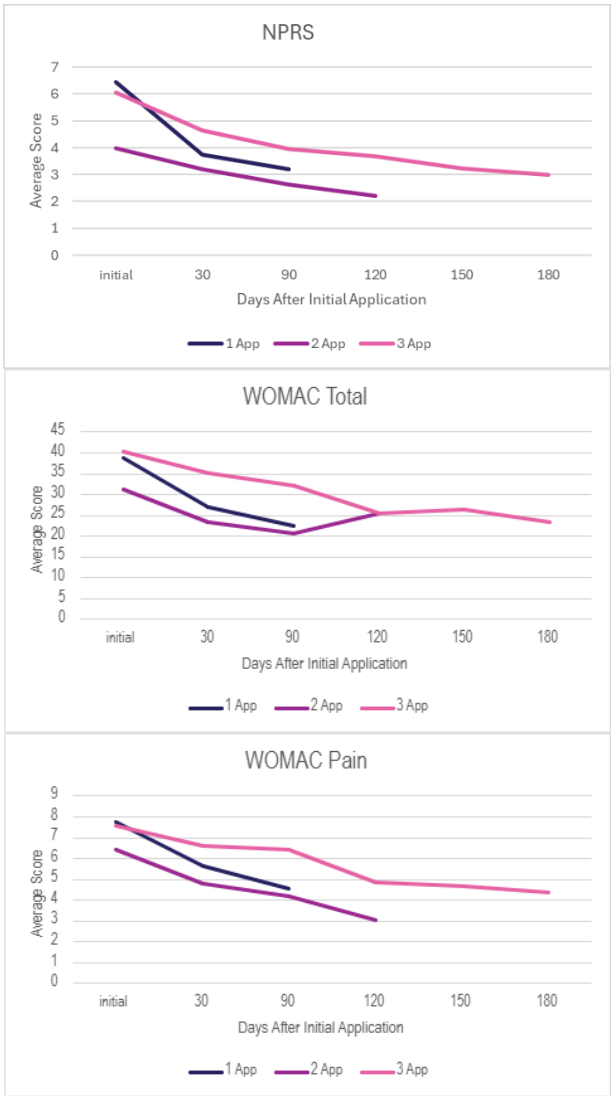
slight increases in pain experienced by patients, which subsequently necessitate reapplication. Figure 2 presents a visual analysis of the average scores for each scale.

Table 1. Percent improvement in each scale by number of applications from the initial to the final visit.

Scale	1 application	2 applications	3 applications
NPRS	50.77%	43.59%	57.10%
WOMAC Total	41.95%	49.80%	47.53%
Pain	40.97%	50.00%	47.69%
Stiffness	45.32%	49.58%	52.54%
Functionality	41.70%	49.78%	46.59%
QOLS	12.00%	3.50%	6.31%



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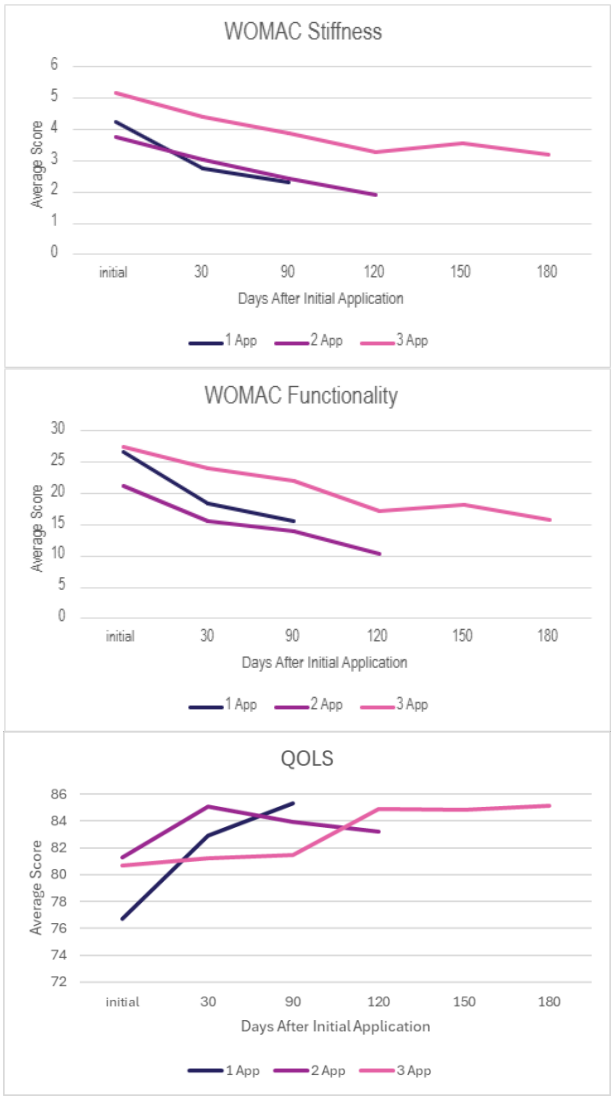

Figure 2. Average scores across each scale compared among each application group.

To assess within-group changes over time, the Wilcoxon Signed-rank test (WSRT) was employed as a non-parametric alternative for the data. Parametric testing was not considered for this study due to the skewness of the data, as shown in the descriptive statistics in Appendix A. The WSRT was utilized on each application group to compare outcomes between the initial and follow-up visits (Table 2). Significant differences between initial and follow-up visits were identified in all application groups, across multiple scales, after applying Bonferroni's correction. All application groups observed significance in the initial to final scores in various scales. A summary of the NPRS, WOMAC, and QOLS scores from initial to final visit is as follows:

- NPRS scores reduced from
  - 6.50 to 3.20 (Single application)
  - 4.03 to 2.16 (Double application)
  - 6.06 to 2.73 (Triple application)
- WOMAC Pain dropped from:
  - 7.73 to 4.56 (Single application)
  - 6.65 to 3.15 (Double application)
  - 8.02 to 4.36 (Triple application)
- WOMAC Stiffness reduced from:
  - 4.23 to 2.31 (Single application)
  - 3.84 to 1.92 (Double application)

 doi:10.20944/preprints202603.1819.v1

- 5.06 to 2.86 (Triple application)

- WOMAC Functionality improved from:
  - 26.7 to 15.6 (Single application)
  - 22.0 to 10.5 (Double application)
  - 28.5 to 15.6 (Triple application)
- WOMAC Total scores decreased from:
  - 38.7 to 22.5 (Single application)
  - 32.5 to 15.5 (Double application)
  - 41.6 to 22.8 (Triple application)
- QOLS scores increased from:
  - 76.7 to 85.9 (Single application)
  - 79.6 to 82.0 (Double application)
  - 79.7 to 86.7 (Triple application)

Table 2. Wilcoxon Signed-Rank Test Statistics in all application groups from initial to follow-up visits (single application adjustment α = 0.05/3 = 0.017; double application adjustment α = 0.05/5 = 0.01; triple application adjustment α = 0.05/8 = 0.0063)**.**

Test Statistics[a]

Dosage		NPRS2-NPRS1	P2-P1	S2-S1	PF2-PF1	W2-W1
Single Application	Z	-4.846[b]	-3.032[b]	-4.105[b]	-3.651[b]	-3.960[b]
	Asymp. Sig. (2-tailed)	**<.001**	**.002**	**<.001**	**<.001**	**<.001**
	r	**.56**	**.31**	**.42**	**.37**	**.40**
Double Application	Z	-3.859[b]	-3.761[b]	-3.310[b]	-4.488[b]	-4.544[b]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**	**<.001**	**<.001**
	r	**.54**	**.48**	**.42**	**.57**	**.58**
Triple Application	Z	-3.504[b]	-2.369[b]	-2.599[b]	-2.489[b]	-2.715[b]
	Asymp. Sig. (2-tailed)	**<.001**	.018	.009	.013	.007
	r	**.44**				

Dosage		Q2-Q1	NPRS3-NPRS2	P3-P2	S3-S2	PF3-PF2
Single Application	Z	-3.443[c]	-2.395[b]	-1.929[b]	-1.179[b]	-1.715[b]
	Asymp. Sig. (2-tailed)	**<.001**	**.017**	.054	.238	.086
	r	**.35**	**.21**			

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Double Application	Z	-2.233[c]	-1.782[b]	-1.009[b]	-1.308[b]	-.970[b]
	Asymp. Sig. (2-tailed)	.026	.075	.313	.191	.332
Triple Application	Z	-1.416[c]	-1.946[b]	-.750[b]	-2.005[b]	-1.496[b]
	Asymp. Sig. (2-tailed)	.157	.052	.453	.045	.135

Dosage		W3-W2	Q3-Q2	NPRS3-NPRS1	P3-P1	S3-S1
Single Application	Z	-1.818[b]	-1.746[c]	-4.873[b]	-3.886[b]	-4.226[b]
	Asymp. Sig. (2-tailed)	.069	.081	**<.001**	**<.001**	**<.001**
	r			**.58**	**.40**	**.43**
Double Application	Z	-1.025[b]	-.162[b]	-2.694[b]	-3.715[b]	-3.203[b]
	Asymp. Sig. (2-tailed)	.305	.872	**.007**	**<.001**	**.001**
	r			**.36**	**.47**	**.41**
Triple Application	Z	-1.616[b]	-.785[c]	-3.911[b]	-1.956[b]	-3.384[b]
	Asymp. Sig. (2-tailed)	.106	.433	**<.001**	.050	**<.001**
	r			**.49**		**.40**

Dosage		PF3-PF1	W3-W1	Q3-Q1	NPRS4-NPRS3	P4-P3
Single Application	Z	-4.049[b]	-4.218[b]	-3.565[c]		
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**		
	r	**.41**	**.43**	**.36**		
Double Application	Z	-3.988[b]	-3.981[b]	-1.208[c]	-3.441[b]	-3.684[b]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	.227	**<.001**	**<.001**
	r	**.51**	**.51**		**.34**	**.36**
Triple Application	Z	-2.942[b]	-3.070[b]	-1.446[c]	-1.158[b]	-3.309[b]
	Asymp. Sig. (2-tailed)	**.003**	**.002**	.148	.247	**<.001**
	r	**.35**	**.37**			**.29**

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Dosage		S4-S3	PF4-PF3	W4-W3	Q4-Q3	NPRS4-NPRS1
Double Application	Z	-3.126[b]	-3.886[b]	-4.020[b]	-1.119[c]	-3.031[b]
	Asymp. Sig. (2-tailed)	**.002**	**<.001**	**<.001**	.263	**.002**
	r	**.31**	**.38**	**.39**		**.31**
Triple Application	Z	-2.420[b]	-3.221[b]	-3.424[b]	-2.279[c]	-4.178[b]
	Asymp. Sig. (2-tailed)	.016	**.001**	**<.001**	.023	**<.001**
	r		**.27**	**.29**		**.37**

Dosage		P4-P1	S4-S1	PF4-PF1	W4-W1	Q4-Q1
Double Application	Z	-3.929[b]	-3.632[b]	-4.013[b]	-4.230[b]	-1.137[c]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**	**<.001**	.255
	r	**.39**	**.36**	**.39**	**.41**	
Triple Application	Z	-3.735[b]	-4.260[b]	-4.058[b]	-4.457[b]	-3.073[c]
	Asymp. Sig. (2-tailed)	**<.001**	**<.001**	**<.001**	**<.001**	**.002**
	r	**.32**	**.36**	**.34**	**.38**	**.26**

Dosage		NPRS5-NPRS4	P5-P4	S5-S4	PF5-PF4	W5-W4
Triple Application	Z	-1.276[b]	-.594[b]	-.390[b]	-.285[c]	-.047[b]
	Asymp. Sig. (2-tailed)	.202	.552	.697	.776	.962

Dosage		Q5-Q4	NPRS6-NPRS5	P6-P5	S6-S5	PF6-PF5
Triple Application	Z	-.589[c]	-2.970[b]	-2.677[b]	-2.549[b]	-3.076[b]
	Asymp. Sig. (2-tailed)	.556	**.003**	.007	.011	**.002**
	r		**.36**			**.36**

Dosage		W6-W5	Q6-Q5	NPRS6-NPRS1	P6-P1	S6-S1
Triple Application	Z	-3.065[b]	-.843[c]	-3.391[b]	-3.155[b]	-3.594[b]
	Asymp. Sig. (2-tailed)	**.002**	.399	**<.001**	**.002**	**<.001**

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	r	**.36**	**.38**	**.34**	**.38**

Dosage		PF6-PF1	W6-W1	Q6-Q1
Triple Application	Z	-3.217[b]	-3.524[b]	-2.594[c]
	Asymp. Sig. (2-tailed)	**.001**	**<.001**	.009
	r	**.34**	**.38**	

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, 2: 30-Day Visit, 3: 90-Day Visit, 4: 120-Day Visit; 5: 150-Day Visit; 6: 180-Day Visit. a. Wilcoxon Signed Ranks Test. b. Based on positive ranks. c. Based on negative ranks.

To determine the difference in overall improvement between specific dosage groups, the Mann-Whitney U test was conducted on initial scores, final scores, and the difference in initial and final scores for each group. Prior to the assessment with the Mann-Whitney test, a Kruskal-Wallis test was utilized to determine if significance was found across all dosage groups. Once significance was confirmed, the analysis with the Mann-Whitney test was considered appropriate. Data sets were completed with a 30-day follow-up after the last application in multi-application groups, which led to fluctuating final visit dates for patients, as the practicing physician determined the reapplication schedule. The final visit scores (F) were the last follow-up submitted for each patient, regardless of timeline. Tables 3-5 display the test statistics for each comparison group (single vs. double application, single vs. triple application, and double vs. triple application). After adjustment with Bonferroni's correction ($\alpha = 0.05/3 = 0.017$), comparisons between the single and double application groups revealed that double application groups had lower baseline NPRS (NPRS1) scores ($U = 297.5$, $z = -3.871$, $p < 0.001$, $r = 0.45$), but had greater improvement in NPRS (DNPRS) scores than the single application group, $U = 313.5$, $z = -3.101$, $p = 0.002$, with a moderate effect size ($r = 0.40$). When comparing double and triple application groups, notable significant differences in baseline scores were found in NPRS ($U = 260.0$, $z = -3.109$, $p = 0.002$, $r = 0.40$) and stiffness ($U = 349.5$, $z = -2.511$, $p = 0.012$, $r = 0.31$) scores, indicating that double application patients began with lower scores than the triple application group. Double application patients also experienced significantly greater NPRS score improvement than the triple application group, $U = 302.0$, $z = -2.838$, $p = 0.005$, with a moderate effect size, $r = 0.37$. No significant differences were found between the single and triple application groups.

Table 3. Test Statistics for single vs double application patients' initial, final, and overall change in scores for all scales (p-value Bonferroni adjusted 0.05 = 0.017)**.**

Single vs Double Applications[a]

	NPRS1	P1	S1	PF1	W1	Q1	FNPRS
Mann-Whitney U	297.500	658.500	647.000	611.000	619.500	731.000	347.000
Wilcoxon W	732.500	1154.500	1143.000	1107.000	1115.500	1907.000	782.000
Z	-3.871	-.861	-.983	-1.336	-1.250	-.131	-2.204
Asymp. Sig. (2-tailed)	**<.001**	.389	.325	.182	.211	.896	.028

 doi:10.20944/preprints202603.1819.v1

r	**.45**						
	FP	FS	FPF	FW	FQ	DNPRS	DP
Mann-Whitney U	634.000	677.000	602.000	619.000	591.000	313.500	682.000
Wilcoxon W	1130.000	1173.000	1098.000	1115.000	1056.000	979.500	1178.000
Z	-1.113	-.684	-1.428	-1.257	-1.326	-3.101	-.625
Asymp. Sig. (2-tailed)	.266	.494	.153	.209	.185	**.002**	.532
r						**.40**	

	DS	DPF	DW	DQ
Mann-Whitney U	720.500	729.000	728.000	572.000
Wilcoxon W	1216.500	1225.000	1224.000	1068.000
Z	-.239	-.151	-.161	-1.730
Asymp. Sig. (2-tailed)	.811	.880	.872	.084

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, F: Last Visit, D: Difference (Final-Initial). a. Grouping Variable: Dosage.

Table 4. Test Statistics for single vs triple application patients' initial, final, and overall change in scores for all scales (p-value Bonferroni adjusted 0.05 = 0.017)**.**

Single vs Triple Applications[a]

	NPRS1	P1	S1	PF1	W1	Q1	FNPRS
Mann-Whitney U	643.000	789.500	679.000	766.500	755.500	814.500	503.500
Wilcoxon W	1204.000	1965.500	1855.000	1942.500	1931.500	1990.500	1133.500
Z	-.868	-.467	-1.501	-.678	-.779	-.235	-1.315
Asymp. Sig. (2-tailed)	.386	.640	.133	.498	.436	.814	.188

	FP	FS	FPF	FW	FQ	DNPRS	DP
Mann-Whitney U	817.500	794.500	796.000	809.000	737.500	585.000	758.000
Wilcoxon W	1993.500	1970.500	1972.000	1985.000	1367.500	1146.000	1388.000
Z	-.209	-.426	-.406	-.286	-.946	-.109	-.759
Asymp. Sig. (2-tailed)	.835	.670	.685	.775	.344	.913	.448

	DS	DPF	DW	DQ
Mann-Whitney U	677.500	739.500	730.500	761.000
Wilcoxon W	1307.500	1369.500	1360.500	1391.000
Z	-1.513	-.927	-1.010	-.730
Asymp. Sig. (2-tailed)	.130	.354	.312	.465

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, F: Last Visit, D: Difference (Final-Initial). a. Grouping Variable: Dosage.

 doi:10.20944/preprints202603.1819.v1

Table 5. Test Statistics for double vs triple application patients' initial, final, and overall change in scores for all scales (p-value Bonferroni adjusted 0.05 = 0.017).

Double vs Triple Applications[a]

	NPRS1	P1	S1	PF1	W1	Q1	FNPRS
Mann-Whitney U	260.000	443.000	349.500	386.000	382.000	519.000	404.000
Wilcoxon W	695.000	939.000	845.500	882.000	878.000	1149.000	839.000
Z	-3.109	-1.283	-2.511	-2.012	-2.063	-.302	-1.450
Asymp. Sig. (2-tailed)	**.002**	.199	**.012**	.044	.039	.763	.147
r	**.40**		**.31**				

	FP	FS	FPF	FW	FQ	DNPRS	DP
Mann-Whitney U	434.500	457.500	396.000	392.000	491.500	302.000	522.500
Wilcoxon W	930.500	953.500	892.000	888.000	956.500	863.000	1152.500
Z	-1.398	-1.112	-1.885	-1.936	-.441	-2.838	-.259
Asymp. Sig. (2-tailed)	.162	.266	.059	.053	.659	**.005**	.796
r						**.37**	

	DS	DPF	DW	DQ
Mann-Whitney U	430.000	479.500	474.000	456.500
Wilcoxon W	1060.000	1109.500	1104.000	952.500
Z	-1.470	-.810	-.881	-1.107
Asymp. Sig. (2-tailed)	.142	.418	.378	.268

Key: NPRS: Numerical Pain Rating Scale, P: WOMAC—Pain, S: WOMAC—Stiffness, PF: WOMAC—Physical Function, W: WOMAC—Total, Q: Quality of life scale, 1: Initial Visit, F: Last Visit, D: Difference (Final-Initial). a. Grouping Variable: Dosage.

Clinically interpretable ranges were calculated for all WOMAC scales (Pain, Stiffness, Functionality, and total) to characterize the variability in treatment response across all dosage groups. Improvements in all scales were observed in each dosage group. In the single application group, the greatest range of response was observed in total WOMAC (112 points), followed by functionality (84 points), pain (30 points), and stiffness (11 points). The double application group demonstrated narrower response distributions, with ranges of 74 (total WOMAC), 54 (functionality), 12 (pain), and 10 (stiffness). For the triple application group. The range of response was higher than the double application, particularly in total WOMAC (84 points) and functionality (57 points). Tables 6-8 present the ranges for each WOMAC scale stratified by dosage frequency, illustrating the variability in application response. Despite the wide ranges, which reflect both substantial improvements in some participants and minimal or negative changes in others, the mean change (Δ) for each WOMAC subcategory remained negative across all application groups, signifying a consistent trend toward improvement.

Table 6. Outcome ranges for WOMAC outcome domains across the single application group.

 doi:10.20944/preprints202603.1819.v1

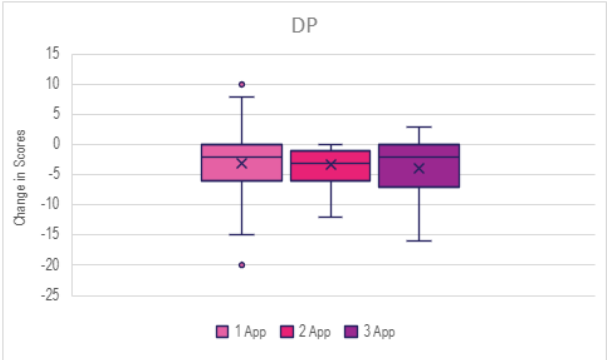
Scale	Best Response (Max Δ)	Worst Response (Min Δ)	Mean Change (Δ)	Outcome range
WOMAC				
Total	-73	39	-16.23	112
Pain	-20	10	-3.17	30
Stiffness	-8	3	-1.92	11
Functionality	-57	27	-11.15	84

Table 7. Outcome ranges for WOMAC outcome domains across the double application group.

Scale	Best Response (Max Δ)	Worst Response (Min Δ)	Mean Change (Δ)	Outcome range
WOMAC				
Total	-67	7	-16.16	74
Pain	-12	0	-3.32	12
Stiffness	-8	2	-1.90	10
Functionality	-47	7	-10.94	54

Table 8. Outcome ranges for WOMAC outcome domains across the triple application group.

Scale	Best Response (Max Δ)	Worst Response (Min Δ)	Mean Change (Δ)	Outcome range
WOMAC				
Total	-68	16	-19.78	84
Pain	-16	3	-3.83	19
Stiffness	-8	2	-2.66	10
Functionality	-46	11	-13.29	57



 doi:10.20944/preprints202603.1819.v1

Figure 3. Distribution of Change Scores Across Application Frequencies (Boxplots depict change scores (final minus initial) for DP, DS, DPF, and DW across participants receiving 1, 2, or 3 applications.).

With a moderate sample size (n = 115), demographic factors were analyzed to determine whether such factors were considered to be significant predictors of score changes. Several tests, including the Jonckheere-Terpstra (J-T) test and the Mann-Whitney test, were used to evaluate statistically significant differences. The J-T test was conducted to assess whether there were ordered trends in the overall change in scores in all measures across age and BMI. No significance was found in either test; therefore, it was excluded from the study. However, the Mann-Whitney test, which was utilized in the analysis between patient sex, found statistically significant differences in overall change in NPRS (DNPRS) scores, reporting that females experienced significantly greater improvements than males, $U = 779.0$, $z = -3.013$, $p = 0.003$, with a small effect size, $r = 0.15$. Figure 4 displays a box plot for the significant difference in overall change in NPRS scores, as identified in Table 9. Due to the significance of patient sex, the cohort was split into dosage groups and evaluated to observe percentage improvements. Only the single group was provided for observation since the multi-application groups, once stratified, were too small for conclusive evidence. From Tables 10 and 11, point reductions and percentage improvement from initial to final scores in the female group were considerably larger than in the male group.

Table 9. Test statistics between genders for single application patients.

Test Statistics[a]

 doi:10.20944/preprints202603.1819.v1

	DNPRS	DP	DS	DPF	DW	DQ
Mann-Whitney U	779.000	1323.000	1371.000	1438.000	1381.500	1479.000
Wilcoxon W	2054.000	2976.000	3024.000	3091.000	3034.500	3019.000
Z	-3.013	-1.430	-1.157	-.754	-1.083	-.516
Asymp. Sig. (2-tailed)	**.003**	.153	.247	.451	.279	.606
r	**.15**					

a. Grouping Variable: Gender.

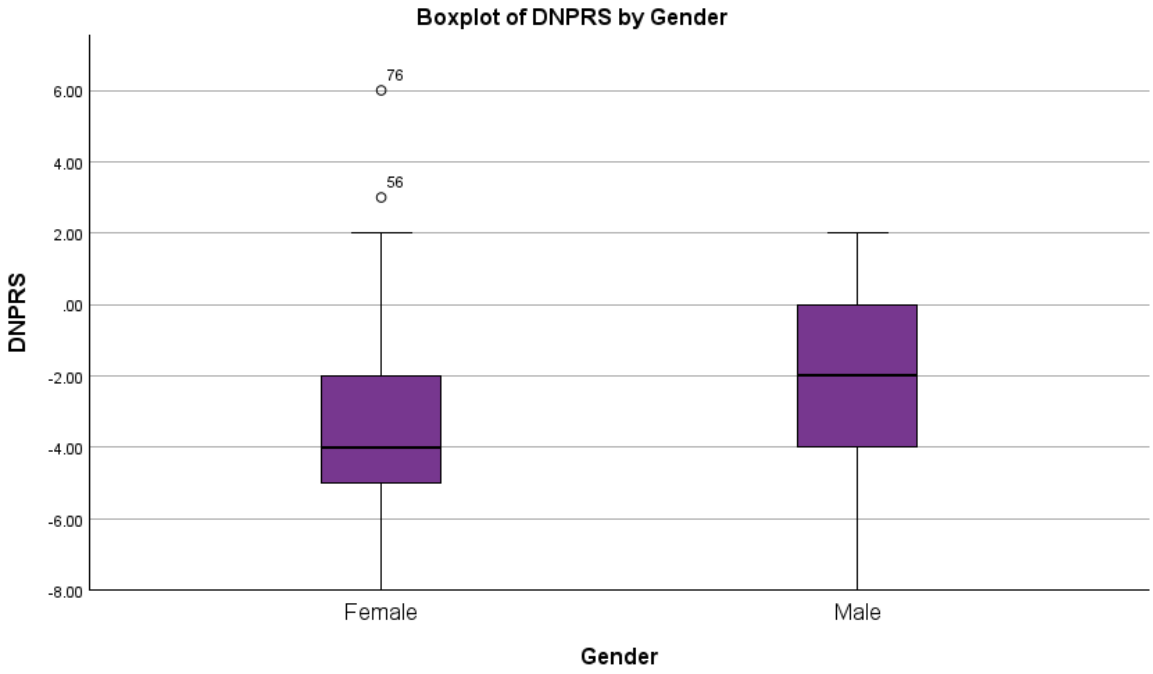


Figure 4. Boxplot of the overall change in NPRS scores (DNPRS) between males and females.

Table 10. Average scores and patient count for male and female patients across each scale in the single application group.

1 app F	n	initial	n2	30 day	n3	90 day	1 app M	n	initial	n2	30 day	n3	90 day
NPRS	22	7.59	19	4.53	18	3.33	NPRS	20	5.20	18	2.94	17	3.06
WOMAC	23	45.30	23	31.78	23	22.57	WOMAC	25	32.60	25	22.36	25	22.36
Pain	23	8.91	23	6.65	23	4.61	Pain	25	6.64	25	4.76	25	4.52
Stiffness	23	4.70	23	3.22	23	2.09	Stiffness	25	3.80	25	2.36	25	2.52
Functionality	23	31.70	23	21.91	23	15.87	Functionality	25	22.16	25	15.24	25	15.32
QOLS	23	72.00	23	78.17	23	81.70	QOLS	25	81.04	25	87.20	25	89.80

Table 11. Percent Improvement for male and female patients across each scale in the single application group.

1 app F	Initial—30-day	Initial—90-day	1 app M	Initial—30-day	Initial—90-day
NPRS	40.37%	56.09%	NPRS	43.38%	41.18%

 doi:10.20944/preprints202603.1819.v1

WOMAC	29.85%	50.19%	WOMAC	31.41%	31.41%
Pain	25.37%	48.29%	Pain	28.31%	31.93%
Stiffness	31.48%	55.56%	Stiffness	37.89%	33.68%
Functionality	30.86%	49.93%	Functionality	31.23%	30.87%
QOLS	8.57%	13.47%	QOLS	7.60%	10.81%

4. Discussion

The outcomes of this study demonstrated the benefits of using umbilical cord tissue allografts for cartilage supplementation in patients with treatment-resistant chondromalacia of the shoulder. Patients were divided into three groups by the number of applications. Patients in all dosage groups averaged lower NPRS and WOMAC scores and higher QOLS scores at the final visit compared to the initial visit, indicating a positive trend of improvement in all scales. All statistical analyses were nonparametric due to the skewed distribution of the data, with Bonferroni adjustments made in the Wilcoxon Signed-Rank test (WSRT) and the Mann-Whitney U test to reduce Type I error. In the analysis of the single application group, significant differences were found between initial and 30-day scores and initial and 90-day scores. No significant differences were found between the 30 and 90-day scores. The evaluation of the statistical significance indicates that considerable improvement occurred within the first month of application, with maintained improvement past the 30-day mark. The significance of the overall improvement demonstrates that single applications of umbilical cord tissue allografts can be beneficial in the management of intra-articular cartilage defects of the shoulder.

In the multi-application groups, the WSRT demonstrated multiple statistically significant differences over time. In the double application group, significant improvements were observed from the initial to 30-day visit and from the initial to 90-day visits, while no significant differences were identified between the 30-day and 90-day assessments. Significant differences were also observed between the 90-day and 120-day visits. These findings correspond with the timing of most reapplications, which occurred during the 30-day or 90-day visit, suggesting that the greatest clinical improvement is observed within 30 days following an application, and is maintained 90 days post-application. The overall significant improvement from initial to follow-up visits supports the clinical benefit of double applications for patients with shoulder chondromalacia. The triple application group observes a similar pattern, where scores improved immediately following applications. The consistent response patterns across these multi-application cohorts suggest the potential relationship between dosage frequency and patient response.

The favorable outcomes identified through the WSRT were complemented by the Mann-Whitney U test, which provides greater clarity regarding the dosage protocol, particularly in determining the number of applications that yield the most pronounced improvements. In the comparison between single and double application patients, significant differences were noted in NPRS scores, specifically in initial and overall change in scores. The analysis indicated that double application patients began with lower baseline scores, but had greater overall improvement compared to the single application group. This highlights the potential significance of greater dosages to provide better outcomes for the management of intra-articular shoulder defects. Single and triple application groups reported no significant differences between dosage groups. In comparisons between the double application cohort and the triple application group, lower scores were reported in the double application cohort. Similar to the comparison with the single application patients, the double application group had significantly greater improvement than the triple application group. This finding suggests that while increased dosage may allow for better outcomes, benefits appear to plateau beyond two applications. The double application group demonstrated the most

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improvements among the three groups; however, future studies with larger sample sizes are warranted to confirm and strengthen these preliminary observations.

In addition to statistical significance testing, ranges were calculated to describe the span of observed clinical response within each application group. These descriptive values captured the differences between the most improved and least improved individuals for each WOMAC domain, providing a practical measure of variability in symptom and functional change. Across groups, ranges demonstrated that although many patients experienced improvement following application, the magnitude of change differed considerably between individuals, including several outliers (Tables 6-8, Figure 3). Patients interpreting the questionnaire differently, as it is not specific to the shoulder, may be one factor in the variability of outcomes. Despite this variability, the direction of the mean change values remained negative across all WOMAC categories, indicating that, on average, patients exhibited reductions in pain and stiffness, as well as increased functionality (Figure 3). This variability reflects heterogeneity in baseline status and application response that may not be fully conveyed by group means or p-values alone. The ranges were reported descriptively rather than used as inferential effect statistics due to the use of nonparametric analyses in the study. NPRS and QOLS outcomes were excluded from the range analysis due to missing data at follow-up that disproportionately influenced the observed spread of values and risked misrepresenting response variability.

Because of this study's moderate sample size (n = 115), demographic factors such as age, BMI, and gender were analyzed to see if these factors were significant predictors of the overall change in scores. Two tests were conducted: the Jonckheere-Terpstra (J-T) test was performed on ordinal groups such as age and BMI categories, and the Mann-Whitney test was utilized for gender, due to its nominal nature. Age and BMI were not considered significant predictors of the overall change in scores across all six measures, and so results were excluded from the study. However, significant differences were found between male and female patients. The analysis revealed that females experienced greater improvement in NPRS scores than males. Based upon this significance, the group was stratified to evaluate differences in their respective dosage groups. Only the single-application group was selected for analysis due to its larger sample size and reduced variability, allowing for more consistent comparison across patient outcomes. Female patients reported a greater percentage improvement than males on all scales. These differences suggest the possibility of intrinsic and extrinsic sex differences, and current literature identifies a range of biological and psychosocial factors that may contribute to higher pain reporting in females. Biologically, studies have shown that hormonal fluctuations, particularly in estrogen and progesterone, may heighten sensitivity to pain in women (Nasser, 2019; Marchesini, 2025). Psychosocial contributors include cultural expectations in gender and the expression of pain, biases in clinical care, and established sex differences in pain thresholds and coping mechanisms (Marchesini, 2025; Puto, 2024). These findings present a difficulty in providing significant improvements between the sexes, and future studies are encouraged to focus on sex-related differences when evaluating UCTa applications.

Despite the statistically significant results from this study, several limitations must be considered when interpreting the results. Nonparametric testing was employed to address the distributional characteristics of the data, which ensured appropriate handling of skewness and outliers. However, compared to parametric alternatives, these methods typically provide less statistical power and more limited options for incorporating covariates. In addition to the limited statistical power of testing, the data reported in this study were exclusively derived from patient-reported outcome measures without any inclusion of objective imaging assessments. The WOMAC scale was used to cover a wide range of homologous use sites submitted to the repository. Still, the Shoulder Pain and Disability Index (SPADI) or Western Ontario Osteoarthritis of the Shoulder (WOOS) would be more specific to cartilage degeneration of the shoulder. Reliance on self-reported scales limited the ability to capture the functional or structural improvements with UCTa fully. Additionally, the absence of a comparison group receiving standard conservative care alone reduced the capacity to evaluate the relative effectiveness of UCT, despite all patients failing the standard of

 doi:10.20944/preprints202603.1819.v1

care for at least three months. The preliminary findings from this study encourage future prospective studies incorporating imaging assessments and comparative analysis with other conservative interventions. Such studies would validate the efficacy, clarify optimal dosage protocols, and allow the use of parametric models for more robust statistical evaluation.

The findings from this study provide evidence for the functional relevance of umbilical cord tissue in chondromalacia of the shoulder. The structural framework of umbilical cord tissue, which consists of high concentrations of collagen types I, II, III, and V, offers protection from tensile stress and cushioning in the umbilical cord (Gupta 2020, Main 2021). Connective tissues in the glenohumeral joint assist in stabilization and cushioning to support the joint and adjacent tendons. The structural profile of the cartilage in the glenohumeral joint consists of high concentrations of collagen type II, with other extracellular matrix components, supporting the structural integrity of the joint (Fox, 2009). The glenoid labrum functions as a passive stabilizing component of the glenohumeral joint, providing attachment for ligaments and acting as a shock absorber to evenly distribute forces across the surfaces of the joint (Almajed, 2021). The structural framework of the glenoid labrum predominantly consists of fibrocartilage, bundled type II collagen fibers with a deeper collagen core (Almajed, 2021; Okert, 2011). Chondromalacia leads to the disruption of the collagen matrix, which can be supplemented with a healthy collagen matrix from UCT.

The results from applying UCTa to patients with treatment-resistant chondromalacia of the shoulder offer guidance for practicing physicians seeking alternative conservative options prior to surgery when conventional care proves ineffective. Routine surgical methods for glenohumeral joint defects, including procedures like palliative, reparative, restorative, or reconstructive surgeries, have not been confirmed as the preferred practice due to complications and risks (Nascimento, 2017). Viscosupplementation (HA therapy) has been recommended for cartilage defects in the glenohumeral joint but is often associated with limited efficacy over time (Yao, 2024; Olson, 2024; Yusuf, 2016). This is further realized by evidence that suggests the use of isolated materials diminishes therapeutic responses (Liu, 2022; Zhao, 2023). Umbilical cord tissue, as indicated by this research and other literature, is a better alternative due to its complete tissue structure, consisting of various ECM components, including hyaluronic acid (HA) (Gupta, 2020). A previous study from the same observational repository used in this paper reported similar efficacy of UCTa applications in patients with rotator cuff defects unresponsive to current standard-of-care protocols (Lai-rotator cuff, 2024). Patients reported statistically significant improvements in pain, stiffness, and functionality (Lai-rotator cuff, 2024). The findings from both studies confirm the efficacy of UCTa in homologous shoulder applications, demonstrating its capacity to supplement various connective tissues in the human body. The favorable effects of UCTa applications in patients with chondromalacia of the shoulder in this observational study provide a reference in evaluating alternative methods to standard-of-care protocols. Future studies are warranted to validate best practice dosage and application protocols for clinical use of UCTa in chondromalacia of the shoulder.

5. Conclusions

The cohort of 115 patients in this observational research reported that the application of umbilical cord tissue allografts decreased their pain and stiffness and increased their functionality, leading to improvements in a patient's quality of life. No adverse events or side effects were reported in the patient group. The results from this investigation are encouraging, but definitive evidence is prevented by its limitations. The current body of literature showcases a rising interest in alternative medicine, primarily due to the complications and side effects associated with surgical practices. Future studies are vital in redefining standardized care and incorporating umbilical cord tissue as a primary option for chondromalacia of the shoulder.

Author Contributions: Conceptualization, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., and T.B.; methodology, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., N.L., and T.B.; software, T.B.; validation, N.L, A.L., T.B.; formal analysis, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., N.L., A.L., and T.B.; investigation, A.L. (Lai), J.B., J.C., H.J., L.P., T.G.,

 doi:10.20944/preprints202603.1819.v1

L.M., and R.D.; resources, N.L. and A.L.; data curation, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., R.D., N.L., A.L., and T.B.; writing—original draft preparation, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., R.D., N.L., A.L., and T.B.; writing—review and editing, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., N.L., A.L., and T.B.; visualization, N.L. and A.L.; supervision, N.L. and T.B.; project administration, R.D. and T.B.; funding acquisition, A.L. (Lai), J.B., J.C., H.J., L.P., T.G., L.M., and T.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This data was collected in accordance with the Declaration of Helsinki and approved by the Institutional Review Board of the Institute of Regenerative and Cellular Medicine (protocol code IRCM-2022-311; Approval date: 12 January 2022).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Data available upon request.

Acknowledgments: The authors would like to thank the staff at each clinic that submitted data to the repository for their assistance in data collection and submission.

Conflicts of Interest: Naomi Lambert, Alexis Lee, and Tyler Barrett are associated with Regenative Labs. Regenerative Labs was involved in the design of the study, data analysis, and writing. Regenative Labs influenced the decision to publish.

Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
GH	Glenohumeral
OA	Osteoarthritis
UCT	Umbilical Cord Tissue
UCTa	Umbilical Cord Tissue allograft
WOMAC	Western Ontario and McMaster University Arthritis Index
NPRS	Numeric Pain Rating Scale
QOLS	Quality of Life Scale

Appendix A

Statistics

Dosage			NPRS1	P1	S1	PF1	W1
Single Application	N	Valid	44	48	48	48	48
		Missing	4	0	0	0	0
	Mean		6.5000	7.7292	4.2292	26.7292	38.6875
	Median		7.0000	8.0000	4.5000	24.0000	37.0000
	Std. Deviation		2.09651	4.89785	2.36319	15.59015	21.14907
	Skewness		-.754	.509	-.377	.256	.214
	Std. Error of Skewness		.357	.343	.343	.343	.343
	Kurtosis		.588	.000	-.808	-1.005	-1.038
	Std. Error of Kurtosis		.702	.674	.674	.674	.674
	Minimum		1.00	.00	.00	3.00	4.00

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	Maximum		10.00	20.00	8.00	57.00	83.00
Double Application	N	Valid	29	31	31	31	31
		Missing	2	0	0	0	0
	Mean		4.0345	6.6452	3.8387	21.9677	32.4516
	Median		4.0000	7.0000	4.0000	22.0000	30.0000
	Std. Deviation		2.61155	4.08696	1.96802	13.53387	19.02952
	Skewness		.554	.004	.128	.170	.180
	Std. Error of Skewness		.434	.421	.421	.421	.421
	Kurtosis		-.692	-.892	-.468	-.945	-.925
	Std. Error of Kurtosis		.845	.821	.821	.821	.821
	Minimum		1.00	.00	.00	.00	1.00
	Maximum		10.00	15.00	8.00	48.00	69.00
Triple Application	N	Valid	33	35	35	35	35
		Missing	2	0	0	0	0
	Mean		6.0606	8.0286	5.0571	28.5143	41.6000
	Median		6.0000	9.0000	5.0000	28.0000	42.0000
	Std. Deviation		2.17858	4.23213	1.87778	12.45786	17.19131
	Skewness		-.546	.097	-.568	-.217	-.122
	Std. Error of Skewness		.409	.398	.398	.398	.398
	Kurtosis		-.375	-.020	.005	.074	.254
	Std. Error of Kurtosis		.798	.778	.778	.778	.778
	Minimum		1.00	.00	.00	1.00	4.00
	Maximum		10.00	19.00	8.00	57.00	83.00

Dosage			Q1	NPRS2	P2	S2	PF2
Single Application	N	Valid	48	37	48	48	48
		Missing	0	11	0	0	0
	Mean		76.7083	3.7568	5.6667	2.7708	18.4375
	Median		76.5000	4.0000	5.0000	3.0000	12.5000
	Std. Deviation		23.69393	2.11352	4.38243	2.28072	14.65621
	Skewness		-.662	.208	.513	.205	.416
	Std. Error of Skewness		.343	.388	.343	.343	.343
	Kurtosis		.218	-.519	-.833	-1.352	-1.226
	Std. Error of Kurtosis		.674	.759	.674	.674	.674
	Minimum		5.00	.00	.00	.00	.00
	Maximum		111.00	9.00	15.00	7.00	48.00

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Double Application	N	Valid	31	27	31	31	31
		Missing	0	4	0	0	0
	Mean		79.6452	3.1481	5.1290	3.1290	16.4194
	Median		83.0000	3.0000	5.0000	3.0000	15.0000
	Std. Deviation		15.23712	2.10683	3.91358	2.02882	12.29844
	Skewness		-.577	1.069	.617	.274	.736
	Std. Error of Skewness		.421	.448	.421	.421	.421
	Kurtosis		-.771	.827	-.201	-1.002	-.053
	Std. Error of Kurtosis		.821	.872	.821	.821	.821
	Minimum		48.00	1.00	.00	.00	.00
	Maximum		101.00	9.00	14.00	7.00	47.00
Triple Application	N	Valid	35	34	35	35	35
		Missing	0	1	0	0	0
	Mean		79.6571	4.5294	7.0857	4.2571	25.1143
	Median		79.0000	5.0000	7.0000	4.0000	27.0000
	Std. Deviation		16.97566	1.86247	4.17536	2.14672	12.72046
	Skewness		.309	-.094	.404	-.374	-.070
	Std. Error of Skewness		.398	.403	.398	.398	.398
	Kurtosis		-.734	.201	.266	-.682	.076
	Std. Error of Kurtosis		.778	.788	.778	.778	.778
	Minimum		51.00	.00	1.00	.00	1.00
	Maximum		112.00	9.00	19.00	8.00	57.00
Dosage			W2	Q2	NPRS3	P3	S3
Single Application	N	Valid	48	48	35	48	48
		Missing	0	0	13	0	0
	Mean		26.8750	82.8750	3.2000	4.5625	2.3125
	Median		19.0000	86.5000	3.0000	4.0000	2.0000
	Std. Deviation		20.69806	20.38421	1.96738	4.29699	1.96952
	Skewness		.421	-.535	.540	1.070	.624
	Std. Error of Skewness		.343	.343	.398	.343	.343
	Kurtosis		-1.181	-.695	.417	.896	.005
	Std. Error of Kurtosis		.674	.674	.778	.674	.674
	Minimum		.00	37.00	.00	.00	.00
	Maximum		69.00	112.00	8.00	18.00	8.00
Double Application	N	Valid	31	31	30	31	31

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		Missing	0	0	1	0	0
	Mean		24.6774	83.9032	2.7667	4.6129	2.6129
	Median		22.0000	87.0000	2.5000	3.0000	3.0000
	Std. Deviation		17.67180	17.14712	1.77499	3.83560	1.80143
	Skewness		.699	.054	1.013	.518	.005
	Std. Error of Skewness		.421	.421	.427	.421	.421
	Kurtosis		-.146	1.212	1.236	-1.056	-.993
	Std. Error of Kurtosis		.821	.821	.833	.821	.821
	Minimum		1.00	49.00	.00	.00	.00
	Maximum		67.00	132.00	8.00	12.00	6.00
Triple Application	N	Valid	35	35	34	35	35
		Missing	0	0	1	0	0
	Mean		36.4571	80.0286	3.7941	6.8286	3.6571
	Median		41.0000	80.0000	4.0000	7.0000	4.0000
	Std. Deviation		17.98094	17.47517	1.93500	4.27362	2.24844
	Skewness		-.021	.180	.096	.499	-.170
	Std. Error of Skewness		.398	.398	.403	.398	.398
	Kurtosis		.204	-.832	-.578	-.085	-.887
	Std. Error of Kurtosis		.778	.778	.788	.778	.778
	Minimum		3.00	51.00	.00	1.00	.00
	Maximum		83.00	112.00	8.00	18.00	8.00

Dosage			PF3	W3	Q3	NPRS4	P4
Single Application	N	Valid	48	48	48		
		Missing	0	0	0		
	Mean		15.5833	22.4583	85.9167		
	Median		13.0000	18.0000	92.0000		
	Std. Deviation		13.28707	19.07316	22.02690		
	Skewness		.816	.882	-.697		
	Std. Error of Skewness		.343	.343	.343		
	Kurtosis		.085	.354	-.601		
	Std. Error of Kurtosis		.674	.674	.674		
	Minimum		.00	.00	39.00		
	Maximum		54.00	80.00	112.00		
Double Application	N	Valid	31	31	31	25	26
		Missing	0	0	0	6	5

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	Mean		15.2581	22.4839	82.1935	2.1600	3.1538
	Median		14.0000	21.0000	86.0000	2.0000	2.5000
	Std. Deviation		10.66761	15.69898	14.32811	1.43411	2.80987
	Skewness		.414	.408	-.605	1.815	.884
	Std. Error of Skewness		.421	.421	.421	.464	.456
	Kurtosis		-.771	-.763	-.482	4.212	-.019
	Std. Error of Kurtosis		.821	.821	.821	.902	.887
	Minimum		.00	.00	49.00	1.00	.00
	Maximum		34.00	50.00	105.00	7.00	10.00
Triple Application	N	Valid	35	35	35	34	35
		Missing	0	0	0	1	0
	Mean		22.5429	33.0286	81.1429	3.5294	5.1429
	Median		24.0000	35.0000	78.0000	3.5000	5.0000
	Std. Deviation		13.43031	19.03323	16.75980	1.86247	3.01118
	Skewness		.298	.270	.140	.355	.602
	Std. Error of Skewness		.398	.398	.398	.403	.398
	Kurtosis		-.047	-.047	-.552	-.266	.909
	Std. Error of Kurtosis		.778	.778	.778	.788	.778
	Minimum		1.00	3.00	51.00	.00	.00
	Maximum		57.00	82.00	112.00	8.00	14.00

Dosage			S4	PF4	W4	Q4	NPRS5
Double Application	N	Valid	26	26	26	25	
		Missing	5	5	5	6	
	Mean		1.9231	10.4615	15.5385	82.0400	
	Median		2.0000	9.0000	14.5000	86.0000	
	Std. Deviation		1.38342	9.11364	12.80697	13.44892	
	Skewness		.345	1.027	.894	-.753	
	Std. Error of Skewness		.456	.456	.456	.464	
	Kurtosis		-.331	.861	.349	-.239	
	Std. Error of Kurtosis		.887	.887	.887	.902	
	Minimum		.00	.00	.00	49.00	
	Maximum		5.00	35.00	46.00	99.00	
Triple Application	N	Valid	35	35	35	35	24
		Missing	0	0	0	0	11

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	Mean	2.9714	17.4571	25.5714	83.9429	3.0417
	Median	3.0000	16.0000	24.0000	81.0000	3.0000
	Std. Deviation	2.06491	10.15857	14.29168	15.21211	1.65448
	Skewness	.062	.171	.200	.217	.242
	Std. Error of Skewness	.398	.398	.398	.398	.472
	Kurtosis	-1.079	-.502	-.310	-.594	-.734
	Std. Error of Kurtosis	.778	.778	.778	.778	.918
	Minimum	.00	.00	.00	54.00	.00
	Maximum	7.00	38.00	58.00	112.00	6.00

Dosage			P5	S5	PF5	W5	Q5
Triple Application	N	Valid	25	25	25	25	25
		Missing	10	10	10	10	10
	Mean		5.0000	3.1600	17.8000	25.9600	83.6800
	Median		5.0000	3.0000	17.0000	25.0000	86.0000
	Std. Deviation		3.01386	1.79536	10.27943	14.19941	14.22650
	Skewness		.069	-.166	.110	-.021	.071
	Std. Error of Skewness		.464	.464	.464	.464	.464
	Kurtosis		-.744	-.779	-.559	-.461	-.542
	Std. Error of Kurtosis		.902	.902	.902	.902	.902
	Minimum		.00	.00	.00	.00	54.00
	Maximum		11.00	6.00	37.00	50.00	111.00

Dosage			NPRS6	P6	S6	PF6	W6	Q6
Triple Application	N	Valid	22	22	22	22	22	22
		Missing	13	13	13	13	13	13
	Mean		2.7273	4.3636	2.8636	15.5909	22.8182	86.7273
	Median		2.0000	5.0000	3.0000	16.5000	23.5000	90.0000
	Std. Deviation		1.48586	3.17048	1.64159	8.93713	12.73404	15.22899
	Skewness		-.058	-.081	.168	.003	-.105	-.326
	Std. Error of Skewness		.491	.491	.491	.491	.491	.491
	Kurtosis		-.682	-1.307	-.142	-.419	-.448	-.439
	Std. Error of Kurtosis		.953	.953	.953	.953	.953	.953
	Minimum		.00	.00	.00	.00	.00	54.00
	Maximum		5.00	10.00	6.00	33.00	46.00	112.00

Figure A1. Descriptive statistics for all application groups across all scales used.

 doi:10.20944/preprints202603.1819.v1

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