J Shoulder Elbow Surg (2024) 33, e261–e277

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

The effect of platelet-rich fibrin, platelet-rich plasma, and concentrated growth factor in the repair of full thickness rotator cuff tears

Mert Celikten, PhD[a,*], Hakan Sahin, MSc[b], Gozde Erkanli Senturk, PhD[b], Kerem Bilsel, MD[c], Anil Pulatkan, MD[d], Mehmet Kapicioglu, MD[d], Bayram Ufuk Sakul, PhD[e]

[a]*Department of Anatomy, Health Sciences Institute, Istanbul Medipol University, Istanbul, Turkey*
[b]*Department of Histology and Embryology, Cerrahpasa Faculty of Medicine, Istanbul University-Cerrahpaşa, Istanbul, Turkey*
[c]*Department of Orthopaedics and Traumatology, Acibadem Mehmet Ali Aydinlar University, Faculty of Medicine, Istanbul, Turkey*
[d]*Department of Orthopedics and Traumatology, School of Medicine, Bezmialem Vakif University, Istanbul, Turkey*
[e]*Department of Anatomy, School of Medicine, Istanbul Medipol University, Istanbul, Turkey*

Background: Rotator cuff lesions rank among the prevalent causes of shoulder pain. Combining surgical interventions with growth factors, scaffolds, and stem cell therapies can effectively decrease the likelihood of rotator cuff repair recurrence. Platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF), isolated from blood and rich in growth factors, have a critical role in cell migration, cell proliferation, and angiogenesis during the tissue regeneration process. Investigations have further substantiated the beneficial impact of PRP and PRF on the biomechanical and histologic attributes of the tendon-bone interface. We aimed to investigate the effectiveness of CGF compared with PRF and PRP in the repair of rotator cuff lesions as a new treatment strategy.
Methods: Incision was performed on both shoulder regions of 21 adult rabbits. After 8 weeks, both shoulders of the rabbits were repaired by suturing. PRF and CGF were administered to 2 separate groups along with the repair. Tissues were collected for biomechanical measurements and histologic evaluations.
Results: Histologically, CGF, PRF, and PRP showed similar results to the healthy control group. The level of improvement was significant in the PRF and PRP groups. In the PRF group, the distribution of Ki67 (+), CD31 (+), and CD34 (+) cells was determined intensely in the tendon-bone junction regions. Apoptotic cells increased significantly in the repair group compared with the healthy group, whereas fewer apoptotic cells were found in the PRF-, PRP-, and CGF-applied groups. In the biomechanical results, no statistical difference was recorded among the groups.
Conclusion: The use of PRF, PRP, and CGF in rotator cuff repair shows promise in shortening the treatment period and preventing the recurrence of rotator cuff lesions.
Level of evidence: Basic Science Study; In Vivo Animal Model; Histology and Biomechanics

Keywords: Platelet-rich fibrin; platelet-rich plasma; concentrated growth factor; rotator cuff tears; anatomy; histology; rabbit

Ethical approval was provided for this study from Bezmialem Vakif University Animal Experiments Local Ethics Committee (BVU-HADYEK; study # 2020/84). All experiments were conducted in the Experimental Animals Laboratory of Bezmialem Vakif University (BEDEHAL), and the procedures were performed in accordance with the applicable national and international guidelines.

*Reprint requests: Mert Celikten, PhD, Experimental Application and Research Center, Bezmialem Vakif University, Topkapi Mah. Adnan Menderes Bulvari, Vatan Cad., Istanbul 34093, Turkey.
E-mail address: mcelikten@bezmialem.edu.tr (M. Celikten).

1058-2746/$ - see front matter
https://doi.org/10.1016/j.jse.2023.09.028

Rotator cuff injuries consist of a wide variety of pathological changes, such as rotator cuff inflammation and full-thickness rupture of 1 or more tendons.[40] Rotator cuff tears disrupt the existing internal balance. Although the mechanism by which a rotator cuff tear develops has not been fully revealed, the generally accepted theory is that the injury develops after acute trauma or on the basis of chronic repetitive trauma.[20] Besides, aging might be a contributing factor for tearing.[25,40,42] Options for treating rotator cuff tears include conservative and surgical approaches. Although surgery is commonly preferred in full-thickness tears, successful results have been reported with conservative treatment.[28,37] Although full-thickness rotator cuff tears can be repaired primarily, the need for additional methods has increased because of the high rates of rerupture.[4,17,19,31,38,50]

Piper et al[43] showed that surgical treatments used in full-thickness rotator cuff tear repair resulted in more favorable outcomes, both specifically and objectively, in patients compared with nonsurgical treatments in their meta-analysis study. Furthermore, in addition to the repair, a microfracture of the acromion can be performed to stimulate the stem cells to leave the bone. The contribution of growth factors from the fat-derived tissue can be achieved in the rotator cuff repair. However, different growth factors, scaffolds, and stem cell studies are prominent research areas due to the longer-term effectiveness of cuff repair and reducing the risk of recurrence.[3,22,33,34,52,60]

During the healing of tendon wounds, the relatively low vascularity and cell populations in tendons can contribute to irregular and excessive extracellular matrix synthesis. Abnormal matrix composition can lead to a deviation of the tendon structure from its original state. The resulting scar tissue not only provides some stability in the tendon but also causes some mechanical functions to weaken. Fragility arises as a consequence of the tendon gradually straying from its initial tissue configuration. The high rate of recurrence after healing in rotator cuff ruptures can be attributed to the tendon's increased vulnerability to injury.[17,22,31,32]

Growth factors are critical for cell migration, cell proliferation, and angiogenesis in the tissue regeneration process.[8] Because these growth factors are found in the plasma, platelet concentrations such as platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) obtained from blood have been used in different studies in the literature for the healing of connective tissue.[6,30]

In order to increase the success of rotator cuff repair, PRP, containing many bioactive proteins such as growth factors crucial for tendon healing, may be employed as adjunctive therapy in addition to arthroscopy. PRP is derived through centrifugation of the blood obtained from the patient's own blood. The material triggers cell proliferation and angiogenesis because it contains platelet-derived growth factor, transforming growth factor-ß (TGF-ß), insulin-like growth factor, epidermal growth factor, and vascular endothelial growth factor (VEGF).[15] In laboratory studies, PRP significantly improves the biomechanical properties and histologic appearance on the tendon-bone surface. Dolkart et al[12] administered a single dose of autologous PRP with intra-articular injection as a complement to the surgical repair with a positive contribution to tendon-bone healing. A meta-analysis study conducted by Wang et al[53] found that PRP treatment, when applied alongside routine arthroscopy for full-thickness rotator cuff tear, led to a notable reduction in certain objective and subjective parameters, particularly in terms of the likelihood of recurrence. However, the same study reported that the positive outcomes did not exhibit significant long-term changes.

The objective of this study is to conduct a histologic and biomechanical comparison between PRP and PRF, well-established treatments for tendon-bone repair, as well as CGF, a novel intervention that has not yet been explored for rotator cuff tears but has demonstrated efficacy in various other tissues with the use of experimental rabbit models.

Materials and methods

Experimental design

In the study, 21 adult New Zealand rabbits weighing 2.8-3.5 kg were used. The animals were cared for under a 12/12-hour light-dark cycle at a 22 ± 3°C ambient temperature and 55%-65% humidity, with as much feed and water as they could reach. A homogeneous and standardized distribution was achieved between the groups in terms of mean weight and age.

Surgical procedure

The most frequently torn rotator cuff muscle in humans is the supraspinatus muscle. Because of its anatomical resemblance to the supraspinatus tendon, subscapularis (SSC) muscle tendon was preferred.[11,14,23] The operation area was shaved and prepared in accordance with the rules of asepsis-antisepsis. Then anesthesia was applied intramuscular injection of 50 mg/kg ketamine (Ketasol; Richter Pharma AG, Austria) and 10 mg/kg xylazine (Rompun; Bayer HealthCare, Leverkusen, Germany). The skin and subcutaneous fascia were passed with a 2 cm incision. After the cut, the tendon of the SSC muscle was defined, liberated from the tuberculum minus, and tenotomy was performed with the deltopectoral approach. A Penrose drain was placed at the free end of the tendon to prevent self-adhesion. The fascia was closed with a 3-0 absorbable braided suture (Vicryl; Ethicon, Somerville, NJ, USA). The skin was closed with a 3-0 permanent Prolene suture (Fig. 1). Postoperatively, unrestricted mobility was allowed in their cages without any immobilization on the operated shoulders. After the first surgical procedure, a chronic tear pattern was formed after 8 weeks. Postoperatively, the rabbits were allowed to move freely in their cages without any immobilization on the operated shoulders.[3] Animals were randomly selected and divided into 4 groups, as shown in Figure 1.[18]

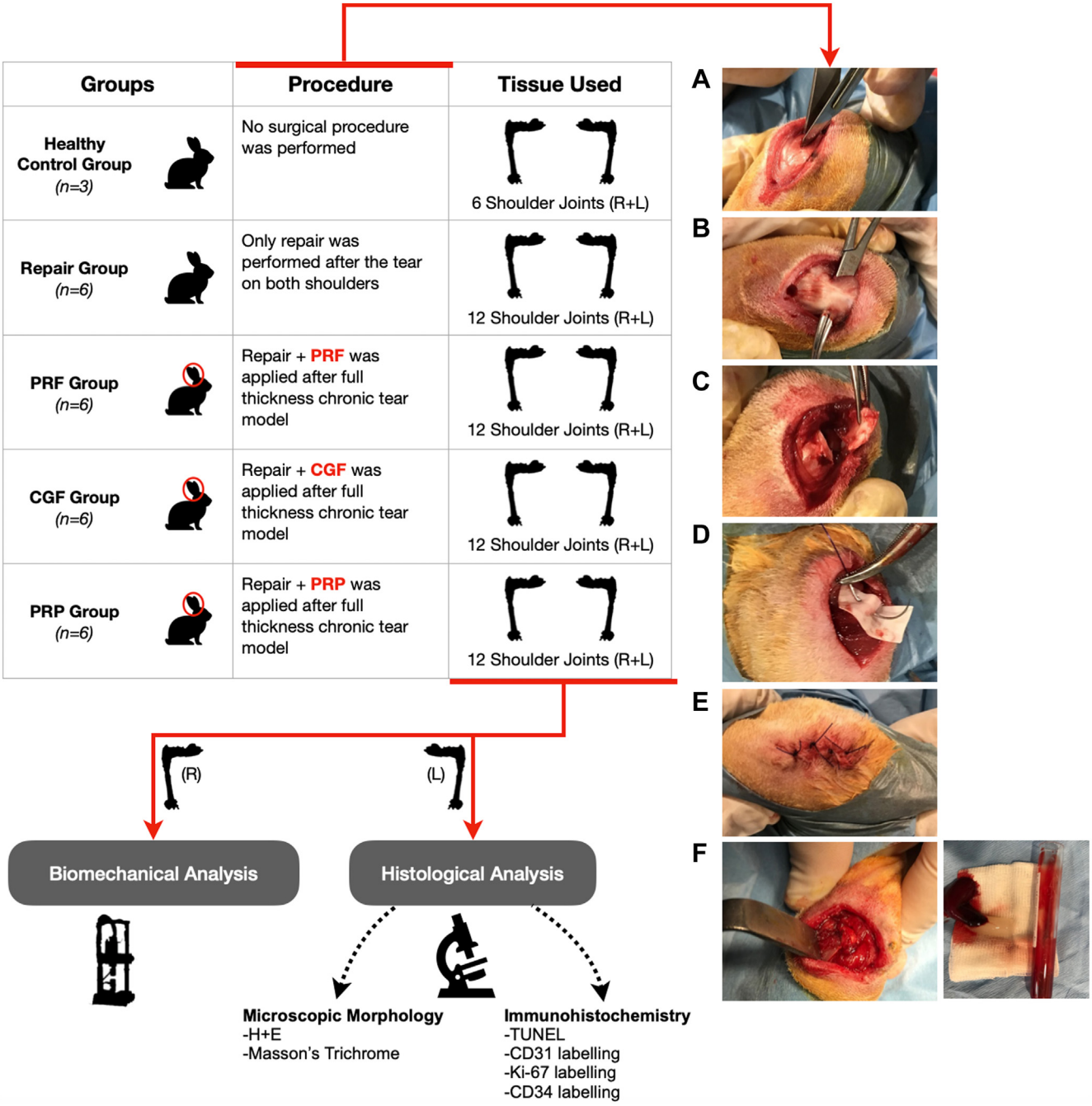


Figure 1 Experimental design of the study. Animals were randomly selected into the healthy control, repair, PRF, CGF, and PRP groups. A summary of each group's procedure is given in the table. Right (R) shoulder joints were used for the biochemical analysis, whereas left (L) shoulder joints were used for the histologic analysis. Surgery performed first with a vertical skin incision with 2 cm. (**A**) Then the deltoid muscle was seen under the skin fascia. (**B**) Through this muscle, the subscapularis muscle and tendon joint were recognized, and (**C**) the muscle was fully cut to get free form. (**D**) The tendon's free edge was fixed with the Penrose drain. (**E**) After that, the deltoid muscle, fascia, and the skin were closed with a permanent Prolene suture. (**F**) The repair of the subscapularis full cut by using the transosseous method and the representative photograph of PRP, CGF, or PRP if given (right and left, respectively). *PRF*, platelet-rich fibrin; *CGF*, concentrated growth factor; *PRP*, platelet-rich plasma; *H+E*, hematoxylin and eosin.

Obtaining and applying PRF, PRP, and CGF

PRF, PRP, and CGF were prepared according to previous studies.[7,27,41] To obtain autologous PRF or PRP, 10 mL of blood was taken from the ear vein of the rabbits into tubes without anticoagulant (for PRF) or sodium citrate tubes (for PRP) before the procedure. For PRF preparation, sample tubes were centrifuged 10 times at 3000 rpm (Nuve NF1200, Turkey). PRF is a second-generation platelet aggregation fibrin-rich gel produced from venous blood by single centrifugation. PRF, a fibrin layer containing platelets and plasma, was thus obtained.[29] For PRP

Table I The content analysis of PRF

	WBC (per μL)	RBC (per μL)	HCT (%)	PLT (per μL)
Whole blood				
PRF (1)	6.43×10^3	4.71×10^6	28.55	209×10^3
PRF (2)	9.06×10^3	5.67×10^6	34.37	326×10^3
Layer				
PRF (1)				627×10^3
ES (1)				0
PRF (2)				1304×10^3
ES (2)				0

PRF, platelet-rich fibrin; *ES*, erythrocyte suspension; *WBC*, white blood cells; *RBC*, red blood cells; *HCT*, hematocrit; *PLT*, platelet.

Table II The content analysis of PRP

	WBC (per μL)	RBC (per μL)	HCT (per μL)	PLT (per μL)
Whole blood				
Sample (1)	10.35×10^3	5.85×10^6	37.99	336×10^3
Sample (2)	9.02×10^3	5.34×10^6	32.34	309×10^3
PRP				
Sample (1)	27.14×10^3	0.43×10^6	3.05	3086×10^3
Sample (2)	7.62×10^3	0.09×10^6	0.60	2057×10^3

PRP, platelet-rich plasma; *WBC*, white blood cells; *RBC*, red blood cells; *HCT*, hematocrit; *PLT*, platelet.

preparation, the sample centrifuged at 1800 rpm for 10 minutes, so the erythrocytes were isolated from the tube. Plasma, thrombocytes, and leukocytes were transferred to another tube in order to centrifuge at 3500 rpm for 15 minutes. After the last step, the lowest layer of the pellet that is 1-2 mL was taken as PRP. Finally, PRP was placed to the articular area of the rabbit model.[15,39] On the other hand, before the preparation of CGF, autologous venous blood was drawn from the ear veins of the rabbits and put into sterile blood tubes without anticoagulant. Ten milliliters of venous blood was collected for each shoulder. These tubes were then immediately centrifuged at 3000 rpm for 12 minutes with a centrifuge device (Medifuge; SilfradentSrl, Sofia, Italy) specially used in CGF preparation. At the end of the centrifugation, the third layer containing the growth factors, stem cells, and leukocytes in the tube and the bottom layer containing the erythrocytes were used in this study.

Approximately 3 mL, 2 mL, and 4 mL was isolated for PRF, PRP, and CGF, respectively, from 10 mL of venous blood of the each animal in order to apply to the animals. The number of platelets was around 3-4 times higher in the PRF samples compared with whole blood, despite the fact that there were no platelets in the erythrocyte suspension, as given in Table I. Besides, PRP included approximately 9 and 6.5 times higher platelet counts for samples 1 and 2, respectively, when compared with whole blood (Table II). Alternatively, CGF had approximately 4.5-5 times higher platelet numbers compared with whole blood. Moreover, 20×10^3/μL platelets were detected for both samples of the erythrocyte suspension of CGF (Table III). The content analysis for PRF, PRP, and CGF is given in Tables I-III, respectively.

All animals except the control group were reoperated 8 weeks after the full-thickness rotator cuff tear model was formed. The Penrose drain was reached and removed via the previous surgical approach. Cuff repair was performed by suturing both shoulders with the transosseous method.[18] Autologous PRF and CGF were obtained and delivered locally to the repair areas on both shoulders of the rabbits except the control group. In order to apply PRF, PRP, and CGF, in the second surgical procedure, the Penrose drain placed in the tendon of the SSC muscle was removed, and the tendon was repaired by suturing with the transosseous technique (3-0 absorbable braided suture [Vicryl; Ethicon]). The PRF, PRP, and CGF materials, which are the subject of our study, were prepared from the blood of each animal as stated above. The concentrates were administered to the suture line immediately after the repair process. Because PRF and CGF were in gel format, they were covered with a forceps as a patch on the repair area. PRP, on the other hand, was injected locally into the suture line with the help of an injector, where it is a liquid-format material. The skin was closed with a 3-0 permanent Prolene suture (Ethicon). A period of 8-week was expected for the recovery process, and animals were rested in the cages.[39]

Killing and tissue obtaining

At the end of the 8-week follow-up period, animals were killed by intracardiac injection of high-dose xylazine hydrochloride and ketamine under general anesthesia. After killing, the humerus and SSC muscles were excised. All other soft tissues and bone tissues were isolated. In the healthy control group, 3 rabbits were used for 6 shoulder joints, 3 tissues were taken for histologic examination, and the other 3 shoulder joint tissues were used for biomechanical examination. In other groups, 6 rabbits and 12 shoulder joint tissues were isolated in each group. Five were reserved for histology and 7 for biomechanical examination. Tissues preserved for histologic examination were fixed in 4% formaldehyde. Routine

Table III The content analysis of CGF

	WBC (per μL)	RBC (per μL)	HCT (%)	PLT (per μL)
Whole blood				
Sample (1)	6.98×10^3	5.44×10^6	32.66	265×10^3
Sample (2)	13.73×10^3	6.45×10^6	39.99	277×10^3
Layer				
CGF (1)				1183.5×10^3
ES (1)				20×10^3
CGF (2)				1375×10^3
ES (2)				20×10^3

CGF, concentrated growth factor; *ES*, erythrocyte suspension; *WBC*, white blood cells; *RBC*, red blood cells; *HCT*, hematocrit; *PLT*, platelet.

paraffin embedding and the sectioning process were performed after the decalcification.

Tissues obtained for biomechanical examination were taken as blocks, preserving the scapula and humerus joint structure and a tendon connection. The system was wrapped in a wet sterile bandage and stored in a deep freezer at −40°C.

Histologic examination

Histochemical stainings

Hematoxylin and eosin (H&E) stains were made on the sections obtained from the experimental groups and evaluated histomorphologically. In addition, Masson triple staining was employed on the sections obtained in order to examine the extracellular matrix. Histomorphological and extracellular matrix evaluation was performed.

Histomorphological scoring was performed under the light microscope (Olympus BX61, Japan). All sections were evaluated according to the modified Watkin's scoring.[35,44,58] The articular area stained with H&E was observed under high magnification (×40). The cellularity and vascularity of both the tendon and its surrounding connective tissue were scored either marked (1), moderate (2), mild (3), or minimal (4). On the contrary, the elongated cells were accepted as fibrocytes in the tendon, and their density was scored as <25% (1), 25%-50% (2), 50%-75% (3), or >75% (4). Their arrangements of those cells were also considered to be scored as a parallel array of cells as <25% (1), 25%-50% (2), 50%-75% (3), or >75% (4). The Masson triple staining was used to score the large-diameter fibers and parallel array fibers. Moreover, tendon-to-bone transitions were scored by means of the bone or collagenous ingrowth and observed fibrocartilage cells in the area as given in Table IV.

Immunohistochmical stainings

In experimental groups, apoptosis was evaluated by the TUNEL (Abcam, UK; Cat# ab206386) method. Cell proliferation was evaluated with Ki67 (Novus Biologicals, Centennial, CO, USA; Cat# NBP2-22112 dilution of 1:200).[13] CD31 for the analysis of neovascularization (Novus Biologicals; Cat# NB100-64796 dilution of 1:100) and CD34 (Novus Biologicals; Cat# NB600-1071 dilution of 1:250) used as a stem cell marker were labeled, and positivity rates in the tissues were evaluated. Immunohistochemistry was applied as the manufacturer's instructions. Mayer's hematoxylin was used for the sections as counterstaining. Immunohistochemical stainings were scored by the double-blind investigator using a ×20 objective under the light microscope as % positive cells in the image in 5 random fields.

Biomechanical examination

Tissues were thawed at a room temperature of 20°C-25°C and prepared for the biomechanical examination. The SSC muscle and humerus complex were placed in a uniaxial biomechanical device at an appropriate angle (MTS Mini Bionix II). The SSC tendon was fixed with a size 5 suture (Ethibond), passing 2 mm intervals from both sides for a total of 5 times, and connected to the sensor in the device. To induce abduction of the joint, a linear pulling force was applied on the humerus perpendicular to the humeral diaphysis and parallel to the scapular plane. According to the test protocol, after 2 minutes of 10 N preload, 60 loading cycles between 5 and 50 N with a frequency of 0.25 Hz were applied. According to the test protocol, after 2 minutes of 10 N preload, 60 loading cycles between 5 and 50 N with a frequency of 0.25 Hz were applied. A sudden decrease in the load-strain curve, fracture of bone tissue, or formation of complete tears in soft tissue was evaluated as a failure.

Killing analysis

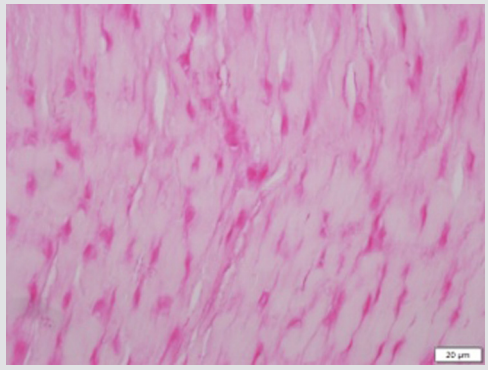
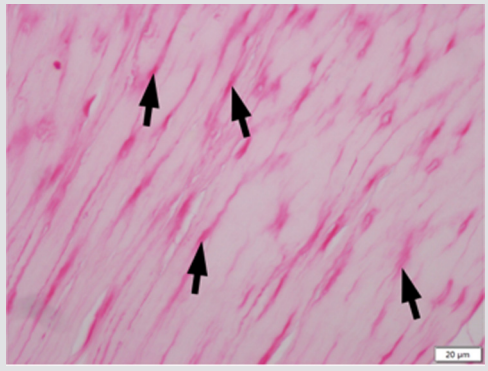
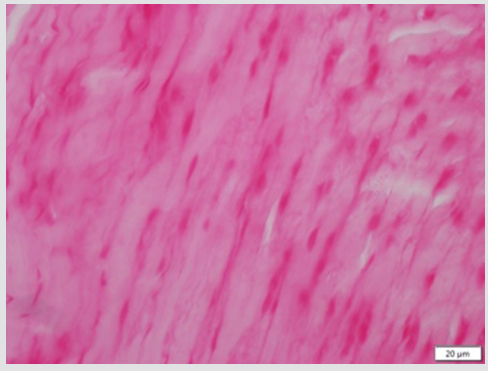
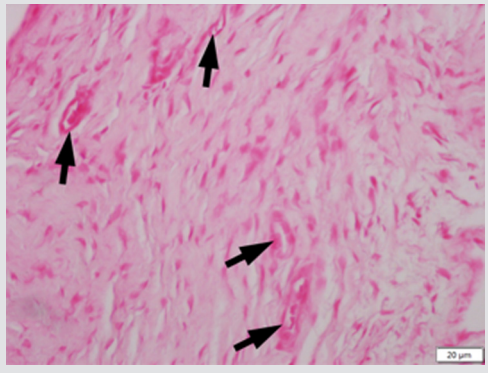
Statistical evaluations were performed via the GraphPad Prism software (version 8.4.3; GraphPad Software, Inc., Boston, MA, USA). While evaluating the histology data, the Kruskal-Wallis analysis of variance was used to compare the groups. In the Kruskal-Wallis analysis of variance, the pairwise comparison of the subgroups was performed using Dunn's test. Two-factor analysis of variance was used to evaluate biomechanical data. In the 2-factor analysis of variance, Dunn's test was used for the pairwise comparison of the subgroups. Armstrong's[2] suggestion was followed for the low sample size; thus, we did not run any correction for multiple comparisons for histologic data. Results are presented as mean (M) ± standard error of mean (SEM), whereas a P value of <.05 was considered significant for all evaluations.

Results

Histologic evaluations

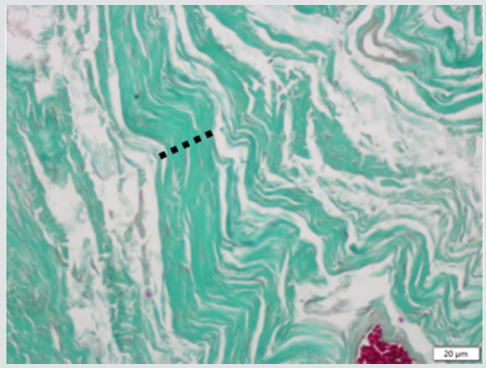
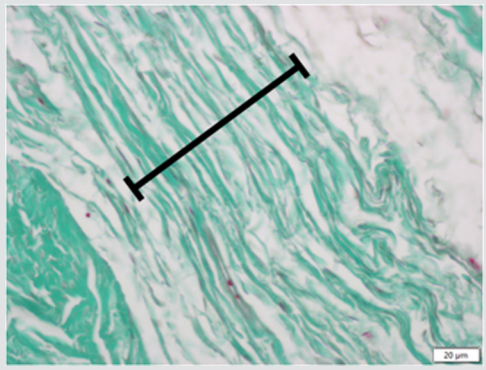
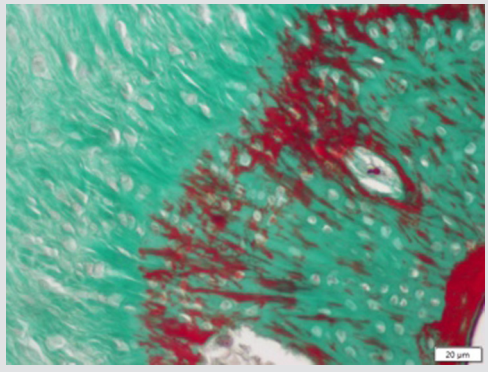
There was a statistically significant difference in large-diameter fibers ($\chi^2(4) = 12.311$, $P = .015$), parallel array of

Table IV Modified Watkin's scoring

Structure	Score	Representative micrograph
Cellularity	Marked (1), moderate (2), mild (3), minimal (4)	
Fibrocytes	<25% (1), 25%-50% (2), 50%-75% (3), >75% (4)	
Parallel array of cells	<25% (1), 25%-50% (2), 50%-75% (3), >75% (4)	
Vascularity	Marked (1), moderate (2), mild (3), minimal (4)	

(*continued on next page*)

Table IV Modified Watkin's scoring (*continued*)

Structure	Score	Representative micrograph
Large diameter fibers	<25% (1), 25%-50% (2), 50%-75% (3), >75% (4)	
Parallel array fibers	<25% (1), 25%-50% (2), 50%-75% (3), >75% (4)	
Tendon-to-bone transition (1-2)	1. Insertion has continuity without bone or collagenous ingrowth (1), insertion has continuity with bone ingrowth but no fibrocartilage cells (2), insertion has continuity with bone ingrowth and fibrocartilage cells but no tidemark (3), and insertion has continuity with bone ingrowth, fibrocartilage cells, and tidemark (4) 2. Mean of collagen continuity, fibrocartilage tissue, and tidemark development: minimal (1), mild (2), moderate (3), marked (4)	

cells ($\chi^2(4) = 15.970$, $P = .003$), parallel array of fibers ($\chi^2(4) = 15.501$, $P = .004$), vascularity ($\chi^2(4) = 13.362$, $P = .010$), cellularity ($\chi^2(4) = 11.876$, $P = .018$), fibrocyte ($\chi^2(4) = 11.079$, $P = .026$), and tendon-to-bone transition (1 and 2) ($\chi^2(4) = 14.012$, $P = .007$). Large-diameter fibers were decreased in all groups compared with the healthy control group. The decrement was statistically significant in the repair (M ± SEM: 1.75 ± 0.48, $P < .01$), PRF (M ± SEM: 2.17 ± 0.17, $P < .01$), and CGF (M ± SEM: 2.25 ± 0.48 $P < .05$) groups compared with the healthy control group (M ± SEM: 4 ± 0) (Fig. 2, *A*).

When the parallel array of cells was scored, the increased score in the repair group (M ± SEM: 3.25 ± 0.48) was statistically higher than the healthy control (M ± SEM: 1.33 ± 0.33) and PRF groups (M ± SEM: 1.33 ± 0.21) ($P < .05$), but there was no

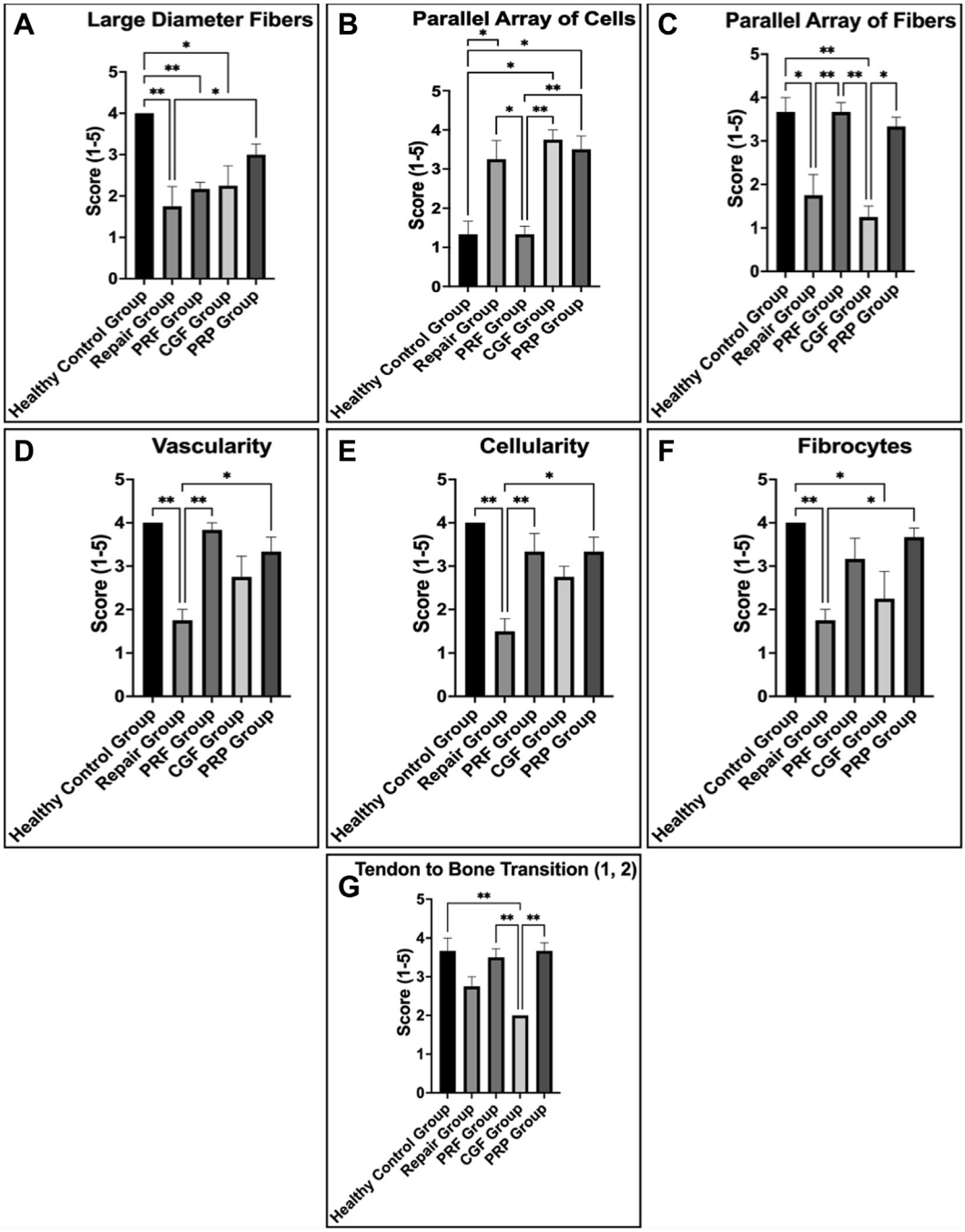


Figure 2 Histologic evaluation of the experimental groups. The graphs represent large diameter fibers (**A**), parallel array of cells (**B**) and fibers (**C**), vascularity (**D**), cellularity (**E**), fibrocytes (**F**), and tendon to bone transition (1,2) (**G**). $*P < .5$, $**P < .01$ according to the Kruskal-Wallis *t* test followed by Dunn's test. *PRF*, platelet-rich fibrin; *CGF*, concentrated growth factor; *PRP*, platelet-rich plasma.

statistical difference between the CGF and repair groups. Conversely, a rise in the score was observed in the CGF (M ± SEM: 3.75 ± 0.25) and PRP groups (M ± SEM: 3.5 ± 0.34). In addition, this increase was found to be statistically significant compared with the healthy control ($P < .05$) and PRF ($P < .01$) groups (Fig. 2, *B*). Moreover, a parallel array of fibers were statistically lower in both repair (M ± SEM: 1.75 ± 0.48, $P < .05$) and CGF (M ± SEM: 1.25 ± 0.25, $P < .01$) groups compared with both healthy control (M ± SEM: 3.67 ± 0.33) and PRF groups (M ± SEM: 3.67 ± 0.21). However, there was no statistical decreased score for the PRF and PRP groups (M ± SEM: 3.33 ± 0.21) compared with the control group (Fig. 2, *C*).

The vascularity in the healthy control (M ± SEM: 4 ± 0, $P < .01$), PRF (M ± SEM: 3.83 ± 0.17, $P < .01$), and PRP (M ± SEM: 3.33 ± 0.33, $P < .05$) groups was statistically

higher than in the repair group (M ± SEM: 1.75 ± 0.25). The increase in vascularity in the CGF group (M ± SEM: 2.75 ± 0.48) was not statistically significant (Fig. 2, *D*).

Parallel to these findings, in terms of cellularity, the scores in the healthy control (M ± SEM: 4 ± 0, $P < .01$), PRF (M ± SEM: 3.33 ± 0.42, $P < .01$), and PRP (M ± SEM: 3.33 ± 0.33, $P < .05$) groups were significantly higher than the repair group (M ± SEM: 1.5 ± 0.29, Fig. 2, *E*).

Although a decreased score was observed in the PRF (M ± SEM: 3.17 ± 0.48) and CGF groups (M ± SEM: 2.25 ± 0.63) in the fibrocyte scoring, which was the lowest in the repair group (M ± SEM: 1.75 ± 0.25), no statistical difference was recorded between the groups compared with the control group (M ± SEM: 4 ± 0). However, the PRP group (M ± SEM: 3.67 ± 0.21) showed a raised score of fibrocytes compared with the repair group ($P < .05$) (Fig. 2, *F*).

In terms of the tendon-to-bone transition (1 and 2), the decreased score in the repair group (M ± SEM: 2.75 ± 0.25) was not statistically significant compared with the healthy control group (M ± SEM: 3.67 ± 0.33). Nevertheless, the CGF group (M ± SEM: 2 ± 0) showed statistical significance compared with the healthy control, PRF (M ± SEM: 3.5 ± 0.22), and PRP groups (M ± SEM: 3.67 ± 0.21, $P < .01$ Fig. 2, *G*).

Finally, when all these values were summed up as described in the Materials and methods section and evaluated as the modified Watkin's score, the scoring in the repair (M ± SEM: 17.25 ± 0.75) and CGF groups (M ± SEM: 19 ± 1.22) exhibited a statistically significant reduction compared with the healthy control group (M ± SEM: 28.33 ± 0.33, $P < .01$). However, the decrease in the PRF (M ± SEM: 24.5 ± 1.36) and PRP (M ± SEM: 27.5 ± 0.89) groups did not differ statistically compared with the healthy control group, and there was a statistical significance in the difference between the repair groups ($P < .05$ and $P < .01$, respectively, Fig. 3).

Immunohistochemical results

Ki67 immunohistochemical results

Ki67 (+) cells were observed in all groups, especially in the bone tendon attachment region, bone marrow, and connective tissue. In addition, in the healthy control, PRF, and PRP groups, Ki67 (+) cells were recorded in large numbers in the tendon attachment region. In the PRF group, Ki67 (+) cells were also documented in the periosteum and the attachment region of the tendon, in addition to other regions. Ki67 (+) cells were not captured in large numbers in the CGF group (Fig. 4).

CD 34 immunohistochemical results

CD34 (+) cells were noted at the tendon-bone junction in all groups, whereas the cells were more abundant within the connective tissue in the repair group. In the PRF group, unlike the other groups, CD34 (+) cells were recognized in the tendon tissue (Fig. 5).

CD 31 immunohistochemical results

Positive cells were noticed in very rare areas at the tendon-bone junction in all groups. CD31 (+) cells were found in rarer areas compared with other immunopositive stainings. CD 31 (+) cells were mostly detected in connective tissue (Fig. 6).

TUNEL results

TUNEL (+) cells were scarcely observed in the control group. TUNEL (+) cells were observed in the connective tissue and tendon damage areas, especially in the repair group. Positively labeled cells were documented in rare areas in other groups. There was a statistically significant difference in TUNEL (+) cells ($\chi^2(4) = 12.791$, $P = .012$). TUNEL (+) cells were recorded to have the highest rate in the repair group (M ± SEM: 38.25% ± 7.74), whereas this rate in the healthy control group was 9.66% ± 2.17. This increase in the repair group was statistically significant in the healthy control group ($P < .01$). Although the TUNEL (+) cells in the PRF group (M ± SEM: 12.37% ± 1.82) were statistically decreased ($P < .01$) compared with the repair group alone, the value of the CGF and PRP groups (M ± SEM: 17.36% ± 2 and M ± SEM: 19.51% ± 4.33) was not statistically significant with any group (Fig. 7).

Biomechanical results

For biomechanical tests, 7 shoulders from the experimental groups (CGF, PRF, PRP, and repair) and 3 shoulders from the healthy control group were included in the experiment. The strength in the region was measured by applying force to the tendon-bone connection. Tendon-bone rupture strengths were determined, and the treatment groups were compared with the healthy control group in terms of strength. Although the PRF, PRP, and CGF groups showed a higher stiffness compared with the other groups, only the CGF group demonstrated a statistical difference compared with the repair group ($P < .05$). Failure displacement was at the highest level in the repair group, whereas the PRF and CGF groups revealed a lower level when compared with the control group with no statistical significance. The resistance of the tendon-bone connection in the CGF group was better than the PRF group, which was contrary to the histology data (Fig. 8).

Discussion

Rotator cuff tears can originate from various factors such as trauma, repetitive microtrauma, hypovascularity, degeneration, and subacromial impingement syndrome.[16] The inflammation in the repair of rotator cuff tears has a pivotal role in the tissue healing process. During the early stages of tendon healing, inflammatory response encompasses cell migration and

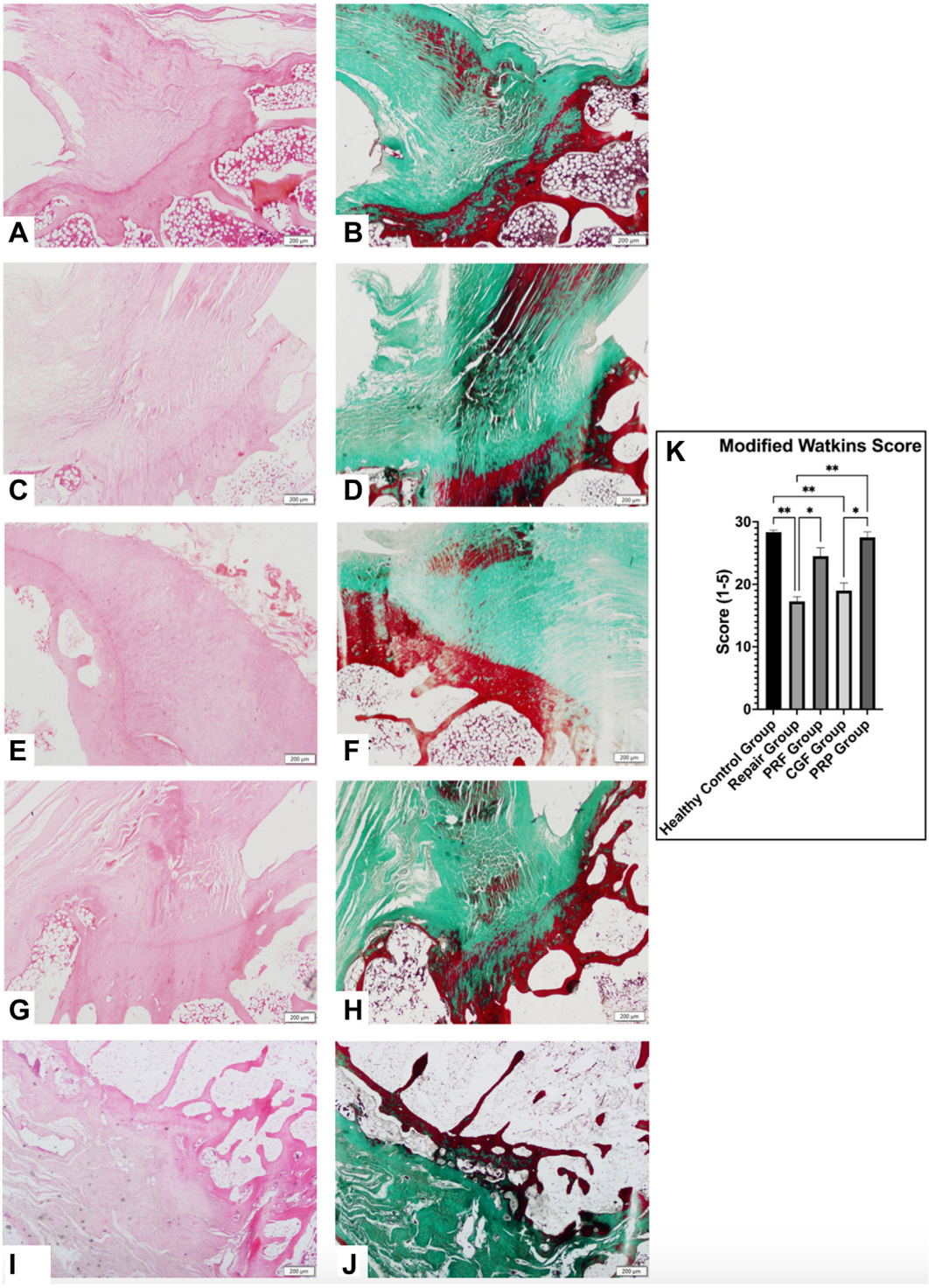


Figure 3 Representative microphotographs of the histologic sections from the (**A** and **B**) healthy control, (**C** and **D**) repair, (**E** and **F**) PRF, (**G** and **H**) CGF, and (**I** and **J**) PRP groups. (**K**) The graph for the modified Watkin's score. $*P < .5$, $**P < .01$ according to the Kruskal-Wallis *t* test followed by Dunn's test. *PRF*, platelet-rich fibrin; *CGF*, concentrated growth factor; *PRP*, platelet-rich plasma.

maturation with a rapid proliferation in fibroblasts. Moreover, new collagen fibers are formed and the cell/matrix ratio undergoes a transformation.[36] The most common complication after surgical treatment is recurrent tears due to inadequate repair or processes such as inflammation that develops after surgery.[19,38] Although recent surgical techniques have lowered the risk of recurrence, they have also prompted the exploration of alternative approaches aimed at fortifying the collagen structure and enhancing biological processes. Among the alternative applications, the most recent approaches are

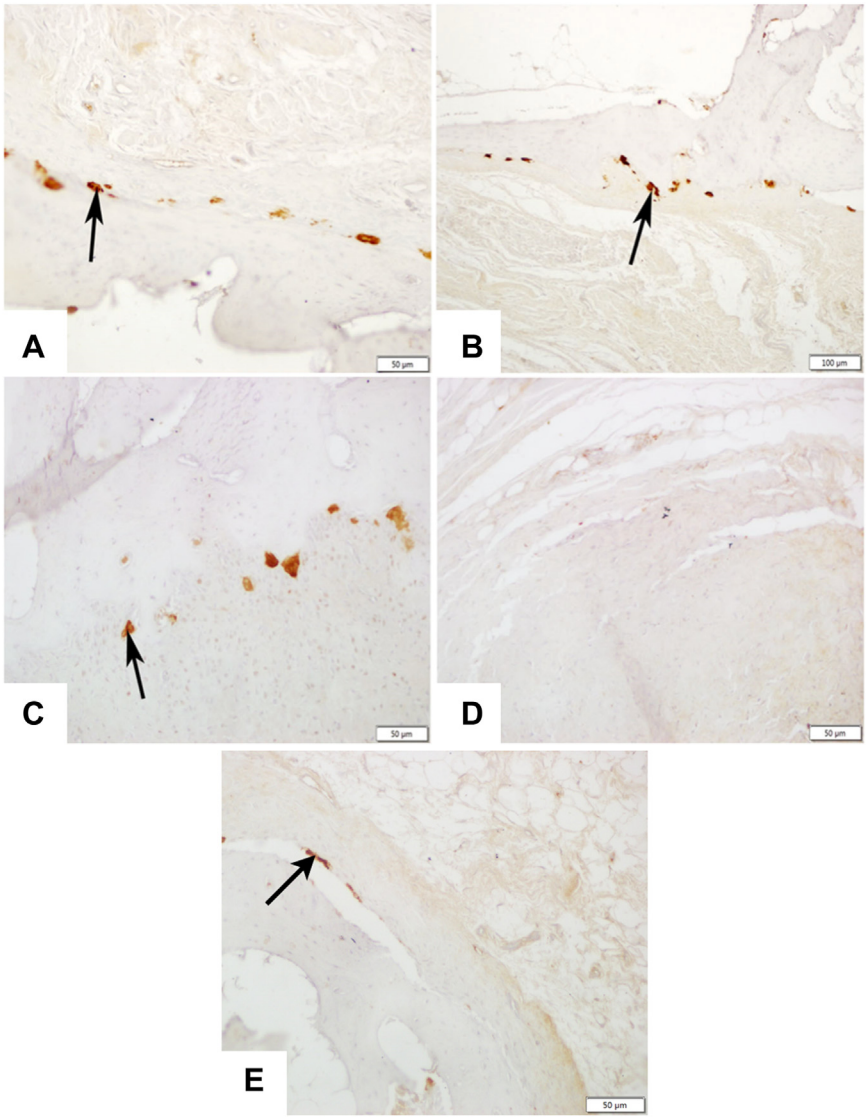


Figure 4 Representative micrographs for the immunohistochemistry of the (**A**) healthy control, (**B**) repair, (**C**) platelet-rich fibrin, (**D**) concentrated growth factor, and (**E**) platelet-rich plasma groups. The ⟶ indicate the Ki67 positive cells.

different interfaces of blood such as PRP, PRF, or CGF obtained by diverse centrifugation techniques.

Rabbit is frequently used as a model organism in rotator cuff pathology.[49,56] Supraspinatus and infraspinatus tendons are preferred in the research of repair models for rabbits. Nevertheless, further studies also reported that the SSC tendon may be a better approximation of human pathology given that it passes under an enclosed arch and fatty accumulation is prominent.[11] Moreover, the SSC tendon is frequently preferred because it has the largest tendon among the rotator cuff tendons. In addition, the most ruptured supraspinatus tendon in human is the anatomically adjacent tendon to the SSC tendon.[23]

With the limited data about PRP, PRF, and CGF comparative application in rotator cuff tear, we evaluated and compared the application of PRP, PRF, and CGF in the repair process of the rotator cuff tear model with SSC in rabbits in terms of histopathological healing, cell death, neovascularization, stem cell potential, and proliferation as well as biomechanical evaluation.

Pulatkan et al[44] performed the rotator cuff rabbit model using the modified Watkin's score to compare repair and in situ repair. They showed that the in situ repair group score is the lowest compared with repair and control. Another study investigating PRP and ozone therapy on the rotator cuff rabbit model exhibited a more favorable outcome according to histopathologic and biomechanical evaluation with collagen fiber continuity and orientation.[24] Chung et al[7] reported a rotator cuff rabbit experiment applying with PRP or without porcine dermal collagen graft augmentation on tendon to bone healing, revealing that PRP application led to a more beneficial treatment in

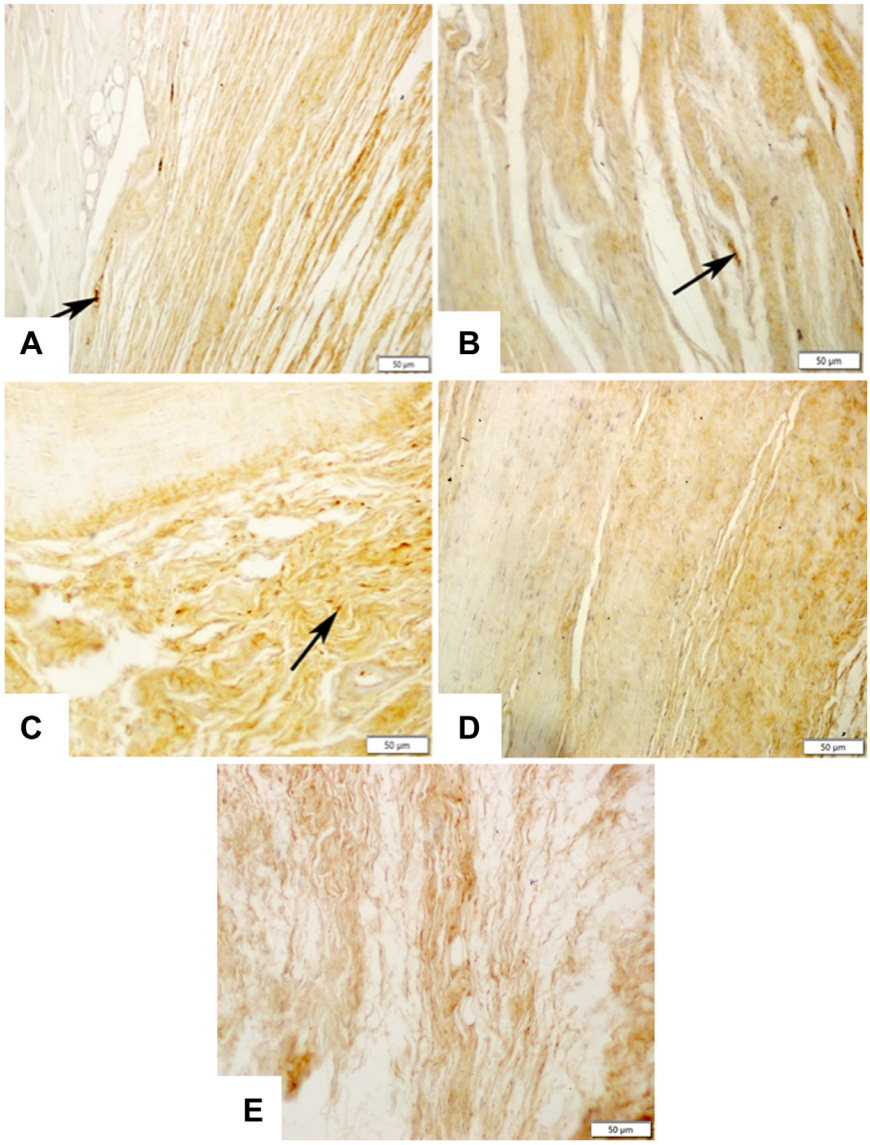


Figure 5 Representative micrographs for the immunohistochemistry of the (**A**) healthy control, (**B**) repair, (**C**) platelet-rich fibrin, (**D**) concentrated growth factor, and (**E**) platelet-rich plasma groups. The ⟶ indicate the CD34 positive cells.

terms of collagen fiber continuity and orientation histopathologically. Furthermore, all PRP treatments had better load-to-failure results according to biomechanical analysis.[7] PRF application may promote the healing process histopathologically in a variety of cases such as cartilage repair, rotator cuff surgery, and anterior cruciate ligament surgery.[21] In a study evaluating the efficacy of PRF in a rabbit model, PRF was effective in accelerating the healing of Achilles tendon injury. In addition, when the healed tissues in the PRF group were examined histologically, more efficiently organized collagen fibers, less vascularity, and low cartilage formation were detected.[54] In another experimental study on rabbits, using a PRF patch contributes to intratunnel tendon-bone healing.[55] Uno et al[51] had a comparative study about PRP, PRF, and bone marrow–derived PRF in a degenerative rotator cuff rabbit model, presenting that bone marrow–derived PRF enhanced and more effective than others in tendon-bone healing histopathologically via VEGF regarded vasculogenesis.

CGF application may enhance bone graft implantation according to previous studies.[46,47,59] Moreover, Arican et al[1] and Yilmaz et al[57] demonstrated that CGF had time-dependent bone healing effects supported by histologic analysis. However, there is no current study on the tendon-bone healing effects of CGF.

In our study, Watkin's scores of the PRP and PRF groups reached the healthy control group, unlike the CGF and repair group. Moreover, PRP showed a slightly higher score compared with the PRF group. When the subscores

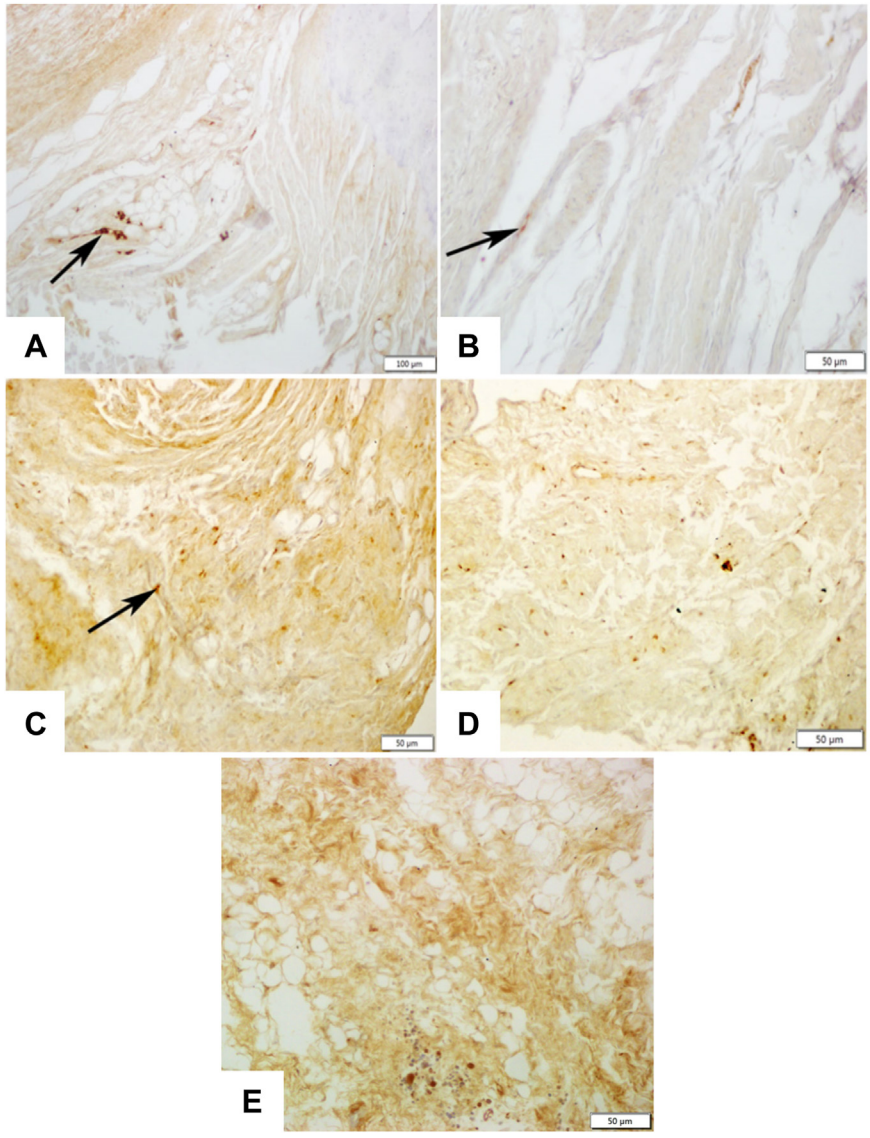


Figure 6 Representative micrographs for the immunohistochemistry of the (**A**) healthy control, (**B**) repair, (**C**) platelet-rich fibrin, (**D**) concentrated growth factor, and (**E**) platelet-rich plasma groups. The ⟶ indicate the CD31 positive cells.

of Watkin were evaluated, vascularity and cellularity were higher in the PRF, PRP, and CGF groups compared with the repair group, and there was no statistical difference compared with the control group. Parallel arrays of fibers, fibrocytes, and tendon-bone transformation lacked statistical significance in the PRF and PRP groups compared with the control group. Insignificance was observed in the PRP group for the large diameter of fibers and in the PRF group for a parallel array of cells compared with the control group. No statistical difference was recorded between the groups according to our biomechanical results.

Carr et al[5] performed a study including 60 randomly selected patients with rotator cuff tendinopathy. Arthroscopic acromioplasty drastically improved long-term clinical results up to 2 years. However, no contribution of PRP was detected along with these results. PRP also altered the tendon's histology in terms of reduced cellularity and vascularity as well as increased levels of apoptosis.[5]

Thrombocytes have an antiapoptotic effect and regulate the balance of cell survival.[9] When CGF treatments were administered to see the potential contribution to the bone defect, the thickness of the membrane and CD31 (+) cells were documented higher in a time-dependent manner with the CGF-applied group. Moreover, CGF also increased the Ki67 (+) and stem cells.[57]

According to our TUNEL and Ki67 results, the PRF-applied group had the lowest number of apoptotic cells among treatment groups compared with the repair group. In addition, the PRP, PRF, and CGF groups were not

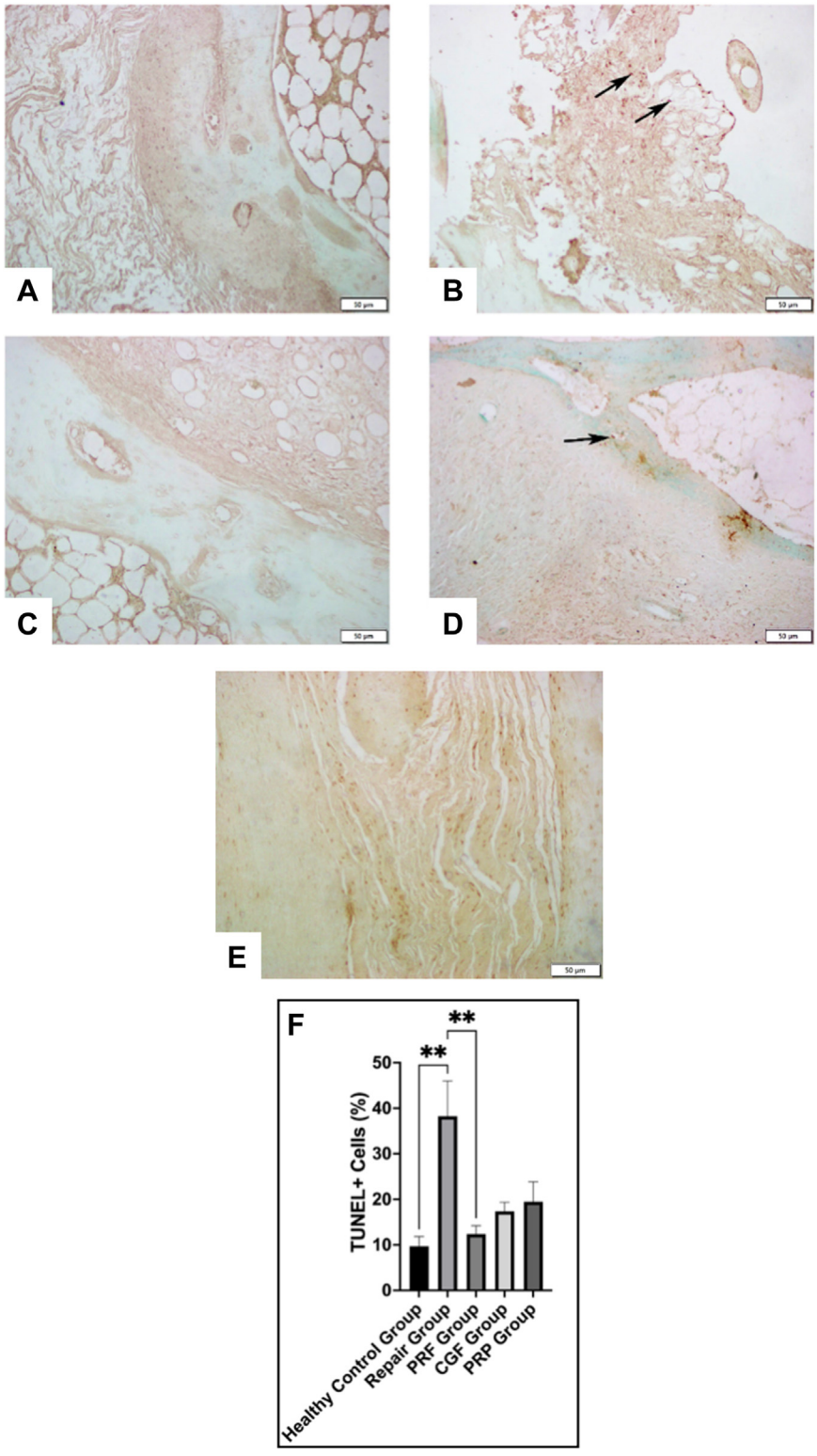


Figure 7 Representative micrographs for the immunohistochemistry of the (**A**) healthy control, (**B**) repair, (**C**) PRF, (**D**) CGF, and (**E**) PRP groups. The ⟶ indicate the TUNEL positive cells. (**F**) $**P < .5$ according to the Kruskal-Wallis *t* test followed by Dunn's test. *PRF*, platelet-rich fibrin; *CGF*, concentrated growth factor; *PRP*, platelet-rich plasma.

statistically significant in the healthy control group. Ki67 (+) proliferative cells were recognized especially in the bone tendon attachment region, bone marrow, and connective tissue in all groups, but the cells were more numerous in the PRF and PRP groups. Stem cell marker CD34 (+) cells were noticed in the tendon-bone junction in

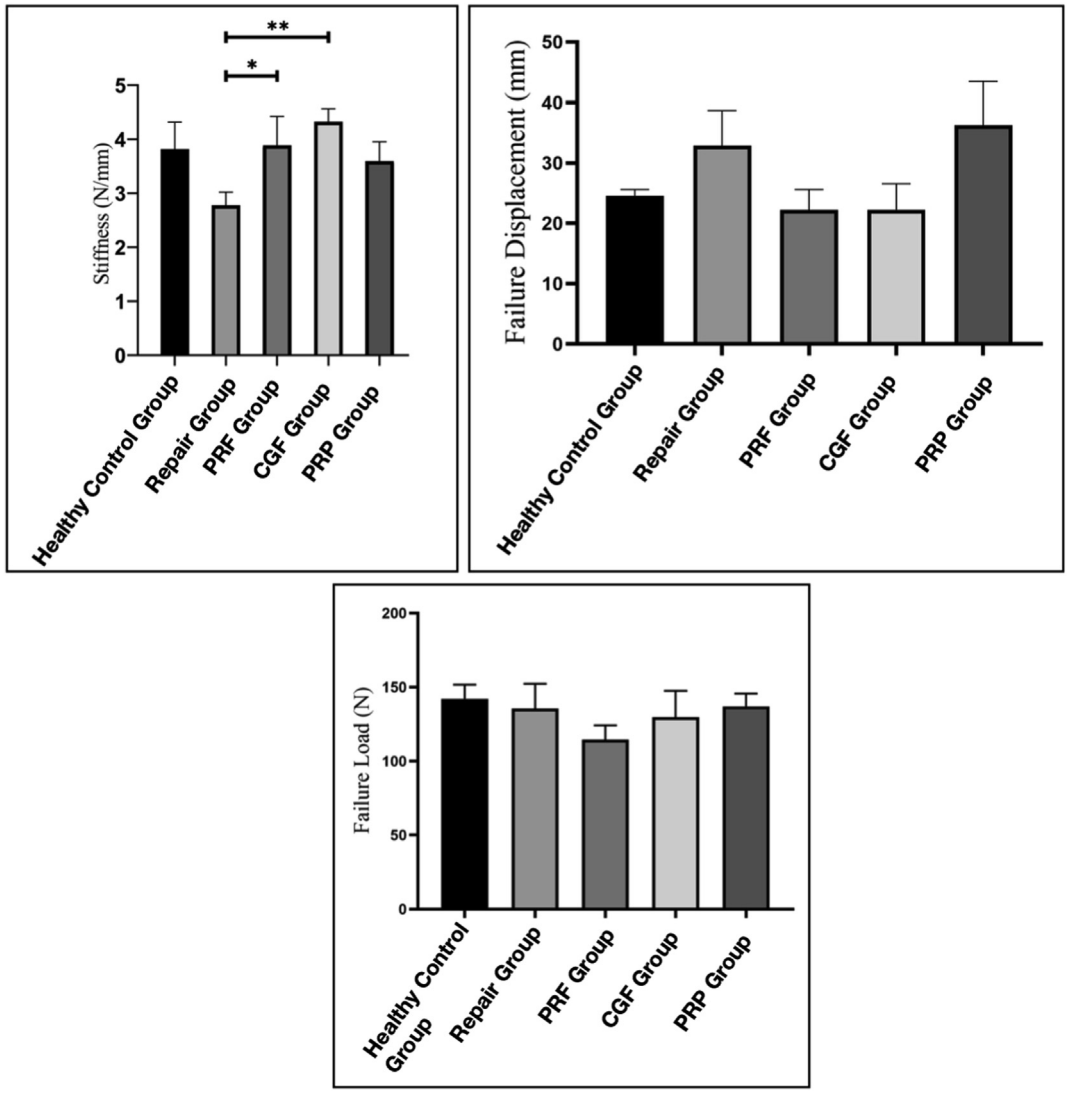


Figure 8 Biomechanical test for stiffness, failure displacement, and failure load. $*P < .5$, $**P < .01$ according to the Kruskal-Wallis *t* test followed by Dunn's test. *PRF*, platelet-rich fibrin; *CGF*, concentrated growth factor; *PRP*, platelet-rich plasma.

all groups. Moreover, stem cells were found in the tendon only in the PRF group. CD31 (+) cells indicating vascularization were noted in tendon-bone junction points and were localized in a rare area in all groups.

PRP contains a variety of blood cells such as platelets, white blood, and red blood cells as well as plasma and fibrin similar to our results compared with the literature. There are also several growth factors such as VEGF, insulin-like growth factor-1, platelet-derived growth factor-AB, and TGF-β1 in PRP content.[26] On the other hand, PRF is composed of a single fibrin membrane containing all the constituents of blood with the incorporation of platelets, leukocytes, cytokines, and circulating stem cells.[45] Also, CGF can influence the synthesis of growth factors such as VEGF, TGF-β1, BMP-2, metalloproteinases, and cells with its ingredients.[48]

A discrepancy in the potential impacts of PRP was evident in a systematic review examining the biological efficacy of these compositions in the rotator cuff and other bone-tendon healing models.[10] Our study, with 3 different compositions in rotator cuff tears, demonstrated that PRF and PRP applications had an enhanced histologic healing effect when compared with CGF. In the comparative analysis of PRF and PRP, PRF exhibited superior parallel arrays of cells, whereas PRP showed a higher score for large-diameter fibers. Consequently, no clear superiority of PRF over PRP, or vice versa, was evident based on the findings.

Conclusion

A distinct discussion was conducted concerning the application of PRP, PRF, and CGF in the treatment of rotator cuff injuries, encompassing various aspects such

as histopathology, cell death, neovascularization, proliferation, presence of stem cells, and biomechanical evaluation. All treatment groups were more effective than the repair group in terms of apoptosis, proliferation, and presence of stem cells. As a consequence, PRP, PRF, and CGF contributed to the healing process, but the contribution was more evident in PRF and PRP than CGF in a histopathologic manner.

Disclaimers:

Funding: This work was supported by the Scientific Research Projects Coordination Unit of Bezmialem Vakif University (Project no. 20200908). This study was also supported by Istanbul Medipol University, Scientific Research Projects Commission (Project no. 2021/12).
Conflicts of interest: The authors, their immediate families, and any research foundation with which they are affiliated have not received any financial payments or other benefits from any commercial entity related to the subject of this article.

References

1. Arıcan G, Özmeriç A, Fırat A, Kaymaz F, Ocak M, Çelik HH, et al. Micro-ct findings of concentrated growth factors (cgf) on bone healing in masquelet's technique-an experimental study in rabbits. Arch Orthop Trauma Surg 2022;142:83-90. https://doi.org/10.1007/S00402-020-03596-Z
2. Armstrong RA. When to use the Bonferroni correction. Ophthalmic Physiol Opt 2014;34:502-8. https://doi.org/10.1111/opo.12131
3. Bilsel K, Yildiz F, Kapicioglu M, Uzer G, Elmadag M, Pulatkan A, et al. Efficacy of bone marrow-stimulating technique in rotator cuff repair. J Shoulder Elbow Surg 2017;26:1360-6. https://doi.org/10.1016/J.JSE.2017.02.014
4. Bishop J, Klepps S, Lo IK, Bird J, Gladstone JN, Flatow EL. Cuff integrity after arthroscopic versus open rotator cuff repair: a prospective study. J Shoulder Elbow Surg 2006;15:290-9. https://doi.org/10.1016/J.JSE.2005.09.017
5. Carr AJ, Murphy R, Dakin SG, Rombach INES, Wheway KIM, Watkins B, et al. Platelet-rich plasma injection with arthroscopic acromioplasty for chronic rotator cuff tendinopathy: a randomized controlled trial. Am J Sports Med 2015;43:2891-7. https://doi.org/10.1177/0363546515608485
6. Chen X, Wang J, Yu L, Zhou J, Zheng D, Zhang B. Effect of concentrated growth factor (CGF) on the promotion of osteogenesis in bone marrow stromal cells (BMSC) in vivo. Sci Rep 2018;8:5876. https://doi.org/10.1038/S41598-018-24364-5
7. Chung SW, Song BW, Kim YH, Park KU, Oh JH. Effect of platelet-rich plasma and porcine dermal collagen graft augmentation for rotator cuff healing in a rabbit model. Am J Sports Med 2013;41:2909-18. https://doi.org/10.1177/0363546513503810
8. Clark RAF. Fibrin and wound healing. Ann N Y Acad Sci 2001;936:355-67.
9. Crisci A, De Crescenzo U, Crisci M. Platelet-rich concentrates (L-PRF, PRP) in tissue regeneration: control of apoptosis and interactions with regenerative cells. J Clin Mol Med 2018;1:1000116. https://doi.org/10.15761/JCMM.1000116
10. DeClercq MG, Fiorentino AM, Lengel HA, Ruzbarsky JJ, Robinson SK, Oberlohr VT, et al. Systematic review of platelet-rich plasma for rotator cuff repair: are we adhering to the minimum information for studies evaluating biologics in orthopaedics? Orthop J Sports Med 2021;9:23259671211041971. https://doi.org/10.1177/23259671211041971
11. Deprés-tremblay G, Chevrier A, Snow M, Hurtig MB, Rodeo S, Buschmann MD. Rotator cuff repair: a review of surgical techniques, animal models, and new technologies under development. J Shoulder Elbow Surg 2016;25:2078-85. https://doi.org/10.1016/J.JSE.2016.06.009
12. Dolkart O, Chechik O, Zarfati Y, Brosh T, Alhajajra F, Maman E. A single dose of platelet-rich plasma improves the organization and strength of a surgically repaired rotator cuff tendon in rats. Arch Orthop Trauma Surg 2014;134:1271-7. https://doi.org/10.1007/S00402-014-2026-4
13. Dzulkifli FA, Mashor MY, Jaafar H. An overview of recent counting methods for Ki67 IHC staining. J Biomed Clin Sci 2018;3:10-7.
14. Edelstein L, Thomas SJ, Soslowsky L. Rotator cuff tears: what have we learned from animal models? J Musculoskelet Neuronal Interact 2011;11:150-62.
15. Everts PAM, Knape JTA, Weibrich G, Schönberger JPAM, Hoffmann J, Overdevest EP, et al. Platelet-rich plasma and platelet gel: a review. J Extra Corpor Technol 2006;38:174-87.
16. Fukuda H. The management of partial-thickness tears of the rotator cuff. J Bone Joint Surg Br 2003;85:3-11. https://doi.org/10.1302/0301-620X.85B1.13846
17. Galatz LM, Sandell LJ, Rothermich SY, Das R, Mastny A, Havlioglu N, et al. Characteristics of the rat supraspinatus tendon during tendon-to-bone healing after acute injury. J Orthop Res 2006;24:541-50. https://doi.org/10.1002/JOR.20067
18. Garofalo R, Castagna A, Borroni M, Krishnan SG. Arthroscopic transosseous (anchorless) rotator cuff repair. Knee Surg Sports Traumatol Arthrosc 2012;20:1031-5. https://doi.org/10.1007/S00167-011-1725-4
19. Gazielly DF, Gleyze P, Montagnon C. Functional and anatomical results after rotator cuff repair. Clin Orthop Relat Res 1994:43-53.
20. Getz CL, Buzzell JE, Krishnan SG. Shoulder instability and rotator cuff tears. Orthop Knowl Update 2011;1:299-315.
21. Grecu AF, Reclaru L, Ardelean LC, Nica O, Ciucă EM, Ciurea ME. Platelet-rich fibrin and its emerging therapeutic benefits for musculoskeletal injury treatment. Medicina (Kaunas) 2019;55:141. https://doi.org/10.3390/MEDICINA55050141
22. Gulotta LV, Kovacevic D, Ehteshami JR, Dagher E, Packer JD, Rodeo SA. Application of bone marrow-derived mesenchymal stem cells in a rotator cuff repair model. Am J Sports Med 2009;37:2126-33. https://doi.org/10.1177/0363546509339582
23. Gupta R, Lee TQ. Contributions of the different rabbit models to our understanding of rotator cuff pathology. J Shoulder Elbow Surg 2007;16(5 Suppl):S149-57. https://doi.org/10.1016/J.JSE.2007.05.002
24. Gurger M, Once G, Yilmaz E, Demir S, Calik I, Say Y, et al. The effect of the platelet-rich plasma and ozone therapy on tendon-to-bone healing in the rabbit rotator cuff repair model. J Orthop Surg Res 2021;16:202. https://doi.org/10.1186/S13018-021-02320-W
25. Hermans J, Luime JJ, Meuffels DE, Reijman M, Simel DL, Bierma-Zeinstra SMA. Does this patient with shoulder pain have rotator cuff disease? The rational clinical examination systematic review. JAMA 2013;310:837-47. https://doi.org/10.1001/JAMA.2013.276187
26. Kaushik A, Kumaran M. Platelet-rich plasma: the journey so far! Indian Dermatol Online J 2020;11:685-92. https://doi.org/10.4103/IDOJ.IDOJ_369_19
27. Kazemi D, Fakhrjou A, Mirzazadeh Dizaji V, Khanzadeh Alishahi M. Effect of autologous platelet rich fibrin on the healing of experimental

articular cartilage defects of the knee in an animal model. Biomed Res Int 2014;2014:486436. https://doi.org/10.1155/2014/486436
28. Kijima H, Minagawa H, Nishi T, Kikuchi K, Shimada Y. Long-term follow-up of cases of rotator cuff tear treated conservatively. J Shoulder Elbow Surg 2012;21:491-4. https://doi.org/10.1016/J.JSE.2011.10.012
29. Kim KH, Brunel D, Gohier A, Sacco L, Châtelet M, Cojocaru CS. Cup-stacked carbon nanotube schottky diodes for photovoltaics and photodetectors. Adv Mater 2014;26:4363-9. https://doi.org/10.1002/ADMA.201400775
30. Kim TH, Kim SH, Sádor GK, Kim YD. Comparison of platelet-rich plasma (PRP), platelet-rich fibrin (PRF), and concentrated growth factor (CGF) in rabbit-skull defect healing. Arch Oral Biol 2014;59:550-8. https://doi.org/10.1016/J.ARCHORALBIO.2014.02.004
31. Kobayashi M, Itoi E, Minagawa H, Miyakoshi N, Takahashi S, Tuoheti Y, et al. Expression of growth factors in the early phase of supraspinatus tendon healing in rabbits. J Shoulder Elbow Surg 2006;15:371-7. https://doi.org/10.1016/J.JSE.2005.09.003
32. Kovacevic D, Rodeo SA. Biological augmentation of rotator cuff tendon repair. Clin Orthop Relat Res 2008;466:622-33. https://doi.org/10.1007/S11999-007-0112-4
33. Lim JK, Hui J, Li L, Thambyah A, Goh J, Lee EH. Enhancement of tendon graft osteointegration using mesenchymal stem cells in a rabbit model of anterior cruciate ligament reconstruction. Arthroscopy 2004;20:899-910. https://doi.org/10.1016/S0749-8063(04)00653-X
34. Lopez-Vidriero E, Goulding KA, Simon DA, Sanchez M, Johnson DH. The use of platelet-rich plasma in arthroscopy and sports medicine: optimizing the healing environment. Arthroscopy 2010;26:269-78. https://doi.org/10.1016/J.ARTHRO.2009.11.015
35. Loppini M, Longo U, Niccoli G, Khan W, Maffulli N, Denaro V. Histopathological scores for tissue-engineered, repaired and degenerated tendon: a systematic review of the literature. Curr Stem Cell Res Ther 2015;10:43-55. https://doi.org/10.2174/1574888X09666140710110723
36. Lui PPY, Cheuk YC, Hung LK, Fu SC, Chan KM. Increased apoptosis at the late stage of tendon healing. Wound Repair Regen 2007;15:702-7. https://doi.org/10.1111/J.1524-475X.2007.00276.X
37. Maman E, Harris C, White L, Tomlinson G, Shashank M, Boynton E. Outcome of nonoperative treatment of symptomatic rotator cuff tears monitored by magnetic resonance imaging. J Bone Joint Surg Am 2009;91:1898-906. https://doi.org/10.2106/JBJS.G.01335
38. Mansat P, Cofield RH, Kersten TE, Rowland CM. Complications of rotator cuff repair. Orthop Clin North Am 1997;28:205-13.
39. Masuki H, Okudera T, Watanebe T, Suzuki M, Nishiyama K, Okudera H, et al. Growth factor and pro-inflammatory cytokine contents in platelet-rich plasma (PRP), plasma rich in growth factors (PRGF), advanced platelet-rich fibrin (A-PRF), and concentrated growth factors (CGF). Int J Implant Dent 2016;2:19. https://doi.org/10.1186/S40729-016-0052-4
40. Matava MJ, Purcell DB, Rudzki JR. Partial-thickness rotator cuff tears. Am J Sports Med 2005;33:1405-17. https://doi.org/10.1177/0363546505280213
41. Mourad SI, Al-Dubai SA, Elsayed SA, El-Zehary RR. Efficacy of platelet-rich fibrin and tacrolimus on facial nerve regeneration: an animal study. Int J Oral Maxillofac Surg 2022;51:279-87. https://doi.org/10.1016/J.IJOM.2021.05.016
42. Nazarian LN, Jacobson JA, Benson CB, Bancroft LW, Bedi A, McShane JM, et al. Imaging algorithms for evaluating suspected rotator cuff disease: Society of Radiologists in Ultrasound consensus conference statement. Radiology 2013;267:589-95. https://doi.org/10.1148/RADIOL.13121947
43. Piper CC, Hughes AJ, Ma Y, Wang H, Neviaser AS. Operative versus nonoperative treatment for the management of full-thickness rotator cuff tears: a systematic review and meta-analysis. J Shoulder Elbow Surg 2018;27:572-6. https://doi.org/10.1016/J.JSE.2017.09.032
44. Pulatkan A, Anwar W, Ayık O, Bozdag E, Yildirim AN, Kapicioglu M, et al. Tear completion versus in situ repair for 50% partial-thickness bursal-side rotator cuff tears: a biomechanical and histological study in an animal model. Am J Sports Med 2020;48:1818-25. https://doi.org/10.1177/0363546520909854
45. Saluja H, Dehane V, Mahindra U. Platelet-rich fibrin: a second generation platelet concentrate and a new friend of oral and maxillofacial surgeons. Ann Maxillofac Surg 2011;1:53-7. https://doi.org/10.4103/2231-0746.83158
46. Sohn D, Moon J, Park J, Jung H. The use of concentrated growth factors (CGF) for sinus augmentation. J Oral Implantol 2009;38:25-38.
47. Sohn DS, Heo JU, Kwak DH, Kim DE, Kim JM, Moon JW, et al. Bone regeneration in the maxillary sinus using an autologous fibrin-rich block with concentrated growth factors alone. Implant Dent 2011;20:389-95. https://doi.org/10.1097/ID.0B013E31822F7A70
48. Stanca E, Calabriso N, Giannotti L, Nitti P, Damiano F, Stanca BDC, et al. Analysis of CGF biomolecules, structure and cell population: characterization of the stemness features of CGF cells and osteogenic potential. Int J Mol Sci 2021;22:8867. https://doi.org/10.3390/IJMS22168867
49. Taniguchi N, Suenaga N, Oizumi N, Miyoshi N, Yamaguchi H, Inoue K, et al. Bone marrow stimulation at the footprint of arthroscopic surface-holding repair advances cuff repair integrity. J Shoulder Elbow Surg 2015;24:860-6. https://doi.org/10.1016/J.JSE.2014.09.031
50. Tashjian RZ, Hollins AM, Kim HM, Teefey SA, Middleton WD, Steger-May K, et al. Factors affecting healing rates after arthroscopic double-row rotator cuff repair. Am J Sports Med 2010;38:2435-42. https://doi.org/10.1177/0363546510382835
51. Uno T, Maruyama M, Satake H, Takakubo Y, Toyono S, Xing L, et al. Effectiveness of bone marrow–derived platelet-rich fibrin on rotator cuff healing in a rabbit degenerative model. Am J Sports Med 2022;50:3341-54. https://doi.org/10.1177/03635465221116084
52. Wang HN, Rong X, Yang LM, Hua WZ, Ni GX. Advances in stem cell therapies for rotator cuff injuries. Front Bioeng Biotechnol 2022;10:866195. https://doi.org/10.3389/FBIOE.2022.866195/BIBTEX
53. Wang C, Xu M, Guo W, Wang Y, Zhao S, Zhong L. Clinical efficacy and safety of platelet-rich plasma in arthroscopic full-thickness rotator cuff repair: a meta-analysis. PLoS One 2019;14:e0220392. https://doi.org/10.1371/JOURNAL.PONE.0220392
54. Wong CC, Huang YM, Chen CH, Lin FH, Yeh YY, Bai MY. Cytokine and growth factor delivery from implanted platelet-rich fibrin enhances rabbit achilles tendon healing. Int J Mol Sci 2020;21:3221. https://doi.org/10.3390/IJMS21093221
55. Wong CC, Yeh YY, Yang TL, Tsuang YH, Chen CH. Augmentation of tendon graft-bone tunnel interface healing by use of bioactive platelet-rich fibrin scaffolds. Am J Sports Med 2020;48:1379-88. https://doi.org/10.1177/0363546520908849
56. Xu J, Han K, Su W, Zhao J. An arthroscopy-assisted mini-invasive technique to create a chronic rabbit model with massive and retracted supraspinatus rotator cuff tears. Arthrosc Tech 2022;11:e999. https://doi.org/10.1016/J.EATS.2022.02.001
57. Yılmaz O, Özmeriç A, Alemdaroğlu KB, Celepli P, Hücümenoğlu S, Şahin Ö. Effects of concentrated growth factors (CGF) on the quality of the induced membrane in Masquelet's technique—an experimental study in rabbits. Injury 2018;49:1497-503. https://doi.org/10.1016/J.INJURY.2018.06.011
58. Yokoya S, Mochizuki Y, Nagata Y, Deie M, Ochi M. Tendon-bone insertion repair and regeneration using polyglycolic acid sheet in the rabbit rotator cuff injury model. Am J Sports Med 2008;36:1298-309. https://doi.org/10.1177/0363546508314416
59. Yu B, Wang Z. Effect of concentrated growth factors on beagle periodontal ligament stem cells in vitro. Mol Med Rep 2014;9:235-42. https://doi.org/10.3892/MMR.2013.1756
60. Zhang L, Zhu Y, Xu T, Fu W. Bone marrow stimulation in arthroscopic rotator cuff repair is a cost-effective and straightforward technique to reduce retear rates: a systematic review and meta-analysis. Front Surg 2023;10:1047483. https://doi.org/10.3389/FSURG.2023.1047483/BIBTEX