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Chapter

rhBMP-2-Coated Acellular Dermal Graft for Chronic Rotator Cuff Healing: Translational Tendon Repair Research

Kwang-Il Lee, Ju-Woong Jang and Kwang-Won Lee

Abstract

A rotator cuff tear is a common shoulder injury in sports medicine. However, a rotator cuff repair still has the high failure rate (57%) in large torn (>8 cm^2) rotator cuff cases. One of the main reasons is failing at suture-tendon cause of continuous tensional and torsional stresses even after surgery, and thus, an ideal biologic augmentation to overcome large tears is an essential challenge. The ECM graft, the biological material can be useful for augment repair of large torn rotator cuff. Recombinant human bone morphogenetic protein 2 (rhBMP-2), which belongs to transforming growth factor-β superfamily, is well known as an osteoinductive growth factor. It plays an important role in the development of bone and cartilage. rhBMP-2 also facilitates chemotaxis in the host tissue. In this study, rhBMP-2-coated acellular dermal graft, which is isolated from human cadaveric donor, was transplanted in the rabbit with the chronic rotator cuff injury. The radiologic image, histomorphometric, histologic image analyses, and tensile test were performed to evaluate the effectiveness. The results showed the enhancement of increased host cell infiltration, new bone formation, and tensile mechanical property. The rhBMP-2-coated acellular dermal graft will be promising for chronic rotator cuff healing.

Keywords: rotator cuff, rhBMP-2, acellular dermis, tendon-bone healing, enthesis

1. Introduction

A rotator cuff plays an important role in shoulder movements and maintaining shoulder joint stability [1]. The rotator cuff is composed of supraspinatus muscle, subscapularis muscle, infraspinatus muscle, and teres minor muscle. The rotator cuff is connected between the scapula and the humeral bone head, forming a cuff at the shoulder joint. The rotator cuff tear, which is partial tear and full-thickness tear, mainly occurs in the supraspinatus tendon under the acromion [2]. A torn rotator cuff weakens shoulder's physical function. Almost 2 million people in the United States visit to see doctors cause of the painful rotator cuff at every year [3]. The rotator cuff repair requires reattachment of the rotator cuff tendon back to the humeral bone by using suture and fixation tools, which is non-biological technique [4, 5]. Rotator cuff repair has showed good long-term follow-up results so far. However, it still shows the high failure rate (57%) in the case of large tear

(more than 8 cm^2) size [6]. The main reason of the pain even after rotator cuff repair surgery is that the shoulder has stiff due to the limited movement [7]. During the surgery, the rotator cuff tendons are sutured to the upper humeral bone. In the case of large tear size, it will be much harder to suture the shortened tendon back to the bone than the repair of the small tear size [8]. More tensile stress will be applied to the sutured gap between the tendon and bone.

The limitations for rotator cuff healing maybe overcome by biological augmentation approaches. A bio-scaffold should have high initial fixation strength, mechanical stability, and biological healing of the tendon-bone interface. And a growth factor should induce host cell infiltration and new tissue formation. Those characteristics are strongly necessary for biological augmentation approaches [9–12]. The dermal graft, which has been used for wound coverage, maybe applicable for large rotator cuff tears. The dermal graft is an acellular dermal extracellular matrix (ECM) scaffold intended for supporting and covering the soft tissue repair. There are various types of the acellular ECM scaffold such as small intestinal submucosa, urinary bladder basement membrane, pericardium, and dermis [13–16]. The only dermal graft has the most thickness (maximum 4 mm), and this will be the only ECM scaffold that can cover the thickness of supraspinatus (avg. 4.9 mm) or infraspinatus (avg. 4.2 mm) tendon [17]. Dermal graft has been used as a grafting material in plastic, dental, and orthopedic surgeries [18–20].

Various growth factors have been applied for enthesis regeneration studies [21–25]. Recombinant human bone morphogenetic protein 2 (rhBMP-2) is an osteoinductive protein that induces differentiation of mesenchymal stem cells into osteoblasts and chondrocytes. rhBMP-2 has shown the potential to improve tendon-bone biomechanical strength during rotator cuff healing [26, 27]. In our previous studies, we found that injectable rhBMP-2 hydrogel increased the biomechanical properties and new bone formation at the tendon-tibia intra articular bone tunnel [28].

The purpose of this translational study is to investigate whether the rhBMP-2-coated dermal graft can improve rotator cuff healing using a rabbit chronic rotator cuff injury model.

2. Materials and methods

2.1 Decellularization of human dermis and rhBMP-2 coating

Dermis was procured from the back of human cadaver and cut into pieces (1 × 2 cm). The tissue pieces were digested in an enzyme cocktail (total 500 mL) mixed with 0.25%(v/v) trypsin, 7.5%(w/v) collagenase A, and 37.5%(w/v) protease in a shaking incubator at 120 rpm, 37°C for 4 hours [29]. The tissues were then washed with the same volume of saline solution at 120 rpm, 4°C for 1 hour. This washing step was repeated for three times and finished with the final saline washing for 12 hours. And then, the washing solution was replaced with the same volume of distilled water and the tissues were cleansed with ultrasonic waves at 240 W for 5 minutes. This step was repeated in fresh saline solution. The processed tissues were lyophilized and sterilized with ethylene oxide gas.

Chinese hamster ovary cell line-derived rhBMP-2 was reconstituted and diluted with distilled water to 50 ug/mL before coating on the scaffold. rhBMP-2 was covered on the both side of the dermal graft and, then, lyophilized.

2.2 Surgery for making a chronic rotator cuff injury model

Adult New Zealand white rabbits (n = 42, male, 5-month old, 3.0 kg) were used for the chronic rotator cuff tear model. All the animal surgical protocols were approved by

the Committee of Experimental Animal Sciences. To make the chronic injury model, the rabbits were anesthetized with ketamine, 40 mg/kg IM and xylazine, 5 mg/kg IM, and the right shoulder joint compartment was exposed. The supraspinatus tendon was cut off from the right proximal humerus bone. The detached end of the tendon was placed in a silicon tube (10 mm length and 4 mm diameter) and fixed by suturing (**Figure 1**). The silicon tube-inserted tendon was relocated and sutured using 5-0 Vicryl. Postoperatively, the animals were allowed free movement without the use of any type of immobilization and had access to food and water from the first day onward. They were monitored daily for 8 weeks to check their mobility and the state of the surgical wound.

2.3 Surgical procedure for dermal graft insertion

For dermal graft implantation, the supraspinatus repair by single-row repair technique was performed in this study. After 4 weeks, the silicon tube was removed from the cut supraspinatus tendon, and two holes (1 mm diameter) were made on the proximal humerus bone for the graft insertion (**Figure 2**). The rabbits were assigned to one of the following treatment groups: normal (n = 6); no grafting (n = 12), the cut supraspinatus tendon was inserted into the hole without graft and fixed by suturing; dermal graft insertion (n = 12), a sheet-shaped dermal graft (1 cm × 2 cm) was inserted and fixed by suturing between the tendon and bone; and rhBMP-2-coated dermal graft insertion (n = 12) with the same method. The animals were allowed to recover and monitored as described for chronic defect surgery, and they were sacrificed at 4 or 8 weeks.

2.4 Micro-computed tomography (CT) analysis of bone mineral density (BMD) and mineralized tissue generation

A micro-CT system was used for quantitative analysis of BMD and mineralized tissue generation between the connected tendon and bone lesion. Rabbit shoulder
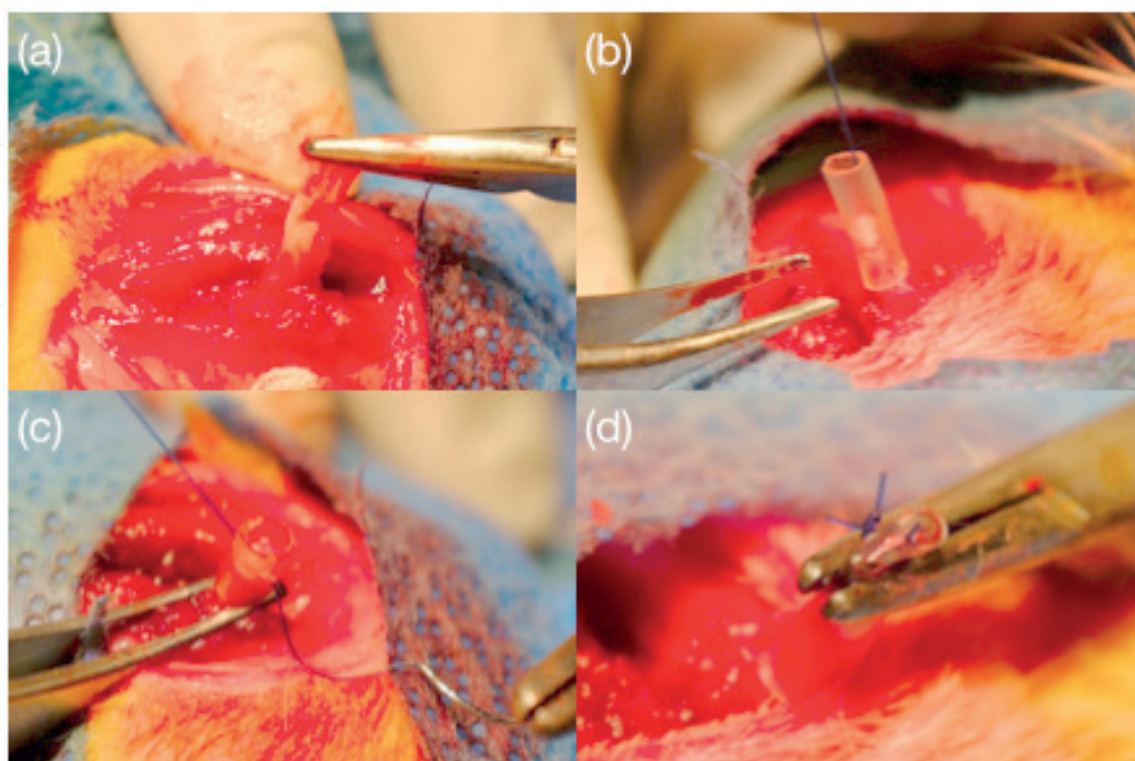

Figure 1.
The surgical procedure of chronic disease model. (a) After detaching the tendon from the proximal humeral bone; (b) the end of a tendon is inserted into the silicon tube; (c, d) they are sutured and fixed for 4 weeks.
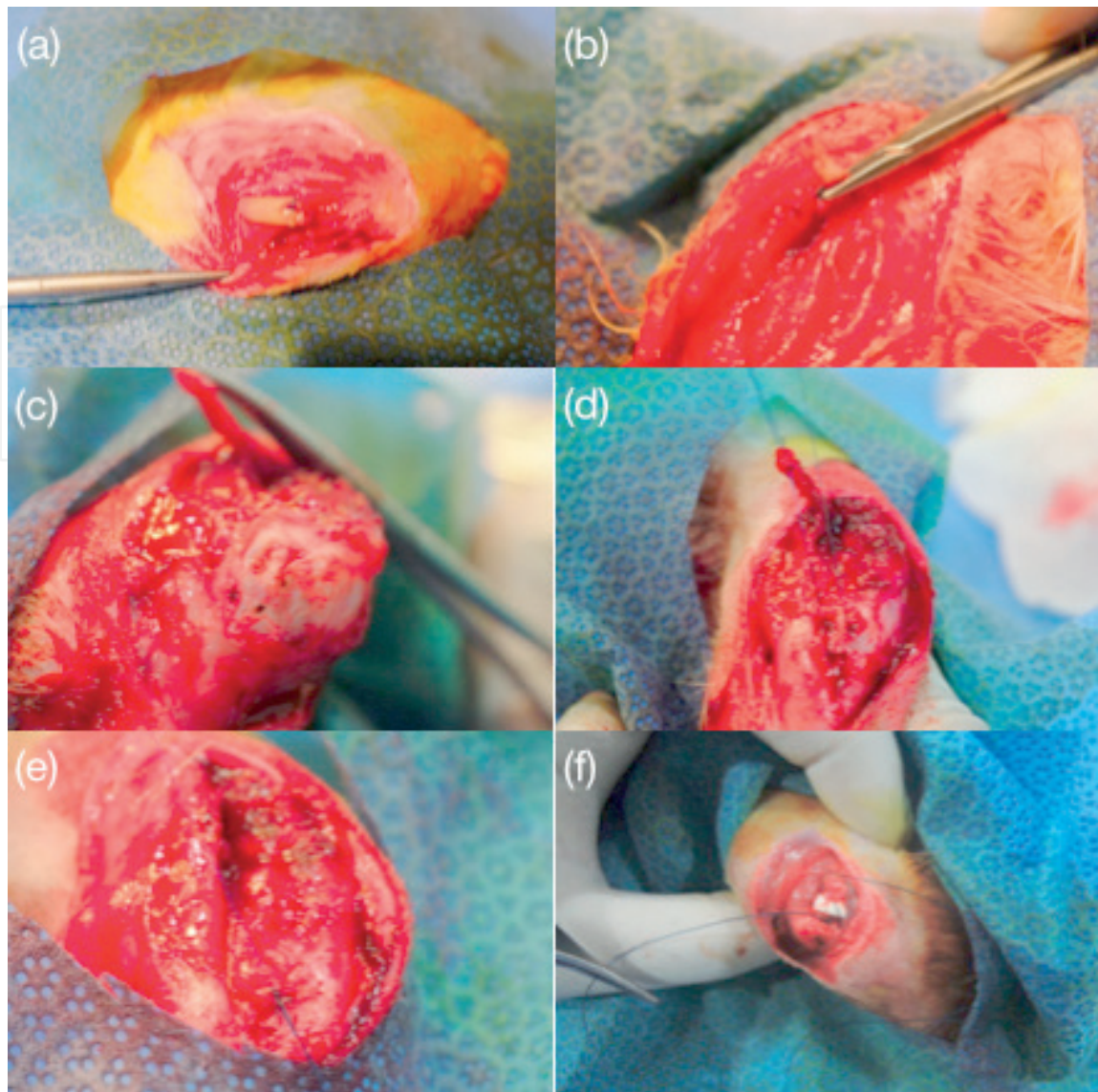
Figure 2.
The surgical procedure of patch insertion. (a) Finding the silicon tube-inserted tendon lesion after 4 weeks; (b) the removed tube from tendon; (c) making a hole for fixing with tendon; (d) the detached tendon is sutured with the bone through the holes; (e) the tendon is fixed with the bone; (f) each conditional dermal patch is inserted and fixed with suturing between the tendon and bone lesion.

specimens were scanned and reconstructed using 3D reconstruction bundle software. To quantify the amount of newly formed mineralized tissue over time, the region of interest (ROI) was chosen and reconstructed using the 3D software. After thresholding, the BMD (mm^3) of the ROI of mineralized tissue was calculated.

2.5 Biomechanical testing

Rabbit shoulder joints including the tendon-connected bone lesion were collected. To analyze the tensile mechanical properties, tensile strength was measured using a universal testing machine. The specimen was fixed vertically on a 5000 N load cell, and tensile strength was measured by pulling the sample at a load-displacement rate of 10 mm/min (**Figure 3**). The failure load and ultimate strength (N) were recorded.

2.6 Histological and histomorphometric analysis

Rabbit shoulder joints were collected and fixed in a neutralized formalin solution for 2 days and decalcified using 10% formic acid. Then, the specimens were
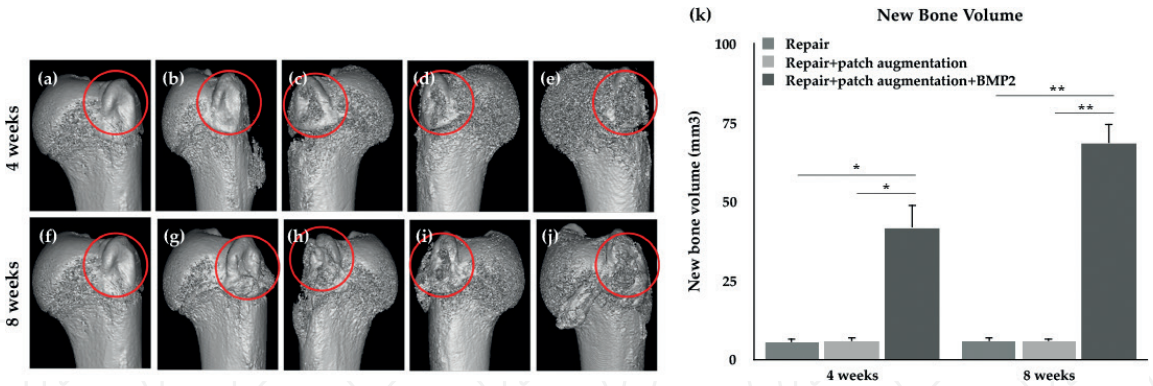
Figure 3.
3D-CT images and new bone formation of each experimental group 4 and 8 weeks after repair. (a) Intact group (PO 4 weeks); (b) defect group (PO 4 weeks); (c) repair group (PO 4 weeks); (d) dermal graft augmentation group (PO 4 weeks); (e) rhBMP-2-coated dermal graft augmentation group (PO 4 weeks); (f) intact group (PO 8 weeks); (g) defect group (PO 8 weeks); (h) repair group (PO 8 weeks); (i) dermal graft augmentation group (PO 8 weeks); (j) rhBMP-2-coated dermal graft augmentation group (PO 8 weeks); (k) quantitative analysis of the new bone formation after rotator cuff surgery after 4 and 8 weeks.

Characteristics	Points (maximum total of 9 points)
Fibrocartilage formation	
Abundant	3
Moderate	2
Slight	1
None	0
New bone formation	
Abundant	3
Moderate	2
Slight	1
None	0
Tendon allograft bonding to adjacent tissue	
75–100%	3
50–75%	2
25–50%	1
0–25%	0

Table 1.
Histomorphometric scoring system used to assess healing of the tendon-patch grafts with the bone.

dehydrated in ethanol and embedded in paraffin. The 4-um-thick sections were stained with H&E and visualized using an optical microscope. Healing of the tendon-bone connected lesion was graded histomorphologically by two observers blinded to treatment group. Histomorphometric analysis was performed to assess healing of the bone-tendon interface on the basis of three histomorphological criteria: fibrocartilage formation, new bone formation, and tendon graft bonding to adjacent tissue, which were scored on a scale of 0–3 (maximum total score of 9) in **Table 1**.

2.7 Statistical analysis

The data are presented as the average from at least triplicate samples. The experiments were repeated three times to ensure the reproducibility of the methods

used. All statistical analyses were performed using SPSS (v.15.0). ANOVA was used to find overall differences among means. The post hoc Sheffé test was used to analyze differences between groups, with significance levels set at $*p < 0.05$ and $** < p < 0.01$.

3. Results

In the postoperative 3D-CT images, the rhBMP-2-coated dermal graft inserted group showed significantly higher new bone formation than the other groups (**Figure 3**). The new bone volume in the rhBMP-2 group at 4- and 8-week post-repair surgery was 41.8 and 68.5 mm^3, respectively, which was ~11.5 times higher than in the control and dermal graft only inserted groups. The latter groups displayed less than 6 mm^3 and, thus, did not show actual new bone formation.
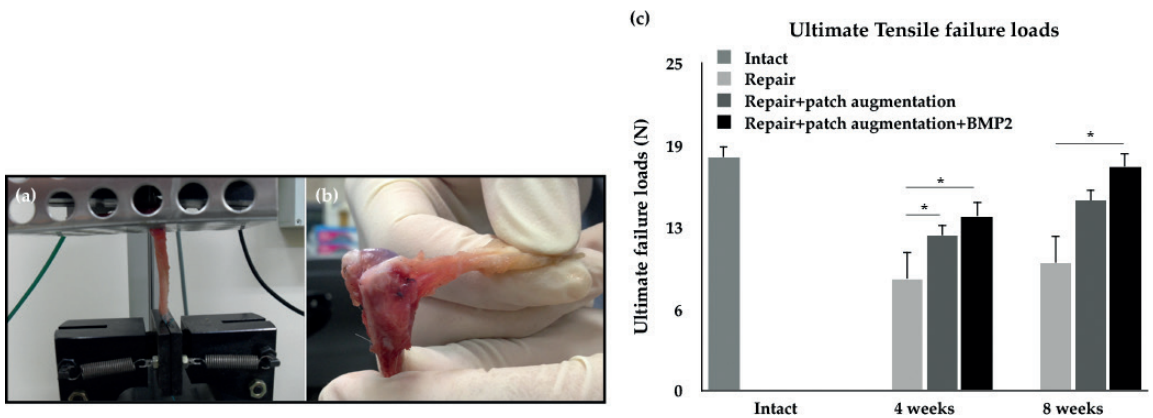

Figure 4.
The rabbit humeral bone is fixed with upper grip and the end of the detached tendon is fixed with lower grip. (a) Installed tissue specimen between the load cells for tensile test; (b) collected rabbit shoulder joint for tensile test; (c) ultimate tensile failure loads: A load-displacement rate was 10 mm/min and ultimate failure loads were measured from each group PO 4 and 8 weeks.
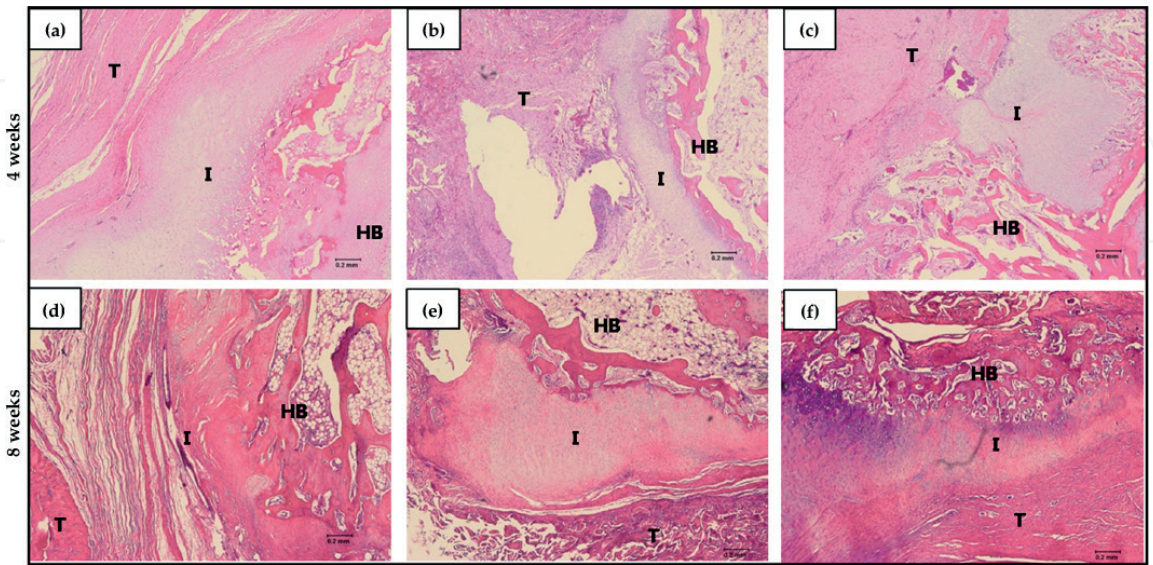

Figure 5.
The conditionally repaired groups in the rabbit tendon injury model. The repair group in which supraspinatus tendon and humeral bone were sutured at 4 weeks (a) and 8 weeks (d) post-surgery. The group that had received only a dermal patch, which covered the tendon-and-bone-suturing lesion, at 4 weeks (b) and 8 weeks (e) post-surgery. The group that had received the rhBMP-2-coated dermal patch, at 4 weeks (c) and 8 weeks (f) after repair. Images are shown at original magnification ×100. H&E, hematoxylin and eosin; T, tendon; HB, host bone; I, interface.

The rhBMP-2-coated dermal graft effectively induced new bone formation in the repaired lesion of the tendon and bone.

The ultimate tensile strength of the repaired tendon-bone interface was significantly higher in the rhBMP-2-coated dermal graft group and dermal graft only group than in the control group (suture only) at 4-week post repair surgery. However, there was a significant difference only in the rhBMP-2-coated dermal graft inserted group at 8-week post repair surgery (**Figure 4**). Moreover, the ultimate failure loads of specimens from the rhBMP-2-coated dermal graft group were similar to those of intact tissues at 8-week post-repair surgery. These results indicated not only that dermal patch provided good mechanical support but also that the rhBMP-2 increased the fusion rates of repaired lesion between the humeral bone and supraspinatus tendon.

Histological analysis indicated that newly differentiated fibrochondrocytes were detected near the host bone in the rhBMP-2-coated dermal graft group at 8-week post-repair surgery (**Figure 5F**). The dermal graft only group showed lower cell penetration into the interface area, although the dermal graft was connected between the bone and tendon (**Figure 5B, E**). However, high cell penetration was observed near the host bone surface, and the interface between the bone and tendon was well connected without any space in the rhBMP-2-coated dermal graft group (**Figure 5C, F**).

Quantitative histomorphometric analysis showed that the dermal graft coated with rhBMP-2 group had the highest analytic score (5.9) such as more fibrocartilage formation, new bone formation, and stronger attachment of the tendon to adjacent bone than the other groups (control group, 3.4; dermal graft only group, 3.9) after 8 weeks (**Figure 6**). As a result, the histological and histomorphometric analyses suggested that the rhBMP-2-coated dermal graft stimulated cell recruitment as well
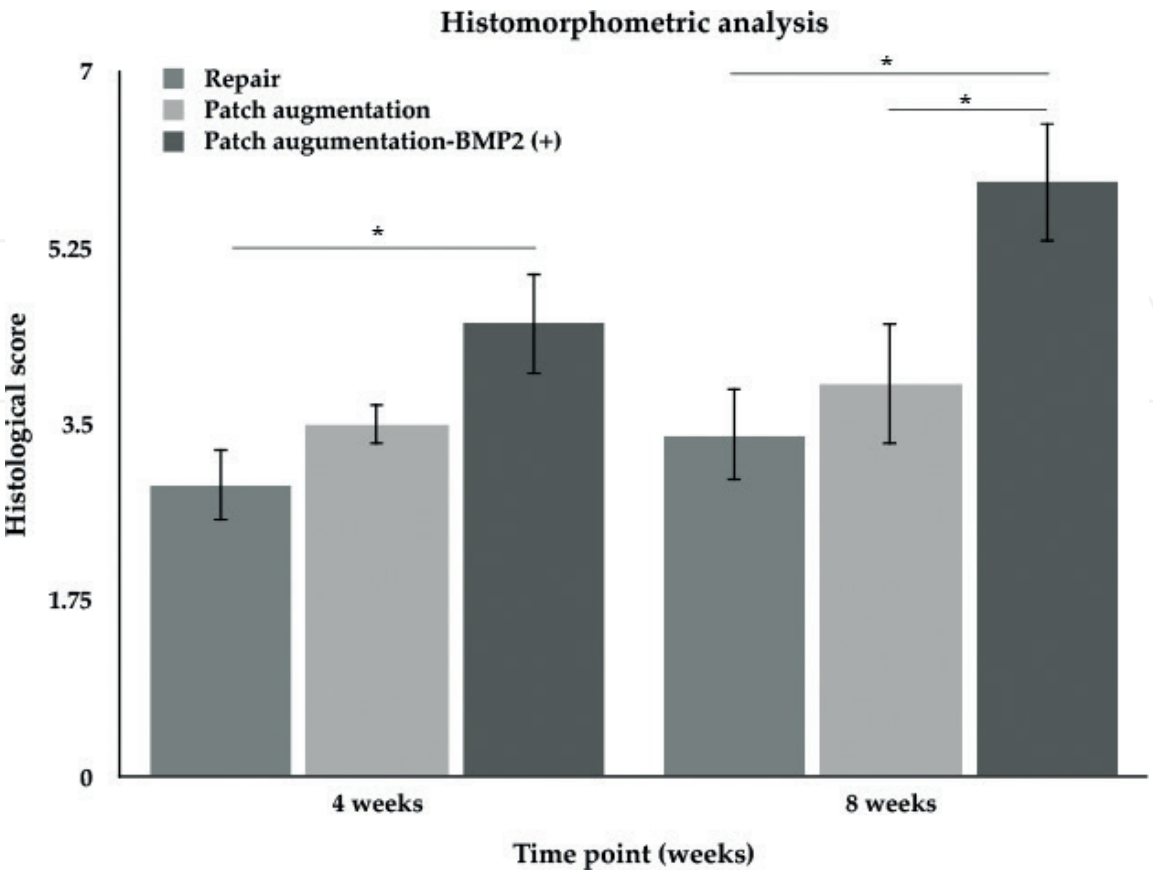

Figure 6.
Histomorphological scores of each group PO 4 and 8 weeks.

as induced fibrochondrogenic differentiation of the undifferentiated mesenchymal cells in the junction between the bone and tendon.

4. Discussion

There have been a number of preclinical and clinical trials for the enhanced tendon-bone healing in the shoulder repair surgery [12, 21, 30]. The augmentation repair of rotator cuff by incorporating growth factors or stem cells into the scaffold is intended to enhance the repair process, improve the mechanical properties, and reduce the possibility of re-rupture [10, 24, 25].

Decellularized human dermis has better mechanical properties than any other ECM-based scaffolds in the previous studies [31, 32]. ECM-based grafts are attractive model for tissue regeneration. However, they may support only short-term reinforcement and retard tissue regeneration [33]. For the enhanced healing process, the grafting material requires good mechanical properties as well as specific differentiation effects. rhBMP-2 has shown biological effectiveness for rotator cuff repair and for tendon-bone interface healing in extra-articular bone tunnel in the previous studies [28, 34]. However, there have been no preclinical and clinical studies on the rhBMP-2-coated acellular dermal graft for rotator cuff repair.

Many limitations of safety and effectiveness still remain for the clinical use of rhBMP-2. The considerations of biomechanical property for better morbidity of bone-tendon, the concentration of rhBMP-2 for the safety in the implanted area, and coating method for sustained release from the scaffold are necessary for growth factor application in the biological augmentation research.

Although the review articles suggested that dermal graft has good biomechanical properties and rhBMP-2 is effective for biological augmentation in bone-tendon, there was no original article that showed the composite of rhBMP-2 and an acellular dermal graft [35, 36]. For this initial study on rhBMP-2-coated dermal graft for rotator cuff repair, we generated a rabbit rotator cuff injury model by using a silicon tube, which covers the supraspinatus tendon that was detached from the humeral bone for 4 weeks. In our previous study, we showed the usability of rhBMP-2 application for tendon-tibia bone interface healing, using viscous collagen gel as an injectable carrier. rhBMP-2 needs to be embedded in a scaffold for an effective delivery to the targeted lesion. Thus, various types of carriers need to be tested for rhBMP-2 delivery.

Acellular dermal graft exhibits higher suture pullout strength than other ECM-based scaffolds. The rotator cuff area is subject to excessive and multidirectional loads by tendon-bone interface motion; therefore, healing following rotator cuff repair largely depends on robust mechanical properties of the junction between the bone and tendon.

On the basis of prior knowledge, rhBMP-2-coated acellular dermal graft was sutured between the rabbit supraspinatus tendon and humeral bone. The rhBMP-2-coated dermal graft group showed significant new bone formation as indicated by 3D-CT data recorded at 4 and 8 weeks after surgical treatment. The ultimate failure loads of the rhBMP-2/acellular dermal graft inserted tendon-bone interfaces increased to the mechanical properties of intact tissues at 8 weeks. The histological images demonstrated rich cell penetration into the tendon-bone interface by rhBMP-2, and the recruited cells induced fibrochondrogenic differentiation. The histomorphometric scores of the dermal graft coated with rhBMP-2 group were significantly higher than the other groups.

In conclusion, the grafting of rhBMP-2-coated human dermal graft enhanced new bone formation and the bone-tendon fusion rate in a rabbit

chronic rotator cuff injury model. This study demonstrated that the combination of an acellular dermal graft and rhBMP-2 can be applied to that rotator cuff injured patients.

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