



Original Article

Reconstruction of large chronic rotator cuff tear can benefit from the bone–tendon composite autograft to restore the native bone–tendon interface



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ABSTRACT

Purpose: We designed a paired controlled study to investigate the advantages of using bone–tendon composite autograft to reconstruct chronic rotator cuff tear compared with primary repair and provide some evidence to use the bone–tendon composite autograft.

Method: Thirty-eight Sprague–Dawley rats were used. The native bone–tendon junctions of supraspinatus and Achilles tendon insertion from two rats were harvested for gross and histological observation. Another thirty-six rats had bilateral supraspinatus tenotomy from the great tuberosity. Three weeks later, primary repair (simple tendon pullout direct repair to bone) was performed on one side and the other side was reconstructed using an Achilles–calcaneus composite autograft from the ipsilateral leg. Nine rats were sacrificed for biomechanical testing and another three were sacrificed for histological evaluation at 3, 6, and 9 weeks after surgery, respectively.

Results: The Achilles–calcaneus composite autograft group showed significantly better biomechanical characteristics at 3 and 6 weeks in terms of maximum load and stiffness. Tissue histology demonstrated an organised extracellular matrix, a clear tidemark, and distinct fibrocartilage layers in the composite graft group, similar to those of the native bone–tendon interface. Additionally, clear bone-to-bone healing and tendon-to-tendon healing were observed. By contrast, the conventional primary repair could not regenerate the structure of the native bone–tendon interface.

Conclusions: Bone–tendon autograft for chronic rotator cuff reconstruction is superior to the primary repair regarding biomechanical property and histological structure. Our study may provide some evidence in support of the reconstruction of a chronic rotator cuff tear using bone–tendon composite autografts in clinical practice.

The Translational potential of this article: The current study finds the bone-tendon autograft can restore the normal bone-tendon interface, which can not regenerate after repair and is the key factor affecting re-tear. The bone-tendon autografts from our body can be the candidates for rotator cuff tear reconstruction especially the large to massive rotator cuff tear in the future to reduce the re-tear after rotator cuff tear.

Introduction

Rotator cuff tendon tear is a significant musculoskeletal disorder, with up to half of the people >50 years old being afflicted [1]. Surgical treatment for the symptomatic rotator cuff tear has evolved over the last few decades. However, many clinical and animal research studies report

limitations in the healing potential of the bone–tendon interface [2–4]. The structure and composition of the native direct bone–tendon interface cannot be restored after primary repair, resulting in a poor mechanical and structural interface and leading to a high rate of re-tear (94.7%, 17 out of 18 recurrent tears) especially after in larger or massive tear [5,6]. During the past decade, strategies to accelerate and improve

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tendon-to-bone healing using various growth factors and cell-based therapies have been studied extensively in orthopedic basic science research [7–11]. However, few of these strategies have been applied in the clinical setting, and the native bone–tendon interface remains a challenge for complete restoration [5,12–14]. In our clinical practice, surgeons repair the tendon-to-bone (rotator cuff tear) using a single or double row anchor and do not address the restoration of the native bone–tendon interface, regardless of the high rate of re-tear [15].

If the native bone–tendon junction cannot be regenerated after primary repair, a bone–tendon composite graft, which preserves the native bone–tendon junction, can be a valuable option. This concept was demonstrated initially in anterior cruciate ligament reconstruction and achieved good results [16]. Recently, Smith et al. used the bone–tendon allograft in the treatment of a rotator cuff tear in a dog rotator cuff tear model and achieved satisfactory outcomes [17]. In addition, Leung et al. showed that bone-to-bone healing and tendon-to-tendon healing are better than tendon-to-bone healing in terms of histological and biomechanical aspects and Urch et al. showed similar results in terms of biological aspects [18,19]. Thus, we have adopted the concept of bone-to-bone and tendon-to-tendon healing by using autogenous bone–tendon composite graft.

In this study, we used composite autografts from the Achilles tendon and calcaneus bone unit, which preserves the native bone–tendon junction, to treat chronic rotator cuff tears and compared the results with those of primary repair (simple tendon pullout direct repair to bone), in a rat model. We hypothesised that the composite autograft would show advantages in regenerating the native bone–tendon interface histologically and result in improved biomechanical properties compared with those using the primary rotator cuff repair technique.

Materials and methods

Experimental design

Thirty-eight adult male Sprague–Dawley (SD) rats (8 weeks old; mean weight: 287 g) were used in this study. This study was approved by the Institutional Animal Care and Use Committee and was carried out in strict accordance with its regulations. Two rats were sacrificed for gross and histological observation of the bone–tendon insertions of the supraspinatus and Achilles tendons. The other rats underwent bilateral detachment of the supraspinatus and Achilles tendons. The other rats underwent bilateral detachment of the supraspinatus tendon. Three weeks later, tendon repair was performed in these animals [20]. Either a primary repair or a bone–tendon composite autograft was performed randomly in each rat shoulder. Twelve rats each were sacrificed at 3, 6, and 9 weeks after repair. Nine of the twelve rats sacrificed at each time point were used for biomechanical tests, and the other three were used for histological evaluation. The detailed information is listed in Figure 1.

Surgical technique

Each animal had two surgical procedures. First, a bilateral full-thickness supraspinatus tendon detachment from the greater tuberosity was performed. Three weeks later, the second surgery reattached the supraspinatus tendon on one shoulder and used a composite graft on the other shoulder. Anesthesia was induced by intramuscular injection of 50 mg/kg zolazepam and tiletamine (Zoletil 50; Virbac, Carros, France) and 10 mg/kg xylazine (Rompun; Bayer HealthCare, Leverkusen, Germany). A skin incision was made over the deltoid muscle, and the muscle was split to expose the insertion of the supraspinatus tendon on the greater tuberosity. The supraspinatus tendon was then transected and wrapped with a drainage tube to prevent spontaneous healing [21]. Three weeks later [3], the supraspinatus tendon was reattached to the

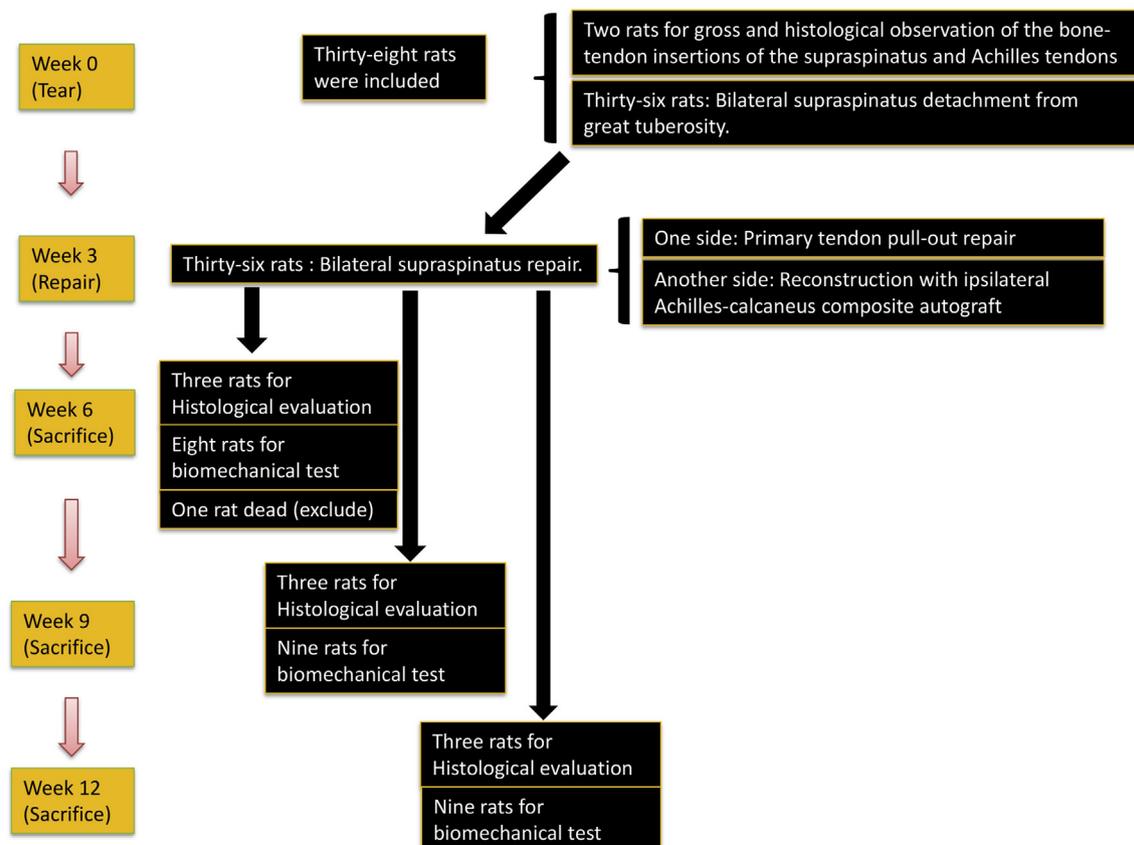


Figure 1. The flow chart of the study.

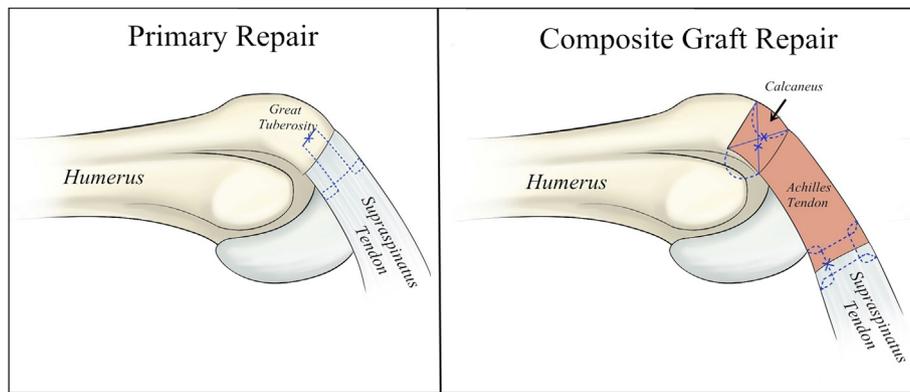


Figure 2. The surgical schema in the two groups. The modified Kessler was used to grasp tendon in the primary repair group. In the composite graft repair group, the orange area is the bone–tendon composite graft. The modified Kessler was used for the tendon-to-tendon repair. The suture bridge was used to fix the calcaneus graft to the bone trough.

footprint using a modified Kessler stitch with 5-0 Prolene suture (Ethicon, Johnson & Johnson, New Brunswick, NJ, USA) after removing the drainage tube and releasing the tendon from the surrounding scar tissue (Fig. 2). On the other shoulder, a 2 cm incision on the back of the ankle joint of the ipsilateral leg was made to expose the junction of the Achilles tendon and cancellous bone. The composite graft was harvested preserving approximately 4 mm of bone length and 5 mm of tendon length. A bone trough approximately 2 mm³ was created at the footprint of the supraspinatus. The bone side of the graft was trimmed to adjust the bone trough and fixed using a transosseous suture bridge technique with 5-0 Ethibond (Ethicon, Somerville, NJ, USA) (Fig. 2). Then, the tendon side of the graft was tailored for proper tension to connect to the leading edge of the torn rotator cuff using a modified Kessler stitch with 5-0 Prolene suture (Figs. 2 and 3). After surgery, all animals were housed individually at 21 °C under a 12 h light and dark cycle. The animals were provided food and water *ad libitum* and allowed to move freely within their cages until they were sacrificed at 3, 6, or 9 weeks postoperatively.

Biomechanical testing

For biomechanical tests, rats were fully anaesthetised and euthanised with carbon dioxide, and the supraspinatus muscle and tendon, as well as the humeral head bone, were harvested. The original suture for repair was removed before testing. The proximal 2/3 of muscle was removed, and a slip of gauze was wrapped around the whole muscle and tendon and fixed firmly with 4-0 black silk sutures. A large needle holder was used to clamp the tendon close to the greater tuberosity. Then, the needle holder and humerus bone were fixed using a custom fixture-clamping system (Instron, Norwood, MA, USA). Based on a similar previous study, the uniaxial testing condition was set using an Instron 3344 materials testing machine (Instron) [22]. The tendon was loaded until it pulled away from the bone or ruptured at its mid-substance. Data from tensile load to failure testing were collected automatically using a digital data acquisition system.

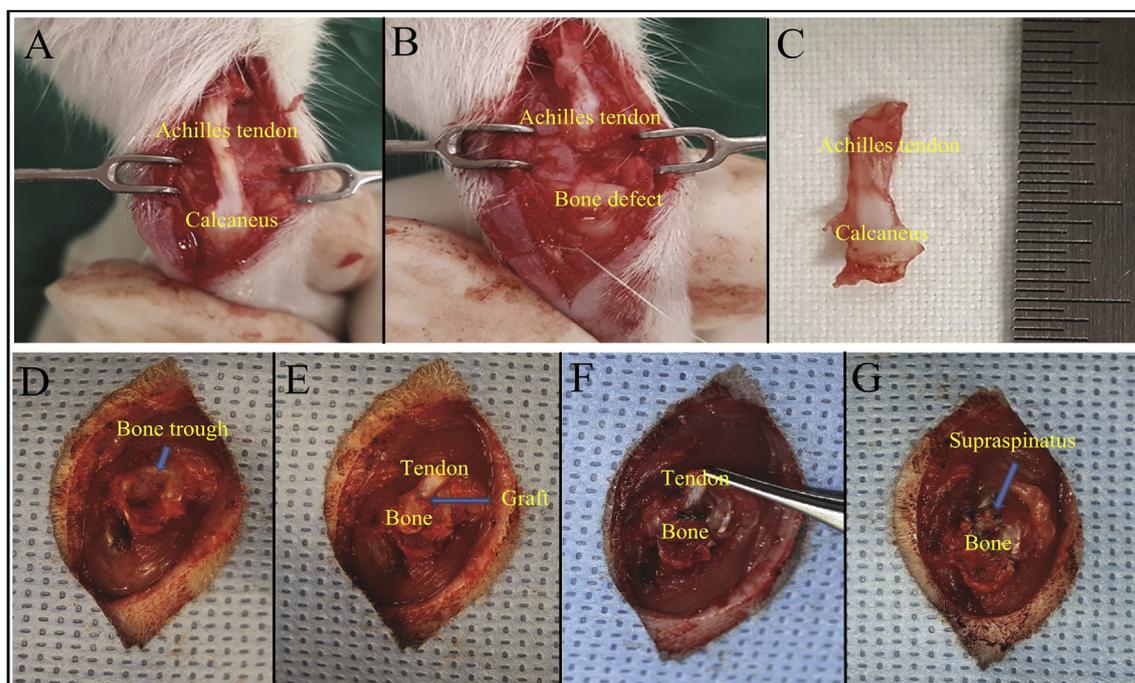


Figure 3. A surgical procedure in the bone–tendon composite graft group. (A) Achilles tendon and calcaneus bone exposed. (B) The remaining Achilles tendon and calcaneus bone after grafting. (C) Achilles tendon and calcaneus bone composite graft. (D) The bone trough on the humerus. (E) Insertion of the graft to the bone trough. (F) Fixation of the bone graft to the bone trough with a suture bridge. (G) Fixation of the tendon graft with a Kessler stitch to the remaining tendon.

Histomorphometric analysis

Immediately after sacrifice, samples were fixed in 10% neutral buffered formalin for 24 h and decalcified for 24 h (Formical-2000; Decal Chemical Corporation, Tallman, NY, USA), processed, and embedded in paraffin. Coronal 3 μm thickness sections of the humeral head and attached supraspinatus tendon were placed on glass slides, and representative sections of each shoulder at the middle of the supraspinatus insertion were stained with hematoxylin and eosin and Masson's trichrome, respectively. Routine histological images were obtained using an inverted microscope (Nikon TS100; Nikon, Melville, NY, USA).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 22.0; SPSS Inc.). Data are reported as mean \pm standard deviation. The normality and equal variance tests of the biomechanical data were performed first. If the data follow the normality and equal variance, biomechanical comparisons across two groups were performed using a paired *t*-test. If not, the Wilcoxon test was used to compare the data from two groups. Statistical significance was set at $p \leq 0.05$.

Results

Gross dissection and histological study of native bone–tendon insertion of the supraspinatus and Achilles tendons were performed.

Gross dissection and hematoxylin and eosin staining of both tendons to bone insertions revealed a similar size and microstructure of the

insertions (Fig. 4).

Biomechanical testing

In the 3 weeks group, one sample was damaged during dissection, so eight rats were tested. The composite autograft showed significantly better biomechanical characteristics at 3 and 6 weeks in terms of maximum load and stiffness. However, there was no significant difference between the two treatment groups at 9 weeks. The primary repair showed progressed biomechanical properties of maximum load and stiffness, as shown in Figure 5. The *p* values and observed powers are shown in Table 1. The site of failure due to load always occurred at the tendon-to-bone junction in the primary repair group. However, in the composite graft group, 50% of the failure sites occurred at the bone graft site in the early healing stage (3 weeks), with the site switched to the tendon-to-bone junction at later time points (Table 2).

Histologic analysis

Tendon-to-bone healing

In the primary repair group, a clear tidemark and distinct clear fibrocartilage layers were not observed at 3, 6, and 9 weeks. However, from 3 to 9 weeks, the bone–tendon interface became more mature as shown by the presence of more mature chondrocyte cells and an improved alignment of collagen fibers (Fig. 6).

In the composite graft group, four layers of the bone–tendon interface, a distinct tidemark, and mature fibrocartilage were preserved from 3 to 9 weeks, which is similar to the native bone–tendon interface

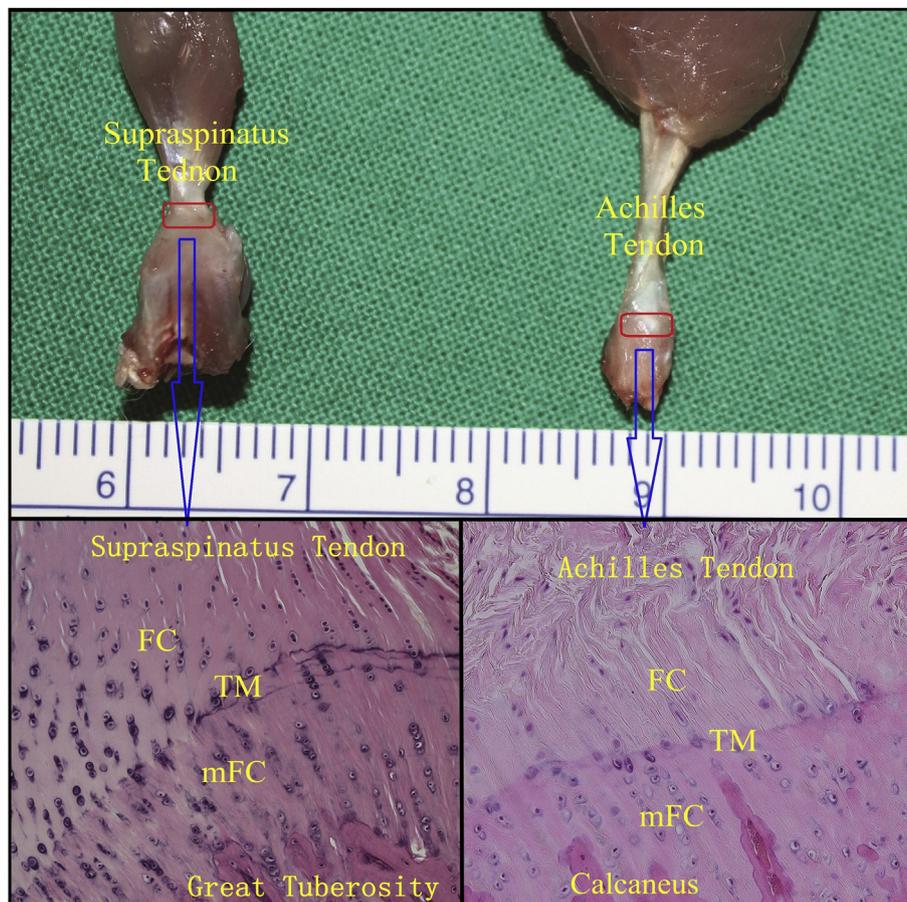


Figure 4. Gross and micro comparison of two different bone–tendon interfaces. The upper row gross dissection shows the similar size of the two different bone–tendon insertions. Histological structures of the supraspinatus tendon insertion and Achilles tendon insertion are similar. Hematoxylin and eosin staining; magnification, $\times 200$.

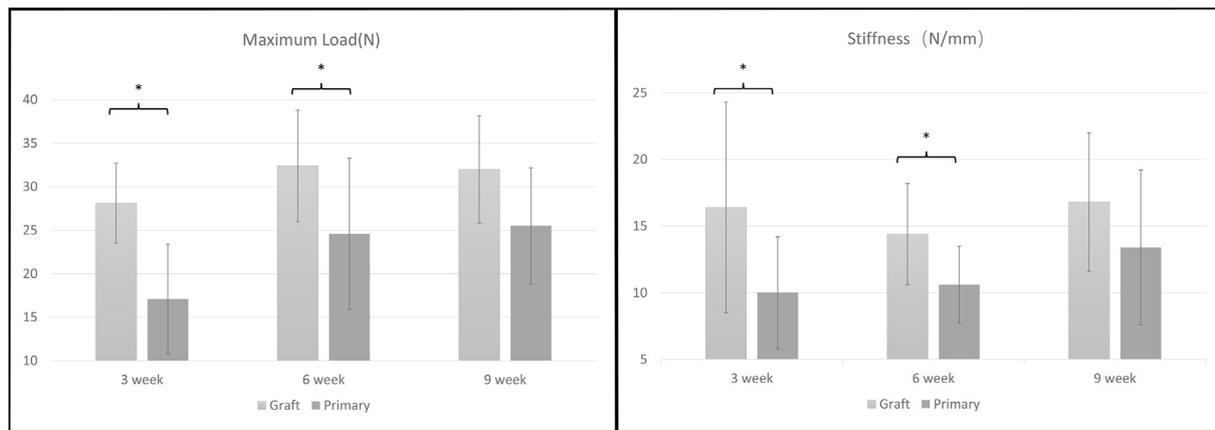


Figure 5. Biomechanical testing results. The figure shows the biomechanical results regarding maximum load to failure and stiffness. *, significant difference.

Table 1

p values and observed powers of biomechanical comparison between graft and the primary repair group.

	3W(P,OP)		6W(P,OP)		9W(P,OP)	
Maximum load	0.008	0.978	0.043	0.607	0.06	0.635
Stiffness	0.02	0.731	0.04	0.623	0.211	0.646

P: *p* value; OP; observed power.

Table 2

Failure site of the biomechanical test.

		Failure site	
		Bone	Bone–tendon junction
3 weeks	Composite graft repair	4	4
	Primary repair	0	8
6 weeks	Composite graft repair	2	7
	Primary repair	0	9
9 weeks	Composite graft repair	1	8
	Primary repair	0	9

(Fig. 6).

Tendon-to-tendon healing

In the primary repair group, tendon-like tissue grew gradually from the torn tendon edge to the greater tuberosity from 3 to 9 weeks (Fig. 7). At 3 weeks, the large gap between the torn tendon edge and bone was filled with fibrovascular granulation tissue. At 6 weeks, the gap became smaller, and tendon-like tissue from both sides, especially from the tendon side, grew into the gap. Immature tendon and more collagenous fiber bundles were observed in the gap at this stage. At 9 weeks, the fibrovascular granulation tissue gap was not observed. More well-organised mature tendon-like tissue was apparent in the gap (Fig. 7).

In the composite graft group, we observed tendon-like tissue that grew gradually from the two tendon leads from 3 to 6 weeks (Fig. 7). At 3 weeks, the gap between the two tendon edges was filled with fibrovascular granulation tissue. At 6 weeks, the gap was not observed. Immature tendon, mature tendon, and well-organised collagenous fiber bundles were observed. At 9 weeks, more mature tendon tissue was present (Fig. 7).

Bone-to-bone healing

In the composite graft group, graft bone remodelling was observed at

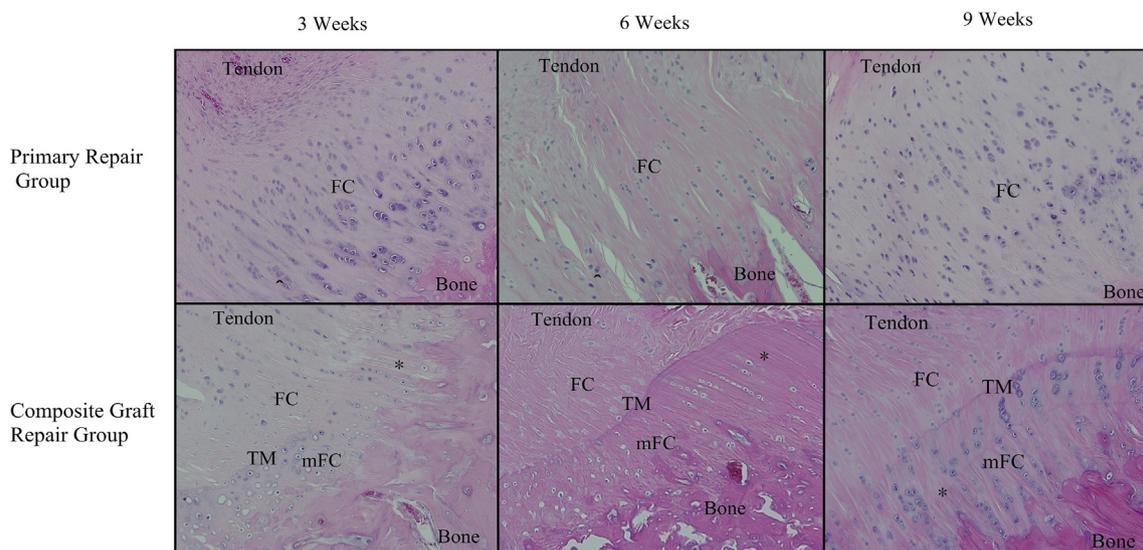


Figure 6. Hematoxylin and eosin staining of bone–tendon interface formation in the primary repair group and the bone–tendon composite graft group. Tendon-to-bone interface formation from 3, 6, and 9 weeks in the primary repair group and composite graft group. No apparent tidemark was observed in all slides in the primary repair group. Clear tidemark was observed in the tendon–bone composite graft group throughout all phases. The native bone–tendon interface can be preserved in the tendon–bone composite graft group from 3, 6, and 9 weeks. †, immature chondrocytes; *, alignment fiber; FC, fibrocartilage; TM, tidemark. Magnification, ×200.

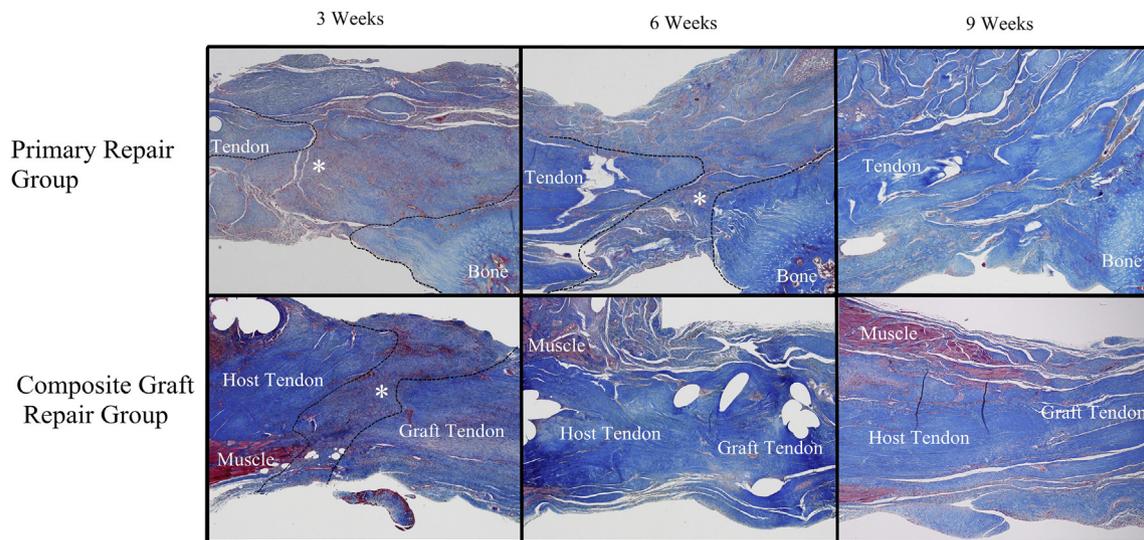


Figure 7. Masson's trichrome stain of the tendon-to-tendon healing in the primary repair group and the bone–tendon composite graft group. Gradual tendon-to-tendon healing at 3, 6, and 9 weeks. Fibrovascular granulation tissue area between the tendon lead and bone–tendon interface reduced from 3 to 9 weeks in the primary repair group. At 9 weeks, there is no clear fibrovascular granulation tissue gap. Fibrovascular granulation tissue area between host tendon lead and graft tendon lead only appeared at 3 weeks, and a good tendon connection appeared from 6 to 9 weeks in the graft repair group. *, fibrovascular granulation tissue. Magnification, $\times 40$.

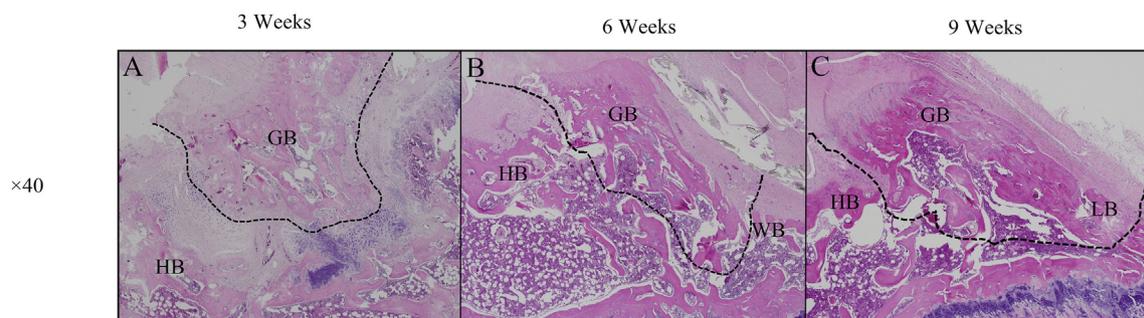


Figure 8. Hematoxylin and eosin staining of bone-to-bone healing in the tendon–bone composite graft group. Graft bone-to-host bone healing at 3 weeks, presenting fiber tissue and chondrocytes connection. Fiber tissue and chondrocytes connection are present on the articular side and weave bone connection on the lateral side at 6 weeks. Fiber tissue and chondrocytes connection combined with small woven bone is on the articular side, and the lamellar bone connection is on the lateral side at 9 weeks. HB, host bone; GB, graft bone; WB, weave bone; LB, lamellar bone.

3 weeks, and chondrocytes and fiber tissue connections were observed between the host bone and graft bone. At 6 weeks, the chondrocytes and fibrous tissue connections disappeared and were replaced by woven bone healing on the lateral side. Chondrocytes and fibrous tissue connections were still observed on the articular side. At 9 weeks, lamellar bony healing without an obvious gap between the two bones was noted (Fig. 8).

Discussion

We investigated the healing process at the bone–tendon interface following primary rotator cuff repairs and bone–tendon composite autograft repairs. Our results demonstrate that the bone–tendon autograft presented faster and better healing than the primary repair in terms of the biomechanical and histological results. The bone–tendon interface structure in the primary repair group was immature and different from that of the graft group at all time points. The four layers of the native bone–tendon interface were preserved in the composite autograft group, but not in the traditional primary repair group, in the chronic rotator cuff tear model. In addition, sound tendon-to-tendon and bone-to-bone healing processes were demonstrated in the composite graft reconstruction group. In this study, we have presented sound evidence to support

the use of bone–tendon composite autograft for the treatment of chronic rotator cuff tear.

The native bone–tendon interface includes a compositionally and mechanically graded fibrocartilage transition area, which can minimise stress concentrations from tendon-to-bone [23]. Thus, the formation of a native graded fibrocartilage zone and well-organised collagen at enthesis play a vital role in force transmission and energy dissipation between tendon and bone, tissues with different biomechanical properties. However, the native bone–tendon interface is difficult to regenerate with current suture fixation techniques resulting in repair failure, especially in chronic large to massive rotator cuff tears. Thomopoulos et al. demonstrated that the biology and zonal arrangement of the enthesis are not regenerated after rotator cuff repair [24]. Recently, Kanazawa et al. also showed that the ultrastructure of a normal tendon insertion could not be regenerated by primary pullout repair, even in an acute tear rat model [2]. We also observed that the primary repair resulted in poor healing at the bone–tendon interface in a chronic tear model. In the current study, we proposed a new technique to regenerate the native bone–tendon interface structure using a bone–tendon composite graft. The composite autograft also provided improved biomechanical testing of the bridge connecting tendon-to-bone.

Clear, faster, and better tendon-to-tendon healing was observed in the

composite graft group at 6 weeks than in the primary group. In the primary repair group, we were surprised that the tendon-to-bone healing also contained tendon-to-tendon healing and bone–tendon interface formation in the chronic repair model. Not like what we thought, tendon tissue would grow into bone directly, on one hand, tendon-like tissue from the tendon side gradually replaced the fibrovascular granulation tissue between the gap of tendon and bone–tendon interface from 3 to 9 weeks. On the other hand, tendon-like tissue from bone–tendon interface also gradually grew to the tendon side, but that speed was much slower than that of the tendon side (Fig. 7). Additionally, the bone–tendon interface became mature simultaneously (Fig. 6). As we all know, the chronic rotator cuff is usually torn from bone–tendon interface rather than the bone, usually, some part of fibrocartilage is still there. Just like making a chronic model, the rotator cuff was just cut from the bone–tendon junction without removing all fibrocartilage layers and then wrapped in the drainage tube; the tendon would retract and degenerate with scar tissue formation. The original fibrocartilage layers were preserved and degenerated with scar tissue formation in the rat. Once we connected the degenerated tendon to the degenerated fibrocartilage layer, the healing progress of chronic tear in the rat started, which included tendon-to-tendon healing and bone–tendon interface formation. We inferred that the healing of human rotator cuff tear after the repair is similar with the fashion we showed in rat that it contains tendon-to-tendon healing and bone–tendon interface formation and both of them progress simultaneously.

Bone-to-bone healing was shown by Leung et al. to be better than tendon-to-bone healing [19]. In the present study, we also found sound bone healing of a laminar bony connection on the lateral side at 9 weeks. However, our result was slightly different from that of Bernhardsson et al. who demonstrated cancellous bone healing at approximately 2 weeks and complete healing at 4 weeks in a rat model [25]. This may be due to no restriction on the range of motion after surgery. In addition, a simple suture fixation cannot attain stable bone contact without an external cast, unlike plate and screw fixation that can fix the bone firmly. Even in clinical practice, patients with a simple rotator cuff repair require a sling to restrict motion. Thus, the graft may experience some micro-motion during the daily motion of the rats, which may affect the bone healing process. Although the healing process of the composite graft (avascular tissue) should be slower than that of the vascular tissue, at 9 weeks, laminar bone connection began to appear to fill the gap (Fig. 8).

Farnebo et al. used a decellularised bone–tendon composite graft to reconstruct acute Achilles tendon rupture from the bone–tendon interface and compared the results with those of direct reattachment of the Achilles tendon to the calcaneus in a rat model [26]. They reported a significant difference at the early time points (weeks 2 and 4) with respect to failure load and histological assessments, but no significant differences were detected at a later time point (week 12). We obtained similar results in the composite graft group, which showed fast healing. However, in the study of Farnebo et al., no clear information was provided concerning bone-to-bone and tendon-to-tendon healing [26]. Smith et al. used decellularised bone–tendon composite grafts compared with dermis-derived patch and debridement to treat a chronic large rotator cuff in a dog model [17]. The bone–tendon composite graft showed better radiographic, histological, and biomechanical results. However, limited information about the bone-to-bone and tendon-to-tendon healing was provided. In the current study, the bone-to-bone and tendon-to-tendon healing process data were demonstrated after reconstruction, and the native bone–tendon interface was preserved. We showed that the bone–tendon interface transplantation is feasible, which may represent a new surgical strategy to treat chronic rotator cuff tears.

Several limitations should be acknowledged in the present study. First, SD rats were used, which certainly have differences in rotator cuff anatomy, function, and healing potential compared with humans. Second, for an autograft, the healthy Achilles and calcaneus were sacrificed. We did not evaluate the degrees of donor site morbidity. Considering creating donor site morbidity when harvesting Achilles–calcaneus

autograft, in the future, an iliotibial band with Gerdy's tubercle [27] or iliac crest may be a better option in human as the composite autografts or a tissue engineered composite graft. Third, the supraspinatus muscle state was not evaluated before and after surgery. Some authors demonstrated that the result of rotator cuff repair has a negative relationship with muscular atrophy before surgery [4,28,29]. Fourth, the tendon-to-tendon healing in the graft group was not tested in the biomechanical test, because the healing junction was fixed by the needle holder. Originally, in our pilot study, we tried to test the tendon-healing junction, but may be because of our fixation problem, the failure site was always at muscle–tendon junction by peeling the muscle from tendon rather than at tendon healing junction. Finally, we just transected the supraspinatus tendon insertion following the previous studies, whether we damaged the enthesis or not, we did not know. Is the enthesis of the rat in this study similar with the clinical scenario in human rotator cuff tear? We did not test it, which may affect the result translation to the clinical practice.

Conclusions

Our results showed that native bone–tendon interface structure could be regenerated using bone–tendon autografts compared with primary pullout repair. Bone–tendon autograft for chronic rotator cuff reconstruction is superior to the primary repair regarding biomechanical property and histological structure (restoring native bone–tendon interface structure). Our study may provide some evidence in support of the reconstruction of a chronic rotator cuff tear using bone–tendon composite autografts in clinical practice.

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Conflict of interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. The animal study was approved by the Institution of Animal Experiments Ethics Committee of Asan Medical Center and Animal Care; the study was conducted in accordance with the rules and regulations of Asan Medical Center.

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