

# Magnetic Resonance Imaging and Biomechanical Analysis of Adipose-derived Stromal Vascular Fraction Applied on Rotator Cuff Repair in Rabbits

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## Abstract

**Background:** Adipose-derived stromal vascular fraction (ADSVF) can be applied to repair tendon and ligament tears. ADSVF treatment has a better therapeutic potential than adipose stem cells alone in promoting the healing of connective tissue injury in rabbit models. Magnetic resonance imaging (MRI) and biomechanical testing were used in this study to evaluate the efficiency of SVF in the healing of tendon-bone interface of a rotator cuff injury after reattachment.

**Methods:** A total of 36 rabbits were studied between March and June 2016, 18 rabbits received the SVF-fibrin glue (SVF-FG) treatment and the other 18 formed the control group. ADSVF was isolated from each rabbit. A bilateral amputation of the supraspinatus tendon and parallel reconstruction was also performed on all the 36 rabbits. Then, a mixture of SVF and FG was injected into the tendon-bone interface of the SVF-FG group, whereas the control group only received FG. The animals were randomly sacrificed at 4, 8, and 12 weeks after surgery ( $n = 6$  per group), respectively. The shoulders were prepared for MRI scanning and analysis of biomechanical properties. Analyses of variance were performed using SPSS 13.0.

**Results:** MRI scanning showed that the signal-to-noise quotient of the SVF-FG group was not significantly higher than that of the control group at either 4 ( $20.1 \pm 3.6$  vs.  $18.2 \pm 3.4$ ,  $F = 1.570$ ,  $P = 0.232$ ) or 8 weeks ( $20.7 \pm 3.3$  vs.  $18.0 \pm 3.0$ ,  $F = 2.162$ ,  $P = 0.117$ ) posttreatment, and only became significant after 12 weeks ( $27.5 \pm 4.6$  vs.  $22.1 \pm 1.9$ ,  $F = 4.968$ ,  $P = 0.009$ ). Biomechanical properties such as the maximum load, maximum strength, and the stiffness for the SVF-FG group were significantly greater than that for the control group at 8 weeks' posttreatment (maximum load:  $166.89 \pm 11.62$  N vs.  $99.40 \pm 5.70$  N,  $P < 0.001$ ; maximum strength:  $8.22 \pm 1.90$  N/mm vs.  $5.82 \pm 0.68$  N/mm,  $P < 0.010$ ; and the stiffness:  $34.85 \pm 3.00$  Pa vs.  $24.57 \pm 5.72$  Pa,  $P < 0.010$ ).

**Conclusion:** Local application of ADSVF might lead to better tendon-bone healing in rabbit models.

**Key words:** Biomechanical; Magnetic Resonance Imaging; Rotator Cuff Healing

## INTRODUCTION

Rotator cuff tear is a common shoulder injury in middle-aged and elderly individuals. On the account of improvements in surgical repair, an increasing number of patients with rotator cuff tears are receiving effective treatments. However, a previous study has shown that the rate of re-tear after the repair of a rotator cuff injury ranges between 38% and 94%.<sup>[1]</sup> It is argued that this is due to a slow healing process, especially in elderly patients with degenerative rupture of the rotator cuff.<sup>[2,3]</sup> Moreover, stem cell technology has been widely considered as a means to repair a re-tear after

tendon-bone reconstruction.<sup>[4-7]</sup> Previous studies have utilized adipose-derived mesenchymal stem cells (ADSCs) to repair tendon and ligament tears and have observed effective

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repair improvements.<sup>[8,9]</sup> Although ADSCs could effectively promote the healing of degenerative rotator cuff injury, the poor self-renewal ability and uncertainties regarding safety remain a concern for patients with a rotator cuff tear. New or substitute treatment methods therefore need to be investigated.

Previous studies have demonstrated that adipose stromal vascular fraction (ADSVF) has a higher therapeutic potential than adipose stem cells alone in promoting the healing of connective tissue injury in animal models.<sup>[10-12]</sup> We, therefore, hypothesized that ADSVF treatment can improve the rotator cuff healing in rabbits. In the study, we used magnetic resonance imaging (MRI) scanning and biomechanical testing to evaluate rotator cuff healing in rabbits treated with or without adipose SVF.

## METHODS

### Animals and study design

Adult, male, New Zealand white rabbits, weighing 2.0–2.5 kg, were obtained from the Experimental Animal Center, Tongji University (License No. SYXK [Shanghai] 2014-0026). The rabbits were housed at the animal facility of the Laboratory Animals Centre of Tongji University. The study was conducted in strict accordance with the guidelines of the Care and Use of Laboratory Animals of the National Institutes of Health. All experimental protocols described in this study were approved by the Ethics Review Committee for Animal Experimentation of Tongji University. Of total, 36 rabbits were randomly divided between the control group ( $n = 18$ ) and the SVF-fibrin glue (SVF-FG) group ( $n = 18$ ). All samples had developed bilateral rotator cuff rupture and underwent surgical repair.

### Surgical procedure

Rabbits were anesthetized by intraperitoneal injection with 1 ml/kg of 3% pentobarbital sodium. Their inguinal yellow-white adipose tissues were harvested and washed with an equivalent amount of phosphate-buffered saline. Next, Type I collagenase was added and the tissue was digested for 4 h, after which it was centrifuged at  $241 \times g$  for 5 min to obtain the SVF suspension that was used to make the SVF-FG gelatinous-sustained release complex. After the animals were anesthetized, disinfected, and draped, a 4-cm longitudinal incision was made above the shoulder to expose the rotator cuff. The supraspinatus tendon was separated using a cured clamp, and the insertion of the tendon was severed from the

greater trochanter with a blade. In the tendon-bone interface, the severed supraspinatus tendon was subsequently sutured to the trochanter through the bones using the mattress suture method, followed by tightening and knotting.<sup>[13,14]</sup> For the SVF-FG group, SVF-FG was injected into the rabbits to uniformly fill in the tendon-bone interface; a total volume of 1 ml SVF-FG per side was injected and solidified after about 10 s [Figure 1]. For the control group, only FG was injected into the tendon-bone interface. After the operation, all the animals were fixed with plaster that was removed after 3 weeks. At 4, 8, and 12 weeks posttreatment, six animals were randomly selected from each group for MRI scanning under general anesthesia followed by execution for biomechanical evaluations. Since a surgical model was developed in the bilateral shoulders of the rabbits, 18 samples were obtained in each group. The study schematic is illustrated in Figure 2.

### Magnetic resonance imaging scanning

Before scanning, the rabbits received general anesthesia with pentobarbital (1 ml/kg) and were placed into a clinical 3.0-T superconducting magnet (3.0-T Magnetom Verio; Siemens, Munich, Germany). Next, the rabbits were laid in a right lateral position in a head-first manner, and the body surface coil (Siemens) was placed on their right shoulder. The oblique axial images were acquired through the long axis of the rotator cuff tendon with a fast spin echo pulse sequence (echo time, 25 ms; repetition time, 5000 ms; 217-Hz/Px receiver bandwidth; 1.1 mm slice thickness). A senior radiologist, blinded to the experiment protocol, reviewed the MRI scans.

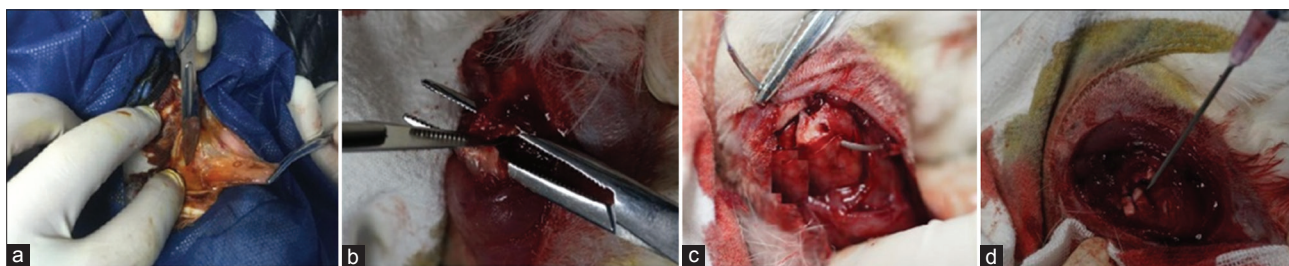
### Quantitative measurement

The quantitative measurement for calculating the signal intensity of the healing tissue was defined as the signal-to-noise quotient (SNQ), where LHBT is the long head of the biceps tendon.

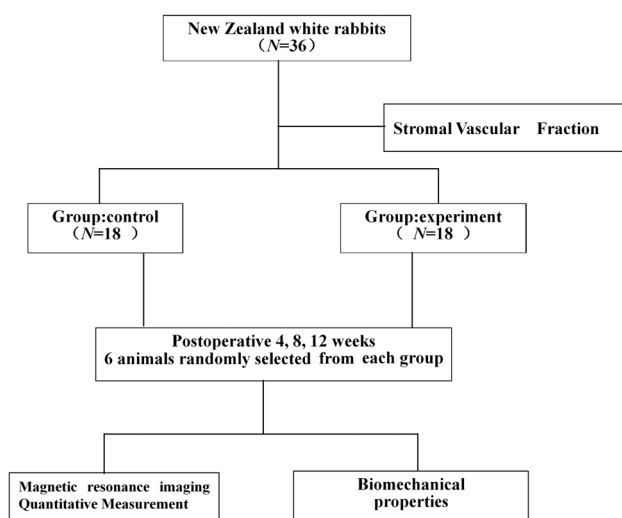
$$\text{SNQ} = \frac{\text{Signal (supraspinatus tendon - bone junction)} - \text{signal (LHBT)}}{\text{Signal (background)}}$$

### Definition of the region of interest

In this study, the region of interest (ROI) was defined as the supraspinatus tendon-bone interface area [Figure 3]. In each specimen, the tendon-bone interface could be seen on 3–4 slices; therefore, all the ROIs on the related images were calculated. The ROI was placed approximately 3 cm anterior to the supraspinatus tendon for the background



**Figure 1:** Surgical procedure of the study. (a) Harvesting adipose tissues; (b) cutting supraspinatus tendon; (c) repairing the tendon-bone interface; (d) injecting stromal vascular fraction-fibrin glue.



**Figure 2:** Flowchart of the study.

measurements. In addition, measurements of the LHBT were recorded as the circular 2 mm diameter ROIs on each image. Each measurement was performed four times by a radiologist, who was blinded to the experiment.

### Biomechanical evaluation

An MTS858 multifunctional biomaterial tester (Instron 8847, Norwood, Massachusetts, UK) was used to measure the maximum load, stiffness, and maximum strength of the tendon-bone specimens.

### Statistical analysis

Statistical analyses were performed using SPSS 13.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as the mean  $\pm$  standard deviation (SD) and were tested by independent *t*-tests. Between-group comparisons were conducted using one-way analysis of variance (ANOVA) with Bonferroni correction. MRI SNQ and biomechanical parameters were first assessed for normality and variance homogeneity before estimating the differences between the groups by ANOVA. A value of  $P < 0.05$  denoted a statistical significance.

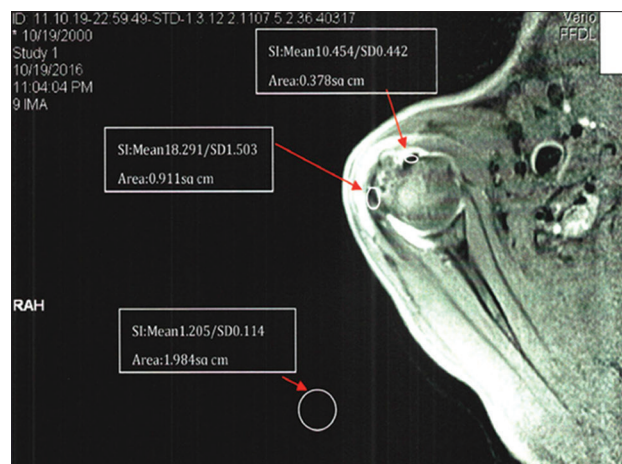
## RESULTS

### Effects of stromal vascular fraction-fibrin glue on magnetic resonance imaging signal-to-noise quotient after rotator cuff tear in rabbits

Four weeks posttreatment, no significant differences were observed in SNQ between the SVF-FG and the control groups ( $F = 1.570$ ,  $P = 0.232$ ). By week 8, SNQ had only slightly increased for both groups ( $F = 2.162$ ,  $P = 0.117$ ). At 12 weeks posttreatment, the SNQ in the SVF-FG group was significantly higher than that in the control group ( $F = 4.968$ ,  $P = 0.009$ ; Table 1 and Figure 4).

### Effects of stromal vascular fraction-fibrin glue on biomechanical parameters after rotator cuff tear in rabbits

To further test the effects of the SVF-FG treatment on the biomechanical properties of healing rotator cuff in rabbits,



**Figure 3:** Definition of regions of interest.

**Table 1: MRI signal-to-noise quotient after rotator cuff tear in rabbits ( $n = 18$ )**

Time of postsurgery	SVF-FG group	Control group	<i>F</i>	<i>P</i>
4 weeks	20.1 $\pm$ 3.6	18.2 $\pm$ 3.4	1.570	0.232
8 weeks	20.7 $\pm$ 3.3	18.0 $\pm$ 3.0	2.162	0.117
12 weeks	27.5 $\pm$ 4.6	22.1 $\pm$ 1.9	4.986	0.009

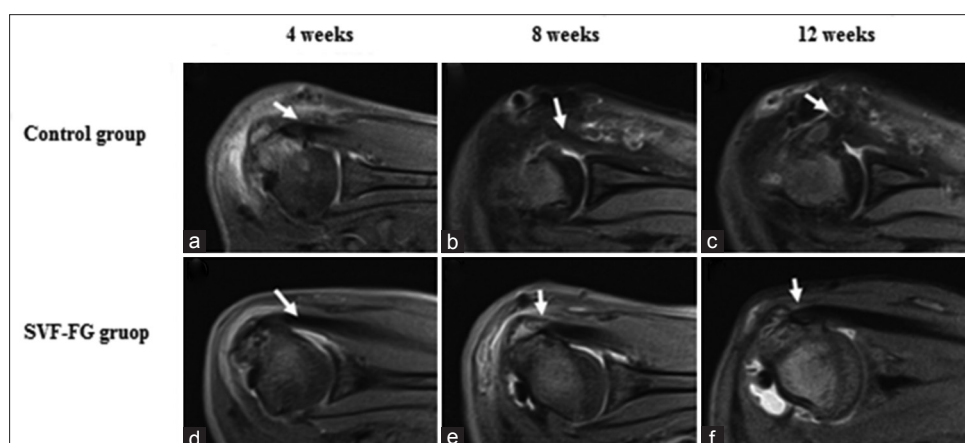
Data are presented as mean  $\pm$  SD. SVF-FG: Stromal vascular fraction-fibrin glue; SD: Standard deviation; MRI: Magnetic resonance imaging; ANOVA: Analysis of variance.

maximum load, maximum strength, and stiffness were assessed. The results demonstrated that the maximum load of the SVF-FG group was significantly higher than that of the control group 8 weeks after the operation. Also, the maximum strength of the SVF-FG group was higher than that of the control group at 8 weeks postoperation, but this was not significant. Similarly, a higher degree of stiffness was recorded in rotator cuff tear models treated with SVF-FG as compared to the control treatment [Tables 2–4].

## DISCUSSION

A previous study has demonstrated how locally injected stem cell suspension at the injured site of the flexor tendon in horses induced regularly arranged collagen postoperatively.<sup>[15]</sup> Moreover, long-term observations did not reveal any ossification or chondrification phenomena. This method, however, did not strengthen the healed tendon, which was still weaker than the normal tendon. Although stem cell treatment can significantly improve the histology, the effect on tendon strength seems inconclusive. Kajikawa *et al.*<sup>[16]</sup> directly injected ADSCs at the injured site of the patellar tendon in rats and set up a control group for comparison. Their study found that the secretion of Type I and Type III collagens increased significantly in the experimental group but that the mechanical strength of the ligament had not significantly improved. Taylor *et al.*<sup>[17]</sup> injected ADSCs to treat the rupture of the patellar tendon in





**Figure 4:** Magnetic resonance imaging scans of the control and SVF-FG groups at 4, 8, and 12 weeks. (a) High signal intensity in the tendon-bone interface in the control group; (b) no effusion or edema in the control group; (c) the tendon-bone junction area could not be identified in the control group; (d) high signal intensity was not obvious in the SVF-FG group; (e) joint effusion and bone marrow edema on the humeral head in the SVF-FG group; (f) the tendon quality and signal intensity improved compared with the 8 weeks images in the SVF-FG group. The tendon-bone interface is marked by arrows. SVF-FG: Stromal vascular fraction-fibrin glue.

**Table 2: Maximum load test results after rotator cuff tear in rabbits (N)**

Group	Maximum load of postsurgery at different time points			Sum	F	P
	4 weeks (n = 6)	8 weeks (n = 6)	12 weeks (n = 6)			
SVF-FG group	133.26 ± 30.93	166.89 ± 11.62	157.49 ± 25.84	148.96 ± 25.67	5.004	0.005 <sup>†</sup>
Control group	75.74 ± 13.23	99.40 ± 5.70	165.86 ± 26.30	102.49 ± 41.39	86.505	<0.001 <sup>†</sup>
Sum	104.50 ± 37.51	128.44 ± 34.92	166.37 ± 19.80	125.72 ± 41.44	44.088	<0.001 <sup>†</sup>
t/F	5.407	6.943	0.113	109.833	12.042	<0.001 <sup>†</sup>
P	<0.001*	<0.001*	0.918	<0.001*		

Data are presented as mean ± SD. \*Significant difference between the SVF-FG group and control group; <sup>†</sup>Significant difference among the 4, 8, and 12 weeks postsurgery. SVF-FG: Stromal vascular fraction-fibrin glue; SD: Standard deviation; ANOVA: Analysis of variance.

**Table 3: Maximum strength test results after rotator cuff tear in rabbits (N/mm)**

Group	Maximum strength of postsurgery at different time points			Sum	F	P
	4 weeks (n = 6)	8 weeks (n = 6)	12 weeks (n = 6)			
SVF-FG group	6.72 ± 1.57	8.22 ± 1.90	9.17 ± 1.22	7.75 ± 1.72	6.394	<0.010 <sup>†</sup>
Control group	4.73 ± 0.90	5.82 ± 0.68	9.88 ± 1.72	6.15 ± 2.48	59.718	<0.010 <sup>†</sup>
Sum	5.73 ± 1.61	7.02 ± 1.85	9.53 ± 1.50	6.95 ± 2.27	23.059	<0.010 <sup>†</sup>
t/F	3.478	3.758	-1.059	17.401	4.174	<0.010
P	<0.010*	<0.010*	0.649	<0.010*		

Data are presented as mean ± SD. \*Significant difference between the SVF-FG group and control group; <sup>†</sup>Significant difference among the 4, 8, and 12 weeks postsurgery. SVF-FG: Stromal vascular fraction-fibrin glue; SD: Standard deviation; ANOVA: Analysis of variance.

**Table 4: Stiffness test results after rotator cuff tear in rabbits (Pa)**

Group	Stiffness of postsurgery at different time points			Sum	F	P
	4 weeks (n = 6)	8 weeks (n = 6)	12 weeks (n = 6)			
SVF-FG group	29.53 ± 2.16	34.85 ± 3.00	36.56 ± 3.03	31.48 ± 5.19	44.465	<0.010 <sup>†</sup>
Control group	32.89 ± 8.62	24.57 ± 5.72	25.74 ± 8.12	23.89 ± 5.98	2.433	0.081
Sum	27.05 ± 4.92	30.29 ± 7.61	31.03 ± 6.63	27.69 ± 6.75	16.907	<0.010 <sup>†</sup>
t/F	2.568	3.308	7.012	63.005	2.435	0.070
P	0.010*	<0.010*	<0.010*	<0.010*		

Data are presented as mean ± SD. \*Significant difference between the SVF-FG group and control group; <sup>†</sup>Significant difference among the 4, 8, and 12 weeks postsurgery. SVF-FG: Stromal vascular fraction-fibrin glue; SD: Standard deviation; ANOVA: Analysis of variance.

New Zealand white rabbits and found that the mechanical properties of the tendon in the experimental group were significantly better than those in the control group during 6–12 weeks' posttreatment. In addition, some investigators

retrospectively analyzed the application of ADSCs for the treatment of chronic tendinopathy and found that there was no significant treatment effect between the treated and control groups. Uysal *et al.*<sup>[18]</sup> established a rabbit Achilles tendon rupture model and used it to compare the treatment effects of ADSCs and platelet-rich plasma (PRP) with PRP alone on tendon healing. The study found that after 4 weeks, the maximum tensile load of the tendon in the ADSC-PRP group was significantly higher than that in the PRP controls. Also, the levels of transforming growth factor beta (TGF- $\beta$ )-1, 2, and 3 were lower, and the fibroblast and vascular growth factors were significantly higher in the ADSC-PRP group as compared to the PRP group. These findings indicated that the adipose-derived stem cells could not only promote tendon healing and improve the quality of newly generated tendon, but also inhibit the synthesis of TGF associated with tendon adhesion. Interestingly, the biomechanical properties of healing tendons have rarely been studied following SVF treatment. The results of the present study suggest that ADSVF treatment of a rotator cuff injury can significantly improve some of the biomechanical parameters postoperatively. An increased secretion of collagen fibers might explain these observations as this could have promoted the mechanical strength of the healed tendon.

Morphologically, mild tissue edema and clearer tendon outlines predicted better healing in the SVF-FG group than those in the control group at each of the three time points. Quantitative measurements of hyperintensity and SNQ confirmed these observations. A high SNQ indicates high water content or hypervascularity and is a sign of pathological change in the normal rotator cuff tendons.<sup>[19-21]</sup> In this study, the SVF-FG group had a significantly higher signal intensity and SNQ than the control group at 12 weeks, while the maximum load and stiffness did not show any significant improvement. The present study was, therefore, unable to correlate the SNQ with the biomechanical properties of the healing rotator cuff injury at 12 weeks. However, during the early stages postsurgery, MRI was presumed to evaluate the integrity of surgical repair and monitor the early inflammation changes morphologically. This study evaluated the effect of ADSVF on tendon healing; however, there were some limitations. First, the animal model might not accurately reflect the healing pattern in humans, and an acute tear was created which does not reflect the usual chronic tear pattern seen in the human rotator cuff. Second, a negative linear correlation between SNQ and biomechanical properties was reported previously in anterior cruciate ligament graft healing research in sheep.<sup>[22,23]</sup> Nevertheless, in this study, the correlation was present after 12 weeks, which implies that SNQ could be utilized as a parameter for predicting the rotator cuff healing in the long term >12 weeks. Furthermore, the pathological and the histological evaluation of the rotator cuff should have been conducted simultaneously for consistency. Finally, there is no evidence that ADSVF treatment is better than conventional rotator cuff repair.

In conclusion, further experiments should focus on marking ADSCs to observe their movement and evolution during the tendon-bone interface changes in the long term.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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