J Shoulder Elbow Surg (2017) ■■, ■■–■■

ELSEVIER

Journal of Shoulder and Elbow Surgery

www.elsevier.com/locate/ymse

ORIGINAL ARTICLE

Enhancement of rotator cuff tendon–bone healing with fibroblast growth factor 2 impregnated in gelatin hydrogel sheets in a rabbit model

Takuya Tokunaga, MD, PhD[a,*], Tatsuki Karasugi, MD, PhD[a], Hitoshi Arimura, MD[a], Ryuji Yonemitsu, MD[a], Hidetoshi Sakamoto, Dr Eng[b], Junji Ide, MD, PhD[c], Hiroshi Mizuta, MD, PhD[a]

[a]*Department of Orthopaedic Surgery, Faculty of Life Sciences, Kumamoto University, Kumamoto, Japan*
[b]*Department of Mechanical System Engineering, Doshisha University, Kyoto, Japan*
[c]*Department of Advanced Joint Reconstructive Surgery, Kumamoto University Hospital, Kumamoto, Japan*

Background: Application of fibroblast growth factor 2 (FGF-2) may improve the healing response after rotator cuff (RC) surgical repair. This study aimed to determine whether FGF-2–impregnated gelatin hydrogel sheet (GHS) incorporation into the bony trough on the greater tuberosity facilitates healing after RC surgical repair in rabbits.

Methods: We assigned 120 adult male Japanese white rabbits treated with unilateral surgery for supraspinatus tendon repair into the following groups: suture-only group (suture); suture and GHS with phosphate-buffered saline (carrier); suture and GHS with 3 μg of FGF-2 (F3); and suture and GHS with 30 μg of FGF-2 (F30). The effect of FGF-2 was assessed using histologic, biomechanical, and microcomputed tomography evaluations at 2, 6, and 12 weeks.

Results: At 12 weeks, loose fibrovascular tissues emerged at the repair site in the suture and carrier groups and dense tendon-like tissues in the F3 and F30 groups, which demonstrated significantly higher ultimate load-to-failure and stress-to-failure at 12 weeks than that in the suture and carrier groups. Microcomputed tomography imaging showed ectopic calcification formation in some specimens from each group. Appearances or frequencies were similar among groups. The histologic and biomechanical effects of FGF-2 on RC healing were obvious at ≥6 weeks postoperatively.

Conclusion: FGF-2-impregnated GHS incorporation into the bony trough on the greater tuberosity before RC surgical repair is feasible and results in histologic and biomechanical improvements during RC healing in rabbits. No detrimental effect on ectopic calcification was observed.

Level of evidence: Basic Science Study; Biomechanics/Histology; Animal Model

Keywords: FGF-2; rotator cuff; histology; biomechanics; gelatin hydrogel sheet; rabbit model; tendon–bone healing

Animal Studies Committee and the Institutional Animal Care and Use Committee of Kumamoto University approved all animal experimental procedures in this study.

*Reprint requests: Takuya Tokunaga, MD, PhD, Department of Orthopaedic Surgery, Faculty of Life Sciences, Kumamoto University, 1-1-1 Honjo, Chuo-ku, Kumamoto 860-8556, Japan.
E-mail address: ttokunaga@kuh.kumamoto-u.ac.jp (T. Tokunaga).

1058-2746/$ - see front matter
http://dx.doi.org/10.1016/j.jse.2017.03.020

Rotator cuff (RC) tears are one of the common causes of shoulder dysfunction and often require surgical repair when symptoms persist after conservative treatment. With remarkable improvement in surgical techniques and devices for repairing RC tears, postoperative clinical outcomes have also been improving. Nevertheless, several problems remain, including a high rate of failed repair[3,7,10,28] and the need for long therapeutic period because of poor healing after the RC tendon–bone repair.[12] Thus, new biologic strategies that enhance the healing response have been studied.[5,6,15,23]

Fibroblast growth factor 2 (FGF-2) is one of the growth factors known to be a potent mitogen for various types of cells.[2] FGF-2, which is endogenously expressed during RC tendon–bone healing, plays a critical role in the healing process.[21,37] Several reports have shown that the application of FGF-2 to the repair site enhances RC tendon–bone healing, as evaluated by biomechanical tests and histologic analyses in rat models.[4,13,14,33] It is even suggested that the effect of FGF-2 on RC healing is possibly mediated by the growth stimulation of tenogenic progenitor cells, which is observed by monitoring tendon-related marker genes such as SRY-box containing gene 9 (*Sox9*), scleraxis (*Scx*), and tenomodulin (*Tnmd*).[33]

Local application of a therapeutic agent with a carrier to the tendon–bone insertion site, such as the bony trough on the greater tuberosity, to stimulate the healing response after surgical RC tendon–bone reattachment appears to be effective. Previous reports[16-19,25,30] demonstrated that biodegradable gelatin hydrogel sheets (GHSs) were carriers for the slow release of various growth factors, including FGF-2, for the repair of various tissues. However, the efficacy of an FGF-2–impregnated GHS into the bony trough on the greater tuberosity in RC healing remains unclear.

A rat RC repair model has been commonly used to investigate the mechanism of RC healing in attempts to enhance healing. However, the model has some limitations in the reproducibility of the surgical technique mimicking clinical conditions because of its small size.[6,27] We selected a previously reported rabbit RC repair model,[11,22,35,36] which has a sufficiently sized supraspinatus tendon and greater tuberosity, to reproduce the surgical technique and to apply the FGF-2–impregnated GHS into the bony trough on the greater tuberosity.

This study aimed to determine whether the application of GHSs impregnated with 2 different doses of FGF-2 into the bony trough on the greater tuberosity would enhance RC tendon–bone healing in a rabbit model. We also verified the effect of the FGF-2–impregnated GHS on ectopic calcification within the healing tissues by microcomputed tomography (micro-CT) analysis.

We hypothesized that the application of FGF-2–impregnated GHSs into the bony trough on the greater tuberosity could improve the biomechanical strength of the reparative site and contribute to the formation of a tendon-like tissue at the repair site. Moreover, the FGF-2–impregnated GHS has no detrimental effects on ectopic calcification within the healing tissues during RC healing.

Materials and methods

Study design

This is a basic science animal study on the effect of FGF-2 on RC healing after repair in rabbits. The 2 experiments in this study are as follows (Fig. 1): examination of the effect of GHS alone or the 2 doses of FGF-2–impregnated GHS in a rabbit RC repair model 12 weeks postoperatively (experiment 1) and the investigation of the effect of FGF-2 at an early phase in the same model (experiment 2). A total of 120 mature male Japanese white rabbits (mean ± standard deviation weight, 3.25 ± 0.18 kg) underwent left shoulder surgery for the supraspinatus tendon. The tendon was transected and acutely repaired into a bony trough on the greater tuberosity.

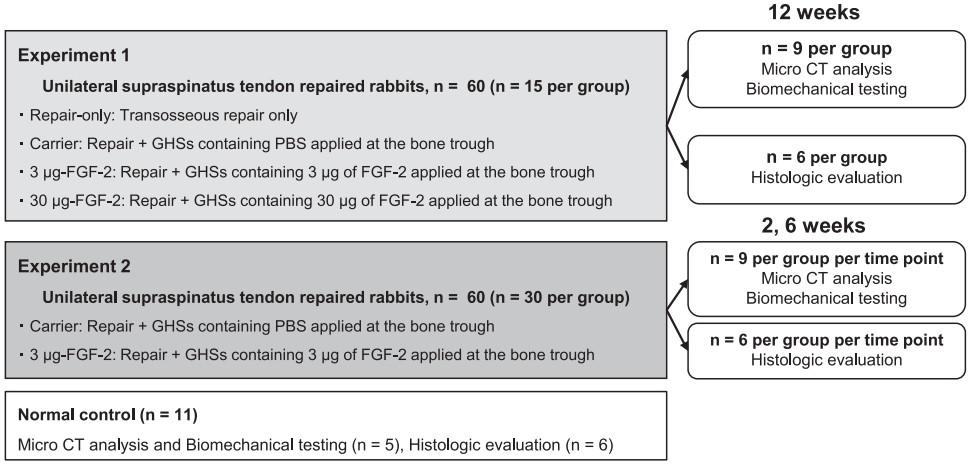

Figure 1 Study design. Each left shoulder received treatment. Rabbits were euthanized at 12 weeks for experiment 1 and at 2 and 6 weeks for experiment 2. *CT*, computed tomography; *FGF*, fibroblastic growth factor; *GHSs*, gelatin hydrogel sheets; *PBS*, phosphate-buffered saline.