Comparison of Autograft and Allograft with Surface Modification for Flexor Tendon Reconstruction

A Canine in Vivo Model

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Background: Flexor tendon injury is common, and tendon reconstruction is indicated clinically if the primary repair fails or cannot be performed immediately after tendon injury. The purpose of the current study was to compare clinically standard extrasynovial autologous graft (EAG) tendon and intrasynovial allogeneic graft (IAG) that had both undergone biolubricant surface modification in a canine in vivo model.

Methods: Twenty-four flexor digitorum profundus (FDP) tendons from the second and fifth digits of 12 dogs were used for this study. In the first phase, a model of failed FDP tendon repair was created. After 6 weeks, the ruptured FDP tendons with a scarred digit were reconstructed with the use of either EAG or IAG tendons treated with carbodiimide-derivatized hyaluronic acid and lubricin. At 12 weeks after tendon reconstruction, the digits were harvested for functional, biomechanical, and histologic evaluations.

Results: The tendon failure model was a clinically relevant and reproducible model for tendon reconstruction. The IAG group demonstrated improved digit function with decreased adhesion formation, lower digit work of flexion, and improved graft gliding ability compared with the EAG group. However, the IAG group had decreased healing at the distal tendon-bone junction. Our histologic findings verified the biomechanical evaluations and, further, showed that cellular repopulation of allograft at 12 weeks after reconstruction is still challenging.

Conclusions: FDP tendon reconstruction using IAG with surface modification has some beneficial effects for reducing adhesions but demonstrated inferior healing at the distal tendon-bone junction compared with EAG. These mixed results indicate that vitalization and turnover acceleration are crucial to reducing failure of reconstruction with allograft.

Clinical Relevance: Flexor tendon reconstruction is a common surgical procedure. However, postoperative adhesion formation may lead to unsatisfactory clinical outcomes. In this study, we developed a potential flexor tendon allograft using chemical and tissue-engineering approaches. This technology could improve function following tendon reconstruction.

A flexor tendon injury is one of the most common traumas of the hand¹. Although direct repair after injury is the standard in clinical practice²⁻⁴, flexor tendon reconstruction is often necessary if direct repair cannot be performed because of a large tendon defect or if direct repair fails because of severe adhesions or rupture of the repaired tendon⁵⁻⁷. Crush injuries, accounting for approximately 30% of all hand injuries⁸, are often associated with severe tendon damage, which is also an indication for tendon-grafting. However, clinical studies have demonstrated that frequent

sequelae of tendon-grafting are restrictive adhesions and poor digit motion⁹⁻¹³, often resulting in multiple surgical revisions, including salvage procedures such as arthrodesis^{14,15}, or even finger amputation^{14,16-18}.

Flexor tendons are classified as intrasynovial tendons because they are located within a synovial environment, similar to the joints. In addition to functioning as a cable, like any other tendon, to transmit muscle forces to bone to perform joint motion, they also experience repetitive abrasion during hand motion¹⁹⁻²¹. However, clinically standard tendon autografts come

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from extrasynovial tendon sources because of a lack of available sources of intrasynovial tendons. In both clinical and animal models, extrasynovial tendon autografts have been associated with more adhesions to the surrounding tissue than intrasynovial tendon autografts, and thus, with diminished function^{20,22-24}. Alternatively, allogeneic intrasynovial tendons are available for flexor tendon reconstruction. However, decellularization and sterilization before graft transplant damage the tendon mechanical properties, especially surface structure, leading to high tendon gliding resistance.

The chemical compound of carbodiimide-derivatized hyaluronic acid combined with lubricin (cd-HA-lubricin) has been used to modify the tendon graft surface²⁵⁻²⁷, with previous studies finding that cd-HA-lubricin effectively increased the graft gliding ability and surface durability against abrasion in an in vitro model^{28,29} and decreased adhesion formation and improved digit functional recovery in an in vivo model^{27,30}. The major adverse effect at short-term follow-up was delayed graft-healing within host tissues at 6 weeks after graft surgery, particularly at the tendon-bone insertion site^{27,30}. However, extrasynovial and intrasynovial grafts with surface modification have not, to our knowledge, been compared. Further, whether longer follow-up would have overcome the deficit of healing at 6 weeks due to surface modification is unknown. Therefore, the purpose of the current study was to compare functional outcomes of intrasynovial allogeneic grafts (IAGs) and extrasynovial autologous grafts (EAGs) with cd-HA-lubricin surface treatment at 12 weeks after flexor digitorum profundus (FDP) tendon transplant. We hypothesized that IAGs treated with cd-HA-lubricin would demonstrate better digit functional recovery than, and healing strength comparable with, EAGs treated with cd-HA-lubricin after 12 weeks following reconstruction.

Materials and Methods

Study Design

Twelve mixed-breed dogs of both sexes (average weight, approximately 20 kg), were used in this study, which was approved by our Institutional Animal Care and Use Committee. The investigation included 3 phases. In the first phase, a model of ruptured FDP tendon repair was created at the second and fifth digits using a previously established canine model³¹. This repair failure model was clinically relevant for the second phase: flexor tendon reconstruction. After 6 weeks of the first phase, the failed FDP tendons in each dog were replaced by either IAG or EAG treated with a biolubricant compound. After flexor tendon reconstruction, the dogs were immobilized with a dog sling and underwent postoperative therapy daily for 6 weeks. The sling was then removed, and the dogs were allowed free-cage activity for 6 weeks. The dogs were killed at 12 weeks after tendon reconstruction, and functional, biomechanical, and histologic analyses were then performed, constituting the third phase.

Model of Failed Flexor Tendon Repair

To mimic the clinical scenario for flexor tendon reconstruction, a failed tendon repair was created on the basis of a previously established protocol³¹. Briefly, the second and fifth FDP ten-

dons in each dog were exposed and sharply transected at the level of the proximal interphalangeal joint and repaired with a modified Kessler suture. Following repair surgery, the dogs were allowed free-cage activity, resulting in a 100% rate of rupture of the tendon repair, with scar formation within the flexor sheath after 6 weeks³¹.

Flexor Tendon Transplant with Allograft or Autograft IAG and EAG Preparation

For the allografts, the FDP tendons from dogs killed in other Institutional Animal Care and Use Committee-approved studies were decellularized and sterilized according to previously established protocols²⁷. Briefly, the tendons were immersed in liquid nitrogen for 1 minute and then thawed in 37°C saline solution for 5 minutes. This procedure was repeated 5 times for decellularization. The decellularized tendons were lyophilized (Millrock Technology lyophilizer). Each allograft was then stored in a sealed, specially designed plastic bag for gas sterilization. At 24 hours before reconstruction, the graft tendon was immersed in a 0.9% NaCl bath for rehydration in an incubator at 37°C³². For the autografts, the peroneus longus tendon from the lower extremity of the nonsurgical hind limb was harvested immediately before graft surgery.

Graft Surface Modification

Before flexor tendon reconstruction, both autograft and allograft tendons were treated with cd-HA-lubricin with the following formula: 1% sodium hyaluronate (95%, 1.5×10^6 molecular weight; Acros Organics), 10% gelatin (Sigma-Aldrich), 1% 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (Sigma-Aldrich), 1% *N*-hydroxysuccinimide (Pierce, Thermo Scientific), 0.1 M 2-(*N*-morpholino) ethanesulfonic acid (MES) (pH 6.0), and 260 µg/mL lubricin³³.

Flexor Tendon Reconstruction

The IAG or EAG tendons were randomly assigned to either the second or fifth digit in which the FDP tendon repair had failed, with a scarred digit. Reconstruction procedures were according to previously developed protocols^{27,30}. Briefly, the failed repaired FDP tendon stumps with scar tissue within the flexor sheath were removed through a distal incision. A bone tunnel was created at the distal phalanx. Through a proximal incision, the normal FDP tendon was exposed. A subcutaneous tunnel was created between these 2 incisions, and the graft tendon was passed through the tunnel. The Bunnell technique was used to attach the distal end of the graft within the bone tunnel³⁴. A 2-weave interlacing technique was used to attach the proximal end of the graft to the recipient FDP tendon³¹. At postoperative day 5, a synergistic wrist and digit rehabilitation protocol was initiated and then performed once daily, 7 days per week for 6 weeks, followed by free-cage activity for another 6 weeks^{35,36}.

Adhesion Formation at the Proximal Repair Site

The adhesions around the proximal tendon graft repair site were evaluated by measuring the adhesion breaking strength, as

previously described³⁷. Briefly, a custom-made device was used to secure the digits and the normal FDP tendon proximal to the proximal repair site with a clamp that connected to a motor and force transducer. The graft tendon was sharply transected at the distal repair site, and the graft and the proximal part of the repair were then pulled by the motor to break any adhesions surrounding the proximal repair site until it was fully pulled out of the digit. The force needed to break the adhesions was used to quantify the adhesion formation around the proximal repair site.

Digit Work of Flexion and Adhesions in Zone II

The graft tendons in the second and fifth digits were evaluated in zone II for digit work of flexion (WOF) normalized by digit joint motion according to a previously reported technique³³. Briefly, the graft tendons were transected at the proximal metacarpal level and connected to a load transducer. A Kirschner wire was used to fix the metacarpophalangeal joint and mounted on the testing device. The actuator pulled the tendon proximally, causing digital flexion. Digital motion was recorded and analyzed by a motion-analysis system (Motion Analysis). After WOF

Fig. 1
Mechanical evaluation of the distal graft tendon-to-bone repair. The distal graft tendon stump (white arrow) was augmented with suture (like a ponytail) to minimize tendon damage and slippage by the clamp. The distal phalanx (black arrow) was blocked by a mounting plate, and the graft tendon was secured with a clamp for testing of distal repair failure.

testing, the graft was carefully exposed in zone II, and adhesions within this area were identified and scored on a scale ranging from 0 (no adhesions) to 8 (severe adhesions) according to previously reported methods³⁸.

Graft Gliding-Resistance Test

The graft tendon in zone II was dissected. Two load transducers were then attached to the graft tendon, proximal and distal to the A2 pulley, respectively. A motor pulled the graft proximally to simulate digit flexion and was then reversed to mimic extension. The graft tendon gliding resistance against the pulley was calculated on the basis of the difference between the force recorded on the 2 load transducers, according to a previously described method³⁹.

Distal Graft Tendon-to-Bone Repair Strength

The distal graft tendon stump was wrapped with 3-0 silk suture, with the distal graft-bone insertion site free of suture. The purpose of the suture wrapping was to enhance graft strength so that the clamp firmly secured the graft tendon with minimal damage; thus, no slippage occurred between the tendon and clamp (Fig. 1). The graft tendon was passed through a hole 8 mm in diameter in a plate that was fixed at the base of the servohydraulic test machine (MTS Systems). The graft tendon was pulled at 20 mm/min until the distal tendon-to-bone repair ruptured. Force and tendon displacement were recorded at a rate of 50 Hz. The peak force and stiffness (calculated using the slope of the linear region of the load-displacement curve) were determined.

Histologic Analysis

Two samples from each graft group were used for histologic analysis. Zone-II portions of the graft tendons, about 1 cm in

length, were dissected and stained with calcein acetoxymethyl (AM) and ethidium homodimer immediately after sacrifice to maintain cell viability after death⁴⁰. Tendon samples were observed with a confocal microscope (LSM 510; Zeiss) immediately after harvesting to evaluate cell viability. Another 1-cm portion of graft tendon in zone II, the proximal tendon-to-tendon repair site, and the distal tendon-to-bone repair site were also harvested and fixed with a 10% formalin solution, embedded in paraffin, and sectioned into 7- μ m-thick slices. Sections were stained with hematoxylin and eosin and qualitatively observed with light microscopy.

Statistical Analysis

The number of grafts with tendon rupture was analyzed using a Fisher exact test. All quantitative data are presented as the mean and standard deviation. The quantitative data, including adhesion score, the strength and stiffness needed to break proximal repair adhesions, normalized work of flexion, graft gliding resistance, and distal repair strength and stiffness, were analyzed with repeated-measures analysis of variance because the comparison groups (IAG [allograft] and EAG [autograft], with normal tendon in some experiments) were from the same animals. Statistical analysis was performed with SPSS Statistics software (version 14; SPSS). Significance was set at the level of $p < 0.05$ in all cases.

Results

In the first phase, all repaired FDP tendons were ruptured uniformly, with retraction of the proximal tendon stump into the palm, extensive scar formation in the flexor sheath, and fixation of the distal tendon stump to the middle phalanx by adhesion formation. Of 12 grafts in the IAG (allograft)

Fig. 2
Outcome measures: mean adhesion score (Fig. 2-A), breaking strength (Fig. 2-B), and stiffness (Fig. 2-C) at the proximal repair site. IAG = intrasyneovial allogeneic graft, and EAG = extrasynovial autologous graft. The error bars indicate the standard deviation, and asterisks indicate a significant difference ($p < 0.05$).

TABLE I Adhesion and Biomechanical Data*

	Normal FDP	IAG	EAG
Adhesion score		2.0 ± 2.6†	5.1 ± 1.5†
Adhesion breaking strength (N)	3.6 ± 1.9	28.8 ± 14.7†‡	44.5 ± 9.2†‡
Adhesion breaking stiffness (N/mm)	0.8 ± 0.4	5.9 ± 3.4†‡	9.2 ± 6.1†‡
Normalized work of flexion (N-mm/°)	0.2 ± 0.1	0.3 ± 0.2†‡	1.0 ± 0.9†‡
Graft gliding resistance (g)	6.5 ± 2.1	13.4 ± 5.1†‡	33.0 ± 17.7†‡
Distal strength to failure (N)		48.5 ± 19.4†	120.7 ± 46.7†
Distal stiffness to failure (N/mm)		14.9 ± 6.5†	40.6 ± 19.1†

*The values are given as the mean and standard deviation. FDP = flexor digitorum profundus. †Significant difference between IAG and EAG.
‡Significant difference as compared with normal FDP.

group, 5 ruptured at the distal tendon-bone junction and 1 ruptured at the proximal tendon-to-tendon repair site. However, only 1 graft ruptured at the proximal tendon-to-tendon repair site in the EAG (autograft) group ($p = 0.06$).

Adhesion Status

The adhesion score, adhesion breaking strength at the proximal repair site, and adhesion stiffness in the IAG group were significantly lower than noted in EAG group ($p < 0.05$) (Fig. 2) (Table I).

Digit Function and Graft Gliding Resistance

The normalized work of flexion (nWOF) in the IAG group was significantly lower than that in the EAG group ($p < 0.05$).

However, the nWOF in both the IAG and EAG groups was significantly higher than that in the normal, nonsurgical digits ($p < 0.05$) (Fig. 3-A). The frictional force in the IAG group was significantly less than that in the EAG group ($p < 0.05$), and both IAG and EAG tendons had greater friction than did the normal FDP tendons in the nonsurgical digits ($p < 0.05$) (Fig. 3-B) (Table I).

Distal Graft-to-Bone Healing

The maximum strength to failure (Fig. 4-A) and stiffness to failure (Fig. 4-B) at the distal tendon-bone junction were significantly decreased in the IAG group compared with the EAG group ($p < 0.05$) (Table I).

Fig. 3

Outcome measures: mean normalized work of flexion (nWOF, **Fig. 3-A**) and graft gliding resistance (friction, **Fig. 3-B**). The greater the normalized work of flexion, the worse the digit function. The less gliding resistance, the better the tendon gliding function. IAG = intrasynovial allogeneic graft, and EAG = extrasynovial autologous graft. The error bars indicate the standard deviation, and asterisks indicate a significant difference ($p < 0.05$).

Fig. 4

Outcome measures: mean failure strength (**Fig. 4-A**) and stiffness (**Fig. 4-B**) of the distal graft-to-bone repair site. IAG = intrasyneovial allogeneic graft, and EAG = extrasyneovial autologous graft. The error bars indicate the standard deviation, and asterisks indicate a significant difference ($p < 0.05$).

Histologic Analysis

Histologically, the intrasyneovial allograft tendon in zone II showed that cells were on the tendon surface only. Twelve

weeks after allograft tendon transplant, the tendon substance was still acellular (**Fig. 5**, right panels). In contrast, the autograft tendon was a viable tendon with randomly aligned

Fig. 5

Histologic findings. Graft tendons from the autograft group (left panels) and from the allograft group (right panels) (light microscopy, hematoxylin and eosin). The autograft tendon presented rough tendon surfaces with adherence-scar tissue around the graft and hypercellularity. In contrast, the allograft tendon had a smooth surface without adhesions. The cells were observed on only the tendon surface. The allograft tendon substance was acellular 12 weeks after implantation.

Fig. 6

Figs. 6-A and 6-B Histologic findings. In some areas of the autograft tendon, adipose cells were present (**Fig. 6-A**, white arrows), and angiogenesis (**Fig. 6-B**, black arrow) appeared within tendon substances ($\times 200$). These findings indicate that an autograft tendon might undergo some degenerative changes after tendon transplant, even in an autologous condition.

tenocytes within the tendon substance 12 weeks after grafting. However, adhesion-scar tissues were present on the autograft tendon surface (Fig. 5, left panels). In some areas of the autograft tendon, adipose cells were present (Fig. 6-A), and angiogenesis (Fig. 6-B) appeared within the tendon substances.

At the distal tendon-bone junction, histologic analysis showed a clear tidemark between calcified fibrocartilage and the fibrocartilage zone at the tendon-bone interface in normal tendon (Fig. 7, left panels). Although autograft tendon showed tendon-to-bone fusion, there was no identifiable transitional fibrocartilaginous zone. Vascularization was noted at the tendon-bone interface (Fig. 7, middle panels). In the allograft group, neither a transitional fibrocartilaginous zone nor solid tendon-to-bone fusion was observed, and the junction had

some gaps at the tendon-bone interface. However, many cells were in the allograft tendon substance, unlike the allograft in zone II, which had no cells migrating into the substance of the graft (Fig. 7, right panels).

At the proximal graft-to-host tendon junction, solid fusion occurred between graft and host tendon in the autograft group (Fig. 8, left panels). However, in the allograft group, a clear gap was observed between allograft tendon and host FDP tendon. Although a hypercellular zone at the interface was observed, cells were barely migrating into the graft substance, except at the suture-tendon interface (Fig. 8, right panels).

Discussion

The IAG group had a significantly lower adhesion score, proximal adhesion breaking strength, adhesion stiffness, nWOF, and gliding resistance than did the EAG group. Histologic assessment verified that more adhesion formation occurred in the EAG group. In contrast, the surface in the IAG group maintained smoothness without adhesions. In addition, cellular repopulation in the allograft tendons was limited to the surface; no cells were found in the tendon midsubstance in zone II. This *in vivo* finding confirmed the theory established in an *in vitro* model: cell migration is difficult in tendon tissue because of its high collagen density⁴¹. In the autograft group, the cellularity seemed to be that of normal tendon, an indication that a viable graft tendon remained. However, adipose cells and vascularization were also observed in the graft substance, and this finding might indicate some pathologic or degenerative changes at 12 weeks following autograft reconstruction.

In the current study, healing of the distal tendon-bone junction was reduced in the IAG group. This insufficient graft-host healing in the IAG group also led to a higher rate of graft failure at the tendon-bone junction than in the EAG group (42% versus 0%). At short-term (6-week) follow-up in a previous study, an allograft with the same surface modification decreased distal healing strength by 50% compared with the repair strength at time 0 or allograft tendon without treatment²⁷. The distal strength at 12 weeks in the current study was double that of the strength at 6 weeks in the previous study, a result that might indicate that the allograft improves healing at the junction over time. Even so, the strength was far below the distal failure strength of the autograft group at 12 weeks. Histologic assessment showed that loosened tendon fiber was seen near the osseous structure, with a gap in the tendon-bone interface in the allograft, whereas the autograft had dense fiber near the osseous structure with solid fusion between tendon and bone. However, neither EAG nor IAG could truly restore a normal tendon-bone junction; a transitional fibrocartilaginous zone was absent in both repair groups.

This study had several limitations. First, the data were obtained only at 12 weeks postoperatively. However, because the methods were similar to those of previous reports with short-term follow-up, the comparison is valid. Second, we did not have control groups (grafts without biolubricant treatment) with which to compare the treated graft in both EAG and IAG groups; these comparisons have been previously reported^{31,34,42}. In those previous studies, the biolubricant treatment demonstrated positive effects

Fig. 7

Histologic findings. Distal tendon-bone junction (enthesis) (hematoxylin and eosin). The normal tendon-bone enthesis (left panels) showed a clear tidemark (striped arrows) between calcified fibrocartilage and the fibrocartilage zone at the interface of the tendon (white arrow) and bone (black arrow). In the autograft tendon (middle panels), fusion between the tendon (white arrow) and bone (black arrow) was observed. However, no identifiable transitional fibrocartilaginous zone as in normal enthesis was noted. Vascularization at the tendon-bone interface was observed (striped arrows). In the allograft tendon (right panels), neither a transitional fibrocartilaginous zone nor fusion between solid tendon (white arrow) and bone (black arrow) was observed. The junction between tendon and bone had some gaps at the interface (striped arrows).

Fig. 8

Histologic findings. Proximal tendon-to-tendon repair site. In the autograft group (left panels), solid fusion occurred between autograft (white arrow) and host tendon (black arrow). However, in the allograft group (right panels), a clear gap was observed between allograft tendon (white arrow) and host flexor digitorum profundus tendon (black arrow). The allograft tendon still appeared acellular at 12 weeks after transplant (white arrow), except at the suture-tendon interface (striped arrows).

on reducing adhesion formation but the side effects of decreasing healing ability. Third, the histologic analyses were performed only in 2 samples in each group, which made quantitative analysis impossible. Additionally, we only performed hematoxylin and eosin staining. Evaluating the other cytokines related to tendon regeneration, such as transforming growth factor-beta (TGF- β) and type-I and III collagens, would provide some molecular information regarding flexor tendon grafting. Fourth, failure strength was not determined for the proximal tendon-to-tendon repair site because the tendon segment was too short to be secured for testing. Finally, we do not know whether the low healing capacity in the IAG group was caused by the surface modification or the nature of the acellular allograft because there was no control group without surface modification. The overall goal was to compare intrasynovial allograft with extrasynovial autograft, as intrasynovial allograft is clinically available.

In summary, we found that intrasynovial allograft tendon with cd-HA-lubricin surface modification improved digit function, decreased adhesion formation, and decreased gliding resistance compared with extrasynovial autograft tendon treated with the same surface modification. However, tendon-to-bone healing in the IAG group was delayed, a result that led to more ruptures and weaker distal attachments. Regardless of this adverse effect, intrasynovial allograft could become a clinically useful alternative to extrasynovial autografts for the recon-

struction of failed tendon repairs in the hand. However, it should be cautioned that intrasynovial allograft could delay healing and tendon regeneration compared with an extrasynovial autograft tendon. Future research should focus on improving allograft tendon vitalization and accelerating turnover, such as by using cell-based therapy or tissue-engineering approaches. ■

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