Reconstruction of the Tendon–Bone Insertion With Decellularized Tendon–Bone Composite Grafts: Comparison With Conventional Repair

Simon Farnebo, MD, PhD, Colin Y. Woon, MD, Maxwell Kim, BSc, Hung Pham, BSc, James Chang, MD

Purpose Injuries involving the tendon–bone interface (TBI) are difficult to address. Standard techniques typically lead to diminished strength of the healed insertion site. We hypothesized that these injuries would benefit from being reconstructed with decellularized composite grafts replacing both tendon and bone. To test this hypothesis, decellularized grafts were compared with conventional pullout repairs in an *in vivo* animal model.

Methods We harvested 48 Achilles TBI grafts from rats and decellularized them. Tendon–bone interface graft reconstruction and pullout repairs were compared using a pair-matched design. Biomechanical properties were evaluated at 2, 4, 8, and 12 weeks. We evaluated histological analysis of insertion morphology and collagen type I/III content.

Results There was a significant increase in ultimate failure load (35 ± 11 vs 24 ± 7 N) and ultimate tensile stress (1.5 ± 0.3 vs 1.0 ± 0.4 N/mm^2) of the TBI grafts compared with pullout repairs at 2 weeks. These differences remained at 4 weeks. At 12 weeks, both TBI grafts and pullout repairs were as strong as native tissue and not significantly different from each other. Histology showed a more organized extracellular matrix in the TBI graft group at the early time points. Repopulation of the decellularized grafts increased over time. At 12 weeks, the insertion points of both groups were richly populated with cells that possessed morphologies similar to those found in native TBI.

Conclusions This study showed that decellularized TBI grafts were stronger compared with conventional pullout repairs at 2 and 4 weeks but were comparable at 12 weeks. A more organized extracellular matrix and different collagen composition in the early time points may explain the observed differences in strength.

Clinical relevance In the future, decellularized TBI grafts may be used to reconstruct tendon–bone insertion tears in multiple areas including the flexor tendon system. *(J Hand Surg Am. 2014;39(1):65–74. Copyright © 2014 by the American Society for Surgery of the Hand. All rights reserved.)*

Key words Flexor tendon, reconstructive hand surgery, tendon–bone interface, tissue engineering.

From the Division of Plastic Surgery, VA Palo Alto Health Care System; and the Division of Plastic Surgery, Stanford University Medical Center, Stanford, CA.

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Corresponding author: Simon Farnebo, MD, PhD, Division of Plastic Surgery, Stanford Medical Center, 770 Welch Road, Palo Alto, CA 94304; e-mail: simon.farnebo@lio.se.

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TENDON–BONE HEALING IS CRITICAL to the ultimate success of several hand surgery and upper extremity surgery procedures (as well as orthopedic injuries such as Achilles tendon ruptures). The native tendon insertion into bone consists of a highly specialized and complex tissue that transmits mechanical loads from elastic tendon to stiff bone.[1–4] Current strategies for surgical reattachment of the tendon to bone involve hardware, suture anchors, and drill holes. However, the insertion site, also called the tendon–bone interface (TBI),

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is never properly reconstituted and typically heals with scar rather than with strong fibrocartilage.[1,5–7] In a previous report, we proposed that a decellularized tendon–bone composite tissue construct could be used to replace the injured TBI, with the benefit of stronger healing between tissues of similar elastic moduli.[8] This approach would thus challenge the existing paradigm of suture-based TBI repair, which suggests that the damaged TBI can be replaced with a biocompatible decellularized off-the-shelf TBI construct. The weaker tendon-to-bone healing could be replaced with a stronger bone-to-bone and tendon-to-tendon healing.[9,10]

We used a rat Achilles tendon–calcaneus TBI model that was previously described[8] to represent the flexor digitorum profundus insertion at the distal phalanx. This rat model allows easy access to surgical transection and subsequent reconstruction of a tendon–bone interface of similar size ratio as human digital flexors and distal phalanx. Furthermore, the rat calcaneus is large enough to tolerate reattachment with a micro drill and screw, and it allows us to stimulate TBI grafts in their native environment by delivering physiological loads to the tendon–tendon and bone–bone repairs beginning the first day after surgery. The physiochemical decellularization protocol (ultrasonication and detergent treatment) used to produce TBI grafts has shown a substantial decrease in total deoxyribonucleic acid and a 92% decrease in cellular elements without damaging the extracellular matrix structure and biomechanical properties.[8]

The risk of disease transmission is a common concern in using allogenic tendons for reconstruction.[11] To reduce disease transmission, strict screening for (human immunodeficiency virus, hepatitis B virus, hepatitis C virus), and syphilis would be required, and the tissues would undergo an established sterilization protocol. Previous experience with allografts in anterior cruciate ligament surgery suggests that the transmission risk for human immunodeficiency virus is 1 in 1.6 million.[12] In addition, in previous studies, peracetic acid (used in our protocol) has been shown to be effective against bacteria, viruses, and spores.[11,13,14]

The purpose of this investigation was to ascertain whether decellularized tendon–bone composite grafts (TBI grafts) could be used to replace an injured tendon–bone attachment. We hypothesized that composite grafts would be stronger than conventional repair at the early healing time points, that the strength and stiffness of the grafts would be regained after 3 months *in vivo*, and that a more organized extracellular matrix and different collagen composition could explain the differences in biomechanical properties between TBI grafts and conventional repairs at early time points after the reconstructive surgery.

MATERIALS AND METHODS

Animals and experimental groups

We used 72 Wistar rats (Charles River, Willimantic, CT) (mean weight, 280 g) based on a power calculation. Twenty-four were used for graft harvest and 48 for *in vivo* reconstruction of bilateral TBI injuries (TBI graft left and pullout repair right) (Fig. 1). We divided rats into 4 groups and killed them after 2, 4, 8, and 12 weeks (n = 12/time point) (Table 1). All animal procedures were performed with an institutional animal care and use committee–approved animal protocol.

Graft harvest

We harvested 48 Achilles tendon-calcaneus TBI grafts from 24 Wistar rats. Animals were killed with carbon dioxide and positioned prone. Both hind limbs were shaved and the TBI was exposed with an incision lateral to the Achilles tendon. Proximally, the Achilles tendon was cut at the musculotendinous junction. Distally, the calcaneus was cut with an oscillating micro sagittal saw approximately 3 mm distal to the tendon insertion. Surrounding connective tissue was removed and a longitudinal drill hole (0.75 mm; Medartis AG, Basel, Switzerland) was made through the center of the bone fragment of each TBI graft before further treatment.

Decellularization

Targeted ultrasonication (VC505; Sonics and Materials, Newton, CT) against the TBI of the grafts was performed in a chilled water bath (10 min; total, 64,800 J).[15] Buffered 5% peracetic acid, 1% ethylenediaminetetraacetic acid, and 2% sodium dodecyl sulfate in 1% ethylenediaminetetraacetic acid were used for chemical decellularization according to a modification of a previously established protocol.[16] All grafts were rinsed with distilled water to ensure that grafts were chemical free before implantation. Our decellularization protocol was used as the sole sterilizing agent, because previous studies have shown that peracetic acid and detergents efficiently minimize disease transmission.[17,18]

Injury model and reconstructive surgery

All rats were kept anesthetized with isoflurane in a prone position. Under sterile conditions, a 1-cm incision was made lateral to the Achilles tendon to

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