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Enhanced tendon-to-bone repair through adhesive films

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Abstract

Tendon-to-bone surgical repairs have unacceptably high failure rates, possibly due to their inability to recreate the load transfer mechanisms of the native enthesis. Instead of distributing load across a wide attachment footprint area, surgical repairs concentrate shear stress on a small number of suture anchor points. This motivates development of technologies that distribute shear stresses away from suture anchors and across the enthesis footprint. Here, we present predictions and proof-of-concept experiments showing that mechanically-optimized adhesive films can mimic the natural load transfer mechanisms of the healthy attachment and increase the load tolerance of a repair. Mechanical optimization, based upon a shear lag model corroborated by a finite element analysis, revealed that adhesives with relatively high strength and low stiffness can, theoretically, strengthen tendon-to-bone repairs by over 10-fold. Lap shear testing using tendon and bone planks validated the mechanical models for a range of adhesive stiffnesses and strengths. *Ex vivo* human supraspinatus repairs of cadaveric tissues using multipartite adhesives showed substantial increase in strength. Results suggest that adhesive-enhanced repair can improve repair strength, and motivate a search for optimal adhesives.

Graphical Abstract

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8. Author contributions

SWL derived the shear lag model with help from VB and GMG. MG created and executed the finite element model to compare to the shear lag model, with guidance from SWL, GMG, VB, and ST. SWL designed and performed all experiments with guidance from ST, VB, and GMG. WNL performed the cadaver rotator cuff surgeries and provided input into how to apply adhesives during surgeries. SWL, MG, and TRG dissected the cadaver shoulders before and after surgical repair, and performed the shoulder biomechanical tests. SWL wrote the manuscript, and ST, GMG, MG, TRG, VB, and WNL provided edits.

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Keywords

Adhesive; film; rotator cuff; tendon-to-bone; shear lag; biomechanics

1. Introduction

Tendon-to-bone repair presents a challenging mechanical problem: repairs require strength and resilience to accommodate forces from activities of daily living and to avoid repair site elongation or rupture; however, the strong anchor sutures used for repairs cause stress concentrations that limit attachment strength. This is compounded by stress concentrations associated with the mismatch between compliant tendon and stiff bone [1]. The healthy tendon enthesis facilitates load transfer from tendon to bone in several ways, including by (i) distributing force over a relatively large footprint area to reduce local stresses, (ii) using a compliant transitional fibrocartilaginous tissue to minimize stress concentrations and toughen the attachment [2, 3, 4, 5], and (iii) using randomness of composition and structure to distribute stress during failure [6].

Surgical repairs have high failure rates, possibly because they not only fail to recreate these resilience mechanisms, but also introduce stress concentrations at sutures. For example, rotator cuff healing after repair is notoriously challenging, with post-repair rupture rates ranging from 20% for young, healthy patients with small tears to as high as 94% for massive tears in elderly patients [7, 8]. These failure rates are not surprising from a mechanical perspective. While current double-row suture bridge repair techniques apply compression to the tendon over a large portion (78%) of the bony footprint [9], almost all of the force from muscle to bone is transferred in shear across only two anchor points, where the suture from a bone anchor punctures through the tendon near the musculotendinous junction (Figure 1A). These stress concentrations, coupled with possible vascular compromise in the same region due to strangulation from inappropriately tensioned repairs [10], lead to the vast majority (86%) of rotator cuff repair ruptures by the tendon pulling through the sutures at those anchor points [11]. Approaches that distribute shear stresses and increase strength without causing tissue strangulation would theoretically decrease failure rates. Approximately half of the US population over 60 years old has a rotator cuff tear, leading to over 500,000 repairs annually [12]. With a growing aging and elderly population, improving on these failure rates is critical to reinstate shoulder function in these patients.

Here, an adhesive-film based approach is proposed to augment standard tendon-to-bone repairs, with a particular focus on supraspinatus tendon rotator cuff repairs for proof-of-concept. This adhesive-based surgical augmentation mimics the natural stress distribution

across the repair site to improve repair strength and limit ruptures. We hypothesized that, unlike conventional suture repairs with only a few anchor points (Figure 1A), this adhesive repair scheme would reinstate load transfer over the entire tendon-to-bone insertion footprint (Figure 1B). This increase in load transfer is expected to result in an improvement in overall repair construct mechanical properties, similar to an adhesive-coated suture case we examined previously [13]. Achieving the full strength of a healthy tendon enthesis may not be necessary, since the enthesis can accommodate higher loads than are applied physiologically during non-traumatic activities. We therefore aim to generate functional repairs that are capable of sustaining activities of daily living and enhanced rehabilitation protocols.

Following a similar approach to [13], we employed a shear lag analysis to predict the ability of adhesive interlayers to improve load transfer across a repaired tendon-to-bone enthesis. We then analyzed a finite element model with the same geometric and material properties to establish the limits of the scaling law from shear lag analysis for adhesive thickness and adhesive shear modulus. Using these models, we identified desirable adhesive mechanical properties for use in adhesive films for tendon-to-bone repair. We then biomechanically tested adhesives between tendon and bone planks and in human cadaver rotator cuff repairs to validate the models and assess adhesives' potential for clinical usefulness.

2. Theory

2.1. Shear lag model

A shear lag model was studied to (i) identify adhesives with desirable properties for tendon-to-bone repair, and (ii) anticipate load transfer in idealized experiments to assess adhesive properties. The model predicted load sharing across an idealized tendon-to-bone insertion site using an interposed adhesive layer at the interface. The idealized repaired tendon and bone were both modeled as isotropic, homogenous tissue planks for this one-dimensional model.

The model, following Volkersen [15] and Cox [16], is based upon the free body diagram in Figure 2A,B and the following assumptions: (i) the tendon, adhesive, and bone are linear elastic materials, (ii) viscous effects are negligible, and (iii) thickness-axis displacements, strains, and stresses are small. The latter assumption is appropriate for thin adhesive layers. These results are also corroborated by 2-dimensional finite element modeling with different assumptions, as described in the following section (2.2 Finite element model). While adhesives and tissues are not isotropic and often exhibit nonlinearity and viscoelasticity [1, 2, 17], the linear analysis is adequate and useful for order-of-magnitude stress estimates, and for the target design range in which the adhesive is not close to failure.

As derived by Volkersen [15] directly from equilibrium, constitutive, and strain-displacement equations for the components (i.e., tendon, adhesive, and bone, Figure 2C), the differential equation governing the normal stress in the tendon at position x is:

$$\frac{d^2 \bar{\sigma}_t(x)}{dx^2} - \beta^2 \bar{\sigma}_t(x) + \frac{\beta^2}{\chi} = 0 \quad (1)$$

where $\bar{\sigma}_t(x)$ is the dimensionless axial stress in the tendon, normalized by the stress P/wt_t at $x = L$, and χ and the characteristic (inverse) length scale β relate to the geometry and material properties:

$$\chi = \frac{E_b t_b}{E_t t_t} + 1 = \frac{1}{E_t^* t_t^*} + 1 \quad (2)$$

$$\beta^2 = \frac{G_a}{t_a} \left(\frac{1}{E_t t_t} + \frac{1}{E_b t_b} \right) = \frac{1}{t_b^2} \frac{G_a^*}{t_a^*} \left(\frac{1}{E_t^* t_t^*} + 1 \right) \quad (3)$$

where E_t^* and G_a^* are, respectively, the Young's modulus of tendon and the shear modulus of adhesive normalized by the Young's modulus of bone E_b ; t_t^* and t_a^* are, respectively, the thickness of the tendon and the thickness of the adhesive normalized by the thickness of the bone cortical layer t_b ; and w is the width of the attachment. Solving and applying the boundary condition $\bar{\sigma}_t(0) = 0$ at the distal end of the insertion footprint and $\bar{\sigma}_t(L) = 1$ at the proximal end of the insertion footprint yields (Figure S1):

$$\bar{\sigma}_t(x) = \frac{1 - \cosh(\beta x)}{\chi} + \frac{\sinh(\beta x)}{\sinh(\beta L)} \left(1 + \frac{\cosh(\beta L) - 1}{\chi} \right) \quad (4)$$

Combining Equation 4 with the equilibrium equation for an infinitesimal segment of tendon, $\frac{d\bar{\sigma}_t}{dx} = \frac{\tau(x)}{P/w}$, yields a prediction for the shear stress distribution $\tau(x)$, normalized by the average shear stress $\tau_{ave} = P/wL$, as predicted by Volkersen:

$$\frac{\tau(x)}{\tau_{ave}} = \frac{\beta L}{\chi \sinh(\beta L)} [\cosh(\beta(L-x)) + (\chi - 1) \cosh(\beta x)] \quad (5)$$

This shear lag model predicts that shear stress is highest at the edges of the lap joint, i.e., at positions $x = 0$ and $x = L$, and that shear stress decreases exponentially toward more central positions (Figure S2). Note that as previously demonstrated for lap joints (e.g. [22]), parametric analysis of Equation 5 confirmed that peak stress is minimized if the adherends (tendon and bone) are “balanced” so that $E_t^* = (t_t^*)^{-1}$ (Figure S2). However, this is not possible for the attachment of tendon to bone. Indeed, the material mismatch at a tendon-to-bone attachment leads to stress concentrations and makes surgical repair particularly challenging.

For the geometric and material properties of a tendon-to-bone repair (Table 2), the peak shear stress occurs at position $x = L$ (Figure S2), with stress concentration factor τ_{SCF} (Figure 3):

$$\tau_{SCF} = \frac{\tau}{\tau_{ave}} \Big|_{x=L} = \frac{\beta L}{\chi \sinh(\beta L)} [1 + (\chi - 1) \cosh(\beta L)] \quad (6)$$

Equating the peak shear stress (at position $x = L$) to the failure shear stress value, τ_{fail} , yields the maximum load transferred across the joint via the adhesive:

$$\left(\frac{P_{max}}{w} \right) = \tau_{fail} L \frac{\sinh(\beta L)}{\beta L} \left[\frac{\chi}{(\chi - 1) \cosh(\beta L) + 1} \right] \quad (7)$$

This scaling law for maximum load transfer enabled prediction of desirable adhesive mechanical properties for surgical use in tendon-to-bone repairs (Figure 4). The shear lag model theory herein is applicable to tendon- or ligament-to-bone repairs generally, by simply updating the properties in (Table 2) according to the soft tissue-to-bone insertion site of interest. Note that τ_{fail} could be limited by failure (i) within the adhesive bulk, (ii) at the interfaces with adherends (i.e., the junction with the tendon or bone), or (iii) within the adherends themselves. This solution is nearly bilinear, with two asymptotes (Figure 4):

$$\lim_{L \rightarrow \infty} \left(\frac{P_{max}}{w} \right) = \tau_{fail} \frac{\chi}{\beta(\chi - 1)} = \tau_{fail} t_b \left[\frac{E_t^* t_t^* t_a^*}{G_a^*} (1 + E_t^* t_t^*) \right]^{\frac{1}{2}} \quad (8)$$

$$\lim_{G_a \rightarrow 0} \left(\frac{P_{max}}{w} \right) = \lim_{\beta \rightarrow 0} \left(\frac{P_{max}}{w} \right) = \tau_{fail} L \quad (9)$$

For a given tendon-to-bone repair, the first limit ($L \rightarrow \infty$) shows that the force the repair can carry increases monotonically with decreasing adhesive shear modulus G_a^* . Below a critical adhesive shear modulus, however, the second limit ($G_a \rightarrow 0$) shows that a cut-off exists that depends on the length of the tendon-to-bone interface L . The intersection between the two asymptotes defines a critical interface length (Equation S1, Figure S3).

2.2. Finite element model

To establish the limits of the scaling law described in the previous section (2.1 Shear lag model), we evaluated a two-dimensional finite element model using the commercial package COMSOL Multiphysics (COMSOL, Inc., Burlington, MA USA). The finite element model was developed using the same geometric and material properties as the shear lag model and evaluated with a range of adhesive thicknesses and shear moduli (Table 2, Figure S4). The tendon, adhesive, and bone were modeled as linear elastic materials for direct comparison to the shear lag model. The adhesive layer was discretized into 8,000 triangular finite elements

sized from 1 – 50 μm . The interfaces between adhesive and tendon or bone were modeled as perfectly fused unions, with the same mesh nodes in each section. Far from the adhesive joint, the bone was held fixed, and the tendon boundary was constrained to stay vertical and loaded in the x -direction with a 50 N force to simulate muscular contraction (Table 2, Figure S4).

3. Materials and Methods

3.1. Idealized ex vivo repairs

To evaluate how the performance of the adhesive system depends upon the adhesive strength between the adherends and the stiffness of the adhesive material, a modified lap shear test was developed. A series of idealized tendon-to-bone plank repairs was performed using 1/8" thick bovine deep digital flexor tendon planks adhered to 1/4" thick bovine femur cortical bone planks (both planks were 15 mm wide, with 10 mm overlap length; Table 2). Fresh-frozen bovine deep digital flexor tendons (age 14–30 months; Animal Technologies, Tyler, TX) were leveled into planks while embedded in Tissue-Plus optimum cutting temperature compound (OCT, Fisher HealthCare, Waltham, MA) using a freezing stage (BFS-30MP, Physitemp, Clifton, NJ) sledge microtome (Leica 1400, Buffalo Grove, IL) to plane both sides to a uniform, desired thickness, similar to previously described methods [23]. The desired thickness was measured using a sacrificial layer of polytetrafluoroethylene (PFTE, commonly called "Teflon", McMaster-Carr, Elmhurst, IL) on the microtome alongside the tendon samples. After being leveled into planks, samples were frozen in PBS-soaked gauze and stored at -20°C . Samples were thawed overnight at 4°C and trimmed to 15 mm wide with a razor blade before use. The width was chosen based on the size of bovine deep digital flexor tendons, and to maintain a high width-to-thickness aspect ratio $\sim 5 : 1$. Pilot experiments performed on tendon samples planed on only one side had high variability in shear strength, likely due to variable tissue curvature, necessitating planing samples on both sides. Fresh-frozen bovine femurs obtained from a local butcher were cut into bone planks using a diamond wafer blade (IsoMet, Buehler, Lake Bluff, IL). In addition, to rapidly assess adhesive mechanical properties with relevant adherends for use in either tendon-to-bone repair or on adhesive-coated sutures, a series of idealized tendon-to-tendon plank repairs were performed using two 1/8" thick bovine deep digital flexor tendon planks but no bone planks.

Effects of adhesive stiffness—To experimentally assess the impact of varying adhesive stiffness without modifying interfacial binding strength, a series of multipartite adhesive systems was evaluated. Each multipartite adhesive consisted of a 1/16" thick bovine tendon to provide a compliant bulk, attached to the adjacent tendon and bone using 50 μL of a flexible cyanoacrylate on each interface (Loctite 4903, based on ethyl and octyl cyanoacrylate [24]; Henkel Corporation, Düsseldorf, Germany) to provide the necessary bond strength. The 1/16" thick tendon bulk was first treated with PBS containing 0 mM, 20 mM, or 100 mM tetrakis (hydroxymethyl) phosphonium chloride (THPC, Sigma Aldrich, St. Louis, MO) for 15 minutes to assess the impact of a twofold stronger adhesive bulk material ($n = 6$ each).¹ After treatment with THPC, the 1/16" tendon bulk was washed twice in excess PBS (40 mL) on a rocker for 5 minutes before use in the multipartite adhesive

system. Two tendon plank samples in this experimental series were discarded because the samples were discolored and drastically stiffer than the other samples, likely due to dehydration and oxidation at some point during the tendon plank processing (a.k.a., “freezer burn”). There were at least $n = 5$ samples in each final group. The adherends and the 1/16” thick tendon bulk pieces were blotted dry with Kimwipes (Kimberly-Clark Professional, Roswell, GA) three times before applying cyanoacrylate. This was cured for 3 hours at room temperature under 100 kPa compressive pressure, wrapped in PBS-soaked gauze, before lap shear testing.

In addition to evaluating the multipartite adhesive directly, the elastic modulus of tendon planks treated with THPC was determined by direct tensile testing. A series of 1/8” thick tendon planks, treated with PBS containing 0 mM, 20 mM, or 100 mM THPC for 15 minutes before two washes in PBS, was mechanically evaluated ($n = 4$ each). Two samples were discarded due to discoloration and stiffness before testing, leaving at least $n = 3$ samples per group.

3.2. Human cadaver rotator cuff repairs

To assess the potential for adhesive application in a clinically relevant rotator cuff repair setting, paired human cadaver rotator cuff samples were dissected. Human cadaver shoulders were obtained from Anatomy Gifts Registry (Anatomic Gift Foundation, Inc., Hanover, MD). Supraspinatus tendons were dissected away from the humeral head to ensure full detachment, then tendons were repaired with an open, double-row suture bridge technique, in a paired fashion either with or without the multipartite adhesive system described above (Loctite 4903 with a 1/16” thick bovine flexor tendon plank compliant interlayer; $n = 2$ per group). Repairs were performed by WNL, an experienced, fellowship-trained orthopaedic surgeon specializing in the shoulder. To assess the strength of the multipartite adhesive system without suture, the infraspinatus tendons from the same cadaver samples were dissected away from the humeral head, then the tendons were adhered to their insertion sites using the same adhesive system before mechanically testing to failure. Tissue was kept hydrated using PBS-soaked gauze throughout this process, once it was dissected. After repair, the humerus and rotator cuff tendons and muscles were carefully dissected from the scapula and surrounding tissue and stored at 4 °C overnight before biomechanical testing the following day.

3.3. Biomechanical testing

Idealized tendon-tendon and tendon-bone plank repairs were tested similar to previously described protocols for testing flexor tendons [25, 26, 27, 28]. After 5 cycles of triangular-ramp preconditioning to 1 mm displacement, samples were pulled in uniaxial tension using a material testing machine (5866; Instron Corp., Norwood, MA, chosen because of a high capacity load cell) at 0.3 mm/s until failure. Video of the test was recorded for optical strain tracking. Immediately prior to testing, tendons were stained with a speckle pattern of freshly prepared VerHoeff stain to provide a surface texture for optical tracking. Elongation measurements from the material testing machine were synced with optical recordings from a

¹THPC covalently crosslinks amine groups in proteins.

high resolution camera at a frame rate of 30 Hz (Google Nexus 6p, Mountain View, CA), similar to described previously [29, 13]. Optical tracking of points on the tendon and bone immediately surrounding the interface enabled accurate determination of semi-local tissue strain. This allowed for more accurate adhesive material property assessment, without the confounding effects of viscoelasticity or strain-energy storage in the tendon plank proximal to the interface. From the force-elongation curves, maximum force and yield force were determined. From the force-strain curves, strain at 20 N force (approximating strains at physiologically relevant load levels [30, 31]), shear modulus (slope of the linear portion), and resilience (area under the curve until yield) were determined.

Human cadaver rotator cuff repairs were tested with an MTS 858 Bionix (MTS, Eden Prairie, MN, USA) testing system, similar to previously methods [32]. Dissected samples were returned to room temperature and secured in black pipe with two orthogonal bolts and Rockite cement. The pipe was secured very close to the humeral head to prevent flexion. The insertion site was speckle-coated with VerHoeff stain to facilitate optical tracking. The rotator cuff muscle being tested was secured in a frozen clamp using liquid CO₂. The humerus was angled so the muscle was being pulled in line with the direction of the tendon fibers at the insertion. Supraspinatus samples (repaired with double-row suture ± adhesive) were first preconditioned with 10 haversine cycles from 1 – 25 N at 0.5 Hz, followed by a ramp to 10 N at 1 N/s and then held at a constant load for 5 seconds. Infraspinatus samples (repaired with adhesive only) were preconditioned with 10 haversine cycles from 1 – 5 N at 0.5 Hz, followed by a ramp to 2.5 N at 1 N/s and then a hold at constant load for 5 seconds. After this preconditioning regimen, samples were pulled in uniaxial tension to failure at 0.5 mm/s with time, force, and MTS grip displacement data measured at a 20 Hz sampling rate. Video was simultaneously recorded from front and side views at 30 Hz. Optical tracking of points on the tendon and bone immediately surrounding the interface, performed using custom MATLAB code, enabled accurate determination of semi-local tissue strain, as with idealized plank tests.

3.4. Biomechanics analysis

Modulus, stiffness, and rigidity were calculated by using random sample correlation (RANSAC) based on Ke Yan's 2011 implementation² to quickly find the best fitting line of sufficient bin width. Data were first trimmed to remove data below 10% of max stress and above 95% of max stress to roughly isolate the region of interest. Two points were selected at random and a line was drawn between them, for $n = 1000$ iterations. All data points within a threshold range of 0.5% of the robust fit stress at the 80th percentile were counted as within an acceptable range of the best fit line. Of the n iterations, the iteration with the most inliers was deemed the best fit. This approach represents a "robust" fit, which minimizes the effect of outlier points on the best fit line compared to a least squared errors fit. This was confirmed by visual inspection. The "yield" point was determined as the point where the smoothed data first deviated from the RANSAC fit line by 0.1% of the expected stress.

²<https://www.mathworks.com/matlabcentral/fileexchange/30809-ransac-algorithm-with-example-of-2D-finding-homography>

3.5. Statistics

Statistical analysis for all experiments was performed by non-parametric Wilcoxon rank-sum using MATLAB, as some results were not normally distributed. Statistical significance was set at $p < 0.05$, unless otherwise noted.

4. Results

4.1. Shear lag and finite element models

Shear lag and finite element modeling revealed an ideal design space for adhesive mechanical properties to improve load transfer across tendon-to-bone repairs (Figure 4, band inside blue dotted box, including the elastomer material class). As with adhesive-coatings on sutures [13], mechanically desirable adhesives should be compliant in shear while maintaining high binding and shear strengths. Higher deformation of compliant adhesives facilitates load distribution over larger lengths than stiff adhesives, reducing the peak stress (Figure S1, S2). Similarly, thick adhesives allow higher deformation than thin adhesives, reducing the shear stress concentration factor. Shear lag analysis predicted stress concentration factors of approximately 1 – 200 for the experimentally relevant ranges of adhesive shear modulus and thickness ($G_a = 10^4 - 10^8$ Pa and $t_a = 1 \mu\text{m} - 1$ mm, respectively) (Figure 3). While these models assumed a 13 mm adhesive interface length based on rotator cuff anatomy, note that much shorter adhesive lengths are expected to transfer nearly the same load (Figure S3).

While shear lag analyses generate simple, closed form solutions, the simplifying assumptions described in the Theory section (2.1 Shear lag model) lead to inaccurate stress predictions at the edges ($x = 0$ and $x = L$) and in cases of stiff or thick adhesives layers. The finite element predictions of normal stress distribution in the tendon and shear stress distribution in the adhesive (Figure S1B and S2B, respectively) closely resembled the shear lag predictions for compliant adhesive layers (Figure S1A and S2A), but deviated for adhesive shear moduli greater than $\sim 10^8 - 10^9$ Pa. However, the predicted peak shear stress (i.e., at position $x = L$ for shear lag predictions, slightly in from position $x = L$ for finite element predictions), remained similar for the two models, even for $G_a > 10^8$ Pa, and only substantially deviated for $G_a \sim 10^{10}$ Pa. The finite element model corroborated the shear stress concentration factor predictions from shear lag analysis for adhesives up to 1 mm thick (Figure S5).

A contour map of maximum load transfer given various adhesive properties was generated from Equation 7 using an adhesive thickness of 0.5 mm (Figure 4). Properties of several real materials were then overlaid on this contour map to identify promising candidate materials. Only a small fraction of the material classes shown are relevant materials; the remainder are included for comparison, as is standard with an Ashby plot, and to highlight the importance of appropriate adhesive material selection. Assuming a compliant adhesive ($G_a = 1$ MPa) with a high shear strength ($\tau = 10$ MPa) and the average adult supraspinatus tendon insertion geometric properties (Table 2), maximum load transfer would approach 3,000 N. This would result in theoretical improvements of up to ~ 10 -fold over current methods using a double-row suture bridge repair, causing repair strength to be limited by tissue strength. The

maximum load transfer prediction herein uses supraspinatus tendon insertions as an example to calculate values, but it is relevant for surgical connective tissue-to-bone attachments throughout the body.

4.2. Ex vivo experiments

Biomechanical tests of idealized tendon-to-bone planks in lap shear using multipartite adhesives (comprised of 1/16" tendon plank interlayers with Loctite 4903 at interfaces) matched model predictions of maximum load (Figure 5). To evaluate a range of adhesive stiffnesses, the 1/16" tendon plank interlayers were first treated with 0 mM, 20 mM, or 100 mM THPC for 15 minutes. Elastic modulus of bovine flexor tendon planks, tested in tension, increased with THPC treatment concentration by 76% for 20 mM THPC and 112% for 100 mM THPC, as expected ($n = 4$ per group, Figure 6A). There was no significant difference in the measured shear modulus for inter-layers treated with different THPC treatment concentrations (Figure 6B). When applied in idealized lap shear tests, multipartite adhesive interlayers treated with 0 mM, 20 mM, and 100 mM THPC yielded maximum average shear stresses ($\tau_{ave} = \frac{P}{wL}$) of 324 kPa (± 61 kPa standard deviation, $n = 5$), 433 kPa (± 132 kPa, $n = 6$), and 494 kPa (± 90 kPa, $n = 5$, $p = 0.008$), respectively, (Figure 6C). This represented a 52% higher failure shear stress and 88% higher yield shear stress ($p = 0.064$, Figure 6D) with strengthened adhesive bulk interlayers crosslinked with 100 mM THPC, as predicted by shear lag analysis (Figure 4). Failure occurred within the tendon plank in all samples with THPC-crosslinked interlayers, as expected since crosslinking strengthened and stiffened the interlayer, leaving the tendon plank as the weakest point. In comparison, some samples without THPC crosslinking failed within the tendon plank while others failed in the interlayer, since the tendon plank and interlayer were approximately the same strength.

The multipartite adhesive system was further evaluated in human rotator cuff biomechanical tests to test a clinically-relevant loading scenario (Figure 7). Cadaver in-fraspinatus repairs with adhesive only (no sutures) had a maximum shear stress of 115 kPa (± 10 kPa, $n = 4$), 35% of the strength of idealized plank tests. This equated to a maximum load of 34.5 N (± 3.0 N), or approximately 10% of the strength of a typical rotator cuff tendon repair [33]. Finally, the multipartite adhesive system was assessed in clinical-style human cadaver supraspinatus tenotomy and repair to assess adhesive strength contributions in parallel to a suture repair. Pilot studies in cadaver human supraspinatus tendons, repaired with double-row suture bridge and multipartite adhesive between the supraspinatus tendon and humeral head yielded approximately 40 – 50 N stronger repairs than paired contralateral control repairs (Figure S6, S7, S8, and S9). This estimated load improvement is similar to loads carried by infraspinatus tendons adhered without suture, indicating that the adhesive had an additive effect on the strength of the double-row suture bridge repair.

5. Discussion

Current operative techniques for rotator cuff tendon repair rely on load transfer in shear across only a few suture anchor points (Figure 1). Variations on this approach have reached a limit for mechanical fixation, where increased numbers of strands or anchor points do not lead to improved outcomes (e.g., most studies have shown that single-row repairs and

double-row repairs are equivalent clinically [34]). Recent research has instead focused on biological augmentation to facilitate improved tendon-to-bone healing [35], but mechanical fixation remains inadequate for holding the tissues together and minimizing micro-motion at the interface long enough for healing to occur. We hypothesized that, similar to adhesive-coatings on sutures for tendon repair [13], tendon-to-bone repair mechanics could be enhanced through better load distribution across the repair site, using an adhesive biomaterial that is simultaneously strong and compliant in shear. Modeling and *ex vivo* experimental results demonstrated that an adhesive interposed between tendon and its bony footprint has the potential to significantly improve the strength of tendon-to-bone repairs using feasible adhesive material properties. This increase in strength, combined with anticipated decreases in interfacial micro-motion from the use of an adhesive, should improve tendon-to-bone healing.

The shear lag model indicated that mechanically desirable adhesives should be of millimeter-scale thickness and compliant in shear while maintaining high binding and shear strengths. This combination of properties minimizes stress concentrations and maximizes load transfer across the repair (Figure 3 yellow shaded region, and Figure 4 green shaded region). Compliant, thick adhesives allow greater deformation, thereby distributing loads over a larger length than stiff, thin adhesives (Figure S1, S2). This is analogous to a native, fibrocartilaginous tendon enthesis, where a compliant zone optimizes stress concentrations and toughens the interface [2, 3, 4, 5]. The derived load transfer isoclines, based on rotator cuff geometric and material properties (Table 2), indicate that adhesives with a wide range of theoretical material properties are expected to improve repair strength. When these isoclines are overlaid on real material properties, as in a standard Ashby plot [36, 37, 38], the model highlights materials with the appropriate properties to improve repair strength (Figure 4, region in blue dotted box). Due to the relatively large surface area compared to adhesive-coated sutures described previously [13], adhesive films would generate meaningful repair strength improvements using a much broader range of adhesive mechanical properties. For example, the entire class of elastomeric materials have appropriate mechanical properties to improve repair strength. Therefore, we are exploring biocompatible, adhesive elastomeric materials as potential bio-adhesives to improve repair strength. Optimal adhesive materials are expected to improve load transfer by over 3,000 N, or 10-fold the strength of a current repair techniques (Figure 4). While this provides a large theoretical opportunity, an improvement of even 100 N (i.e., 22.5% of the strength of double-row suture bridge repairs) that reduces local stress concentrations would provide a clinically meaningful improvement to surgical repairs [39, 40].

The shear lag model used here is one-dimensional, with several limiting assumptions (detailed in the Theory section, 2.1 Shear lag model) that lead to errors predicting stress distribution around edges and for stiff, thick adhesives on the same thickness order of magnitude as the adherends [41]. Therefore, we employed a finite element model that confirmed that the shear lag model was inaccurate for thick adhesives ($t_a > 1$ cm) and stiff adhesives ($G_a > \text{approximately } 1 \text{ GPa}$; Figure S5). This finite element modeling corroborated the shear lag predictions for adhesives in the desirable range, i.e., compliant, strong adhesives with millimeter-scale or lower thickness. To further refine modeling predictions, future models could incorporate (i) non-linear elastic material assumptions and

(*ii*) cohesion within the adhesive instead of assuming catastrophic failure [42, 43], especially to predict sensitivity to flaws in the adhesive material. Nevertheless, the current model provides sufficient predictions of load transfer to guide adhesive material development.³

In order to evaluate adhesive properties with relevant adherends and assess adhesive usefulness for tendon-to-bone repair, we developed a new method for lap shear testing using tendon and bone planks (Figure 5). Tendon planks were fabricated using a sliding microtome to create highly uniform, geometrically standardized planks. Similarly, bone planks were manufactured using a diamond blade to create precisely-sized samples. This protocol enabled rapid testing of adhesive properties via lap shear with relevant adherends for clinical application. However, note that the failure shear strength, τ_{fail} , used in the shear lag model can be limited by: (*i*) the bulk adhesive strength (cohesion), (*ii*) the interfacial binding strength to the surrounding tissue, and/or (*iii*) the ability of the surrounding tissue to accommodate load transfer (e.g., through distributing shear stress among tendon fibers). Since the adherends are relevant to the repair setting, the failure shear stress measured in these lap shear experiments is reflective of the failure shear stress of the adhesive.⁴

Proof-of-concept experiments demonstrated substantial improvements in load transfer for multipartite cyanoacrylate adhesives in idealized tendon-to-bone plank tests and human cadaver rotator cuff repairs. Off-the-shelf cyanoacrylate adhesives (Loctite 4903) are far more stiff than the ideal material predicted by the shear lag model. Therefore, we used a multipartite adhesive comprised of an interlayer (1/16" plank of bovine flexor tendon) adhered to tendon and bone using Loctite 4903 to assess a more relevant adhesive shear modulus range. The $324 \text{ kPa} \pm 61 \text{ kPa}$ failure shear stress found experimentally in idealized plank tests (Figure 6C), equating to a $84.3 \text{ N} \pm 15.8 \text{ N}$ failure load over a 2.6 cm^2 supraspinatus insertion footprint, closely matched the predicted maximum load from the shear lag model (Figure 4, yellow circle). Furthermore, when the tendon plank interlayer was stiffened and strengthened by crosslinking with 100 mM THPC for 15 minutes, the experimental results ($494 \text{ kPa} \pm 90 \text{ kPa}$, equating to $128.5 \text{ N} \pm 23.4 \text{ N}$) again closely matched the theoretical predictions. Thus, based on idealized plank tests, even the fairly stiff, off-the-shelf cyanoacrylate-based adhesives carry enough load to improve repair strength by approximately 25 – 40% over a 2.6 cm^2 supraspinatus repair footprint, when used in conjunction with current repair techniques [33]. That 25 – 40% increase in load tolerance could substantially decrease repair rupture risk during activities of daily living, thereby facilitating improved healing.

³The shear lag model employed herein is one dimensional and ignores loads that are not directly in line with the tendon (considered isotropic, linear elastic herein). This is a simplification of the rotator cuff, where the high degrees of freedom during rotation and other movements would apply multi-dimensional load to the supraspinatus attachment. However, (*i*) the majority of that load will be carried by other muscles and ligaments and (*ii*) the adhesive and repair are able to withstand some load in off-axis directions.

⁴The shear strength used in the shear lag modeling to predict load tolerance was the failure shear stress τ_{fail} at the local, material level. The shear stress measured in idealized plank tests was averaged over the interface (τ_{ave}). The optical tracking performed in the experiments used semi-local strain determination, which is more relevant than grip-to-grip strain measurements since it does not include the strain-energy stored in tissues outside the repair site. However, this analysis did not include a local strain assessment to determine the peak shear stress within the adhesive layer. Such local assessments have been effectively used for tracking strains and detecting cracks forming in biological tissues [44]; however, they are difficult to measure in thin adhesive layers due to insufficient number of pixels. Regardless, they are largely unnecessary for determining adhesive efficacy.

In human cadaver rotator cuff experiments, the load transferred by the adhesive was $115 \text{ kPa} \pm 10 \text{ kPa}$, equating to $34.5 \text{ N} \pm 3.0 \text{ N}$, or 35% of the anticipated load from idealized plank tests (Figure 6C). It is likely that the human rotator cuff tenotomy and adhesion experiments demonstrated lower strength than the idealized plank tests due to the irregular, curved bony surface of the humeral head causing microscopic stress concentrations and the non-idealized adhesive application and testing conditions. Furthermore, the adhesive only cured for approximately 2 hours in the cadaver experiments, compared to overnight in the idealized plank tests, which may have further limited strength. The cadaver rotator cuff repairs with and without adhesive demonstrated approximate repair strength increases commensurate with the expected additive improvement based on load transferred in the adhesive-only repairs (Figure 7).

Taken as a whole, the multipartite adhesive experiments with and without THPC treatment provide evidence that (i) the shear lag model accurately predicted load transfer across tendon-to-bone for a relevant range of adhesive shear moduli ($100 \text{ kPa} - 1 \text{ MPa}$, Figure 6C), and (ii) clinical style repairs demonstrate approximately one-third of the additive load tolerance improvement expected based on the shear lag model and idealized tests. Even this sub-optimal multipartite adhesive material enabled load tolerance increases on the necessary order to improve rotator cuff repair outcomes. Optimal adhesive materials are theoretically expected to increase load transfer by approximately 10-fold compared to current repairs.

It is interesting to note that the proposed combination of a compliant, strong adhesive layer with a suture repair resembles bonded-bolted joints in composite structures that have been considered in engineering since 1985 [45]. Kelly conducted and experimentally validated a three-dimensional finite element analysis, which concluded that bonded-bolted joints with a thick, low-modulus adhesive layer effectively distribute load transfer between the adhesive and the bolts [46]. High-modulus adhesives provided a stiffer load path and thus transferred the majority of the load, minimizing the value of the bolts and making the joint more susceptible to crack propagation [46]. Thus, previous studies of bonded-bolted joints and the shear lag model employed here both indicate that compliant, strong adhesives are desirable. The strength of bonded-bolted joints exceeded that of bonded or bolted counterparts by 52% and 127% in experimental assessments, respectively [47]. The combination of adhesive bonds and bolts increases joint strength while minimizing peeling stresses and fracture cracks [48].

The mechanical models and experiments here provide the theoretical underpinnings of a previous study showing that a biological adhesive secreted by the Australian frog *Notaden bennetti* increased the strength of cadaver sheep infraspinatus repairs by approximately 70 – 80 N, or 2-fold, over a $16.4 \pm 0.2 \text{ mm}$ by $13.2 \pm 0.1 \text{ mm}$ infraspinatus insertion site [49]. Indeed, this robust improvement follows the same mechanical principals outlined here: the protein-based frog adhesive is elastic ($G_a = 402 \pm 7 \text{ kPa}$) with approximately 65% of the adhesive strength of cyanoacrylate and a high shear strength ($\tau_{fail} = 1.7 \text{ MPa}$ between wood adherends) [50, 51]. The adhesive set in approximately 30 – 60 seconds and could work while hydrated [49]. While this frog-secreted adhesive, secreted and immediately applied in the operating room, is not clinically applicable in its current form, it further provides proof-

of-concept validation that adhesives that are both compliant in shear and strong can substantially improve repair strength.

Translating this theoretical and experimental foundation into a clinically useful adhesive for tendon-to-bone repair will require co-optimization of several properties, including the adhesive mechanical properties defined here, biocompatibility, degradation *in vivo*, adhesive curing in a hydrated environment, and production cost [52]. While this study applies particularly to the time of repair and does not consider the healing process, results from many studies in orthopedic repair indicate that time zero strength properties correlate with long-term repair outcomes, e.g., [39, 40]. Ideal adhesives could either be biologically inert or guide the healing response as with a tissue engineering approach [53]: the same biomechanical design principles apply to minimizing stress concentrations for tissue engineered biomaterials at interfaces between soft and hard tissues. Current adhesive approaches to orthopedic repair primarily use bone cements (e.g., [54]), cyanoacrylate- [55, 56, 57, 58, 59] or methacrylate-based chemistries [60, 61, 62, 63], which may be appropriate for fracture repair but are significantly more stiff than desirable for tendon-to-bone repair. Furthermore, biocompatibility is limited unless all free acrylate moieties are consumed. At the other extreme, fibrin glues such as TISSELL (Baxter) form compliant clots but do not provide sufficient strength [64, 65]. Mussel-inspired, catechol-derived adhesives offer versatile, high-strength binding in hydrated environments which may be engineered into compliant, energy-dissipating, and possibly bioactive biomaterial matrices [66, 67, 68, 69, 70]. In addition to manipulating the chemical binding moiety, several recent studies of interest have incorporated carbonate, calcium phosphate, or mineral trioxide groups, as well as bone morphogenic protein 2, to enhance integration into bone [60, 71, 72, 73]. While these approaches are promising, there are no adhesives successfully used clinically for tendon-to-bone repair. We hope this work may serve to inform further bioadhesive development to maximize benefit to soft tissue-to-bone repairs.

6. Conclusion

Strengthening tendon-to-bone repairs is essential to enable adequate healing and functional recovery, particularly for the rotator cuff, where repair outcomes are poor. Modeling and experimental validation indicate that adhesive films can augment current surgical approaches by transferring stress between tendon and bone over the entire en-thesis footprint area, instead of relying only on a small number of anchor points. Even the sub-optimal multipartite adhesives evaluated here for model validation led to load tolerance improvements that are attractive for rotator cuff repair. Future studies investigating compliant, strong adhesive biomaterials have promise for enhancing rotator cuff and other interfacial tissue repair strength and enabling the requisite tissue apposition for healing.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Statement of Significance

Current surgical techniques for tendon-to-bone repair have unacceptably high failure rates, indicating that the initial repair strength is insufficient to prevent gapping or rupture. In the rotator cuff, repair techniques apply compression over the repair interface to achieve contact healing between tendon and bone, but transfer almost all force in shear across only a few points where sutures puncture the tendon. Therefore, we evaluated the ability of an adhesive film, implanted between tendon and bone, to enhance repair strength and minimize the likelihood of rupture. Mechanical models demonstrated that optimally designed adhesives would improve repair strength by over 10-fold.

Experiments using idealized and clinically-relevant repairs validated these models. This work demonstrates an opportunity to dramatically improve tendon-to-bone repair strength using adhesive films with appropriate material properties.

Figure 1.

A double-row suture bridge technique is shown for repairing human supraspinatus tendon tears [14]. Green shading indicates location and magnitude of load transfer. (A) Current repair techniques generate stress concentrations at anchor points where the sutures from bone anchors puncture through the tendon, correlating with tissue failure at those points [11]. (B) Adhesive films interposed between the tendon and bone could distribute load transfer over the entire insertion footprint, similar to native tissue, thereby reducing peak stresses and improving overall repair construct mechanics.

Figure 2.

Diagram of an idealized tendon-to-bone insertion site, repaired with an interposed adhesive layer (A). Simultaneously analyzing the free body diagrams (FBD) of a section of the repair (B) and each component independently (i.e., tendon, adhesive, and bone; C) allows derivation of a shear lag model to estimate shear stress within the adhesive. Note that this model reduces to a one-dimensional set of equations along the x -axis.

Figure 3.

Shear lag modeling predicted the lowest stress concentration for compliant, thick adhesives. Line color represents thickness of the adhesive layer (labeled on right). Hatched, shaded regions highlight the relevant ranges of adhesive shear modulus ($G_a = 10^4 - 10^8$ Pa) and thickness ($t_a = 1 \mu\text{m} - 1 \text{ mm}$), with the overlapping relevant property range highlighted in yellow. The shear lag modeling closely matched finite element modeling for adhesive thickness below 1 mm, as shown in the supplemental material (Figure S5).

Figure 4.

A contour map showing the design space for adhesive biomaterials for tendon-to-bone repair, using an adhesive thickness of 0.5 mm and human supraspinatus tendon attachment parameters (Table 2) as a representative attachment. The x -axis shows the shear modulus of the adhesive material, the y -axis shows the shear stress at which the adhesive material fails, and the contours show the total maximum force transferred across the repair site via the adhesive. $P_{standard}$ indicates the order of magnitude of strength of standard rotator cuff repairs. This domain map is overlaid with real material properties (shaded zones) to highlight promising materials for further adhesive development. The region highlighted by the blue dotted box is expected to increase rotator cuff repair strength.

Figure 5.

(A) Schematic and (B) picture of biomechanical testing setup for idealized single lap shear experiments using tendon and bone planks as adherends. (C) Representative force-displacement curves using multipartitite adhesives comprised of cyanoacrylate and 1/16" tendon planks treated with various concentrations of THPC.

Figure 6.

(A) Elastic modulus of 1/8" thick THPC treated tendon planks tested in tension (no adhesive or repair). (B) Shear modulus, (C) maximum shear stress, and (D) yield shear stress (τ_{ave}) of multipartite adhesive evaluated in idealized lap shear tests. Stronger adhesive materials (100 mM THPC-crosslinked) failed at 52% greater average shear stress. The middle line within the box plots represents the median, the outer edges denote the 25 percentile and 75 percentile samples, and the whiskers extend to the extreme data points. Outliers are denoted by (+). Asterisks denote statistically significant differences compared to idealized lap shear tests for 0 mM THPC group (* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, & $p = 0.064$).

Figure 7.

Human cadaver rotator cuff tendons were repaired to the humeral head with adhesive only (infraspinatus), double-row suture only, or adhesive and suture (supraspinatus). (A) Schematic drawing of biomechanical testing setup for clinically relevant repairs. (B) Front view and (C) side view pictures of biomechanical tests. (D) Representative force-displacement curves for biomechanical tests of cadaver supraspinatus repairs with and without adhesive, and for infraspinatus repairs with adhesive only.

Table 1

Abbreviations and variables used throughout the manuscript.

PBS	phosphate buffered saline	THPC	tetrakis (hydroxymethyl) phosphonium chloride
x	position along adhesive lap	L	adhesive lap length
$\tau(x)$	shear stress in the adhesive layer	τ_{ave}	average shear stress, i.e., P/wL
τ_{fail}	failure shear stress of adhesive	$\tilde{\sigma}_\lambda(x)$	normal stress in tendon normalized by normal stress at $x = 0$
E_b	bone elastic modulus	x/L	position along adhesive lap normalized by lap length
E_t	tendon elastic modulus	E_t^*	tendon elastic modulus normalized by bone elastic modulus
G_a	adhesive shear modulus	G_a^*	adhesive shear modulus normalized by bone elastic modulus
t_t	tendon thickness	t_t^*	tendon thickness normalized by bone thickness
t_a	adhesive thickness	t_a^*	adhesive thickness normalized by bone thickness
t_b	bone thickness	P	normal force across joint far from insertion, i.e., $x = 0$ and $x = L$
P_{max}	force P causing joint failure	$L_{intersect}$	lap length where asymptotic limits for load transfer intersect
χ	variable related to geometry and material properties	β	characteristic (inverse) length scale related to geometry and material properties

Table 2

Property values used throughout modeling and testing for shear lag analysis (SLA), finite element modeling (FEM), idealized tendon-to-bone plank tests, and human cadaver supraspinatus repair tests. Model geometry was chosen to replicate human rotator cuff supraspinatus anatomy as closely as possible [18]. Tendon and bone elastic modulus and Poisson's ratio were based on literature values [19, 20, 21].

Geometric properties		SLA	FEM	Plank tests	Human
L	adhesive lap length i.e., supraspinatus tendon insertion size (medial-lateral)	13 mm	13 mm	10 mm	13 mm
$L_{b/free}$	free length of bone plank before grip	—	26 mm	5 mm	—
$L_{t/free}$	free length of tendon plank before grip	—	26 mm	25 mm	—
w	lap width i.e., supraspinatus tendon insertion size (anterior-posterior)	∞	∞	15 mm	20 mm
t_t	tendon thickness	2 mm	2 mm	3.2 mm	2 mm
t_a	adhesive thickness	[1 mm – 1 cm]	[1 μ m – 1 cm]	$\approx$ 0.5 mm	$\approx$ 0.5 mm
t_b	bone cortical shell thickness	7.5 mm	7.5 mm	7.5 mm	7.5 mm
Mechanical properties					
P	force applied to tendon to model shear and normal stresses	50 N	50 N	to failure	—
E_t	tendon elastic modulus	$2 \cdot 10^8$ Pa	$2 \cdot 10^8$ Pa	—	—
E_b	bone elastic modulus	$2 \cdot 10^{10}$ Pa	$2 \cdot 10^{10}$ Pa	—	—
G_a	adhesive shear modulus	$[10^3 - 10^{11}]$ Pa	$[10^4 - 10^{11}]$ Pa	—	—
E_a	adhesive elastic modulus	—	$2G_a(1 + \nu_a)$	—	—
ν_t	tendon Poisson's ratio	—	0.2	—	—
ν_a	adhesive Poisson's ratio	—	0.49	—	—
ν_b	bone Poisson's ratio	—	0.3	—	—
τ_{adil}	adhesive shear ultimate strength	$[10^3 - 10^{10}]$ Pa	—	—	—