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Lubricin Surface Modification Improves Tendon Gliding After Tendon Repair in a Canine Model in Vitro

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Abstract

This study investigated the effects of lubricin on the gliding of repaired flexor digitorum profundus (FDP) tendons in vitro. Canine FDP tendons were completely lacerated, repaired with a modified Pennington technique, and treated with one of the following solutions: saline, carbodiimide derivatized gelatin/hyaluronic acid (cd-HA-gelatin), carbodiimide derivatized gelatin to which lubricin was added in a second step (cd-gelatin + lubricin), or carbodiimide derivatized gelatin/HA + lubricin (cd-HA-gelatin + lubricin). After treatment, gliding resistance was measured up to 1,000 cycles of simulated flexion/extension motion. The increase in average and peak gliding resistance in cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin tendons was less than the control tendons after 1,000 cycles ($p < 0.05$). The increase in average gliding resistance of cd-HA-gelatin + lubricin treated tendons was also less than that of the cd-HA-gelatin treated tendons ($p < 0.05$). The surfaces of the repaired tendons and associated pulleys were assessed qualitatively with scanning electron microscopy and appeared smooth after 1,000 cycles of tendon motion for the cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin treated tendons, while that of the saline control appeared roughened. These results suggest that tendon surface modification can improve tendon gliding ability, with a trend suggesting that lubricin fixed on the repaired tendon may provide additional improvement over that provided by HA and gelatin alone.

Keywords

lubricin; surface modification; flexor tendon; gliding resistance; hyaluronic acid

Although many flexor tendon repair techniques have been developed over the years, the resulting finger function after flexor tendon repair in finger Zone II is still occasionally poor. Stronger repairs have been advocated to permit early mobilization in the hopes that adhesion formation would be reduced,¹⁻⁵ but adhesions and tendon rupture remain a problem even with stronger repairs.⁶⁻⁸ The role of friction as a source of adhesions has been recently investigated, with data suggesting that many strong repairs also have higher friction,⁹⁻¹¹ and that this higher friction is associated with poorer results, at least in an animal model.¹²

The lubrication mechanism between the intrasynovial tendon and its pulley has only recently been investigated.¹³ Among the candidates for the principal lubricants in the lubrication

mechanism are hyaluronic acid (HA),¹⁴ phospholipids,^{15,16} and lubricin [also known as superficial zone protein (SZP) or proteoglycan 4 (PRG4)].^{17,18}

Lubricin is a mucinous glycoprotein responsible for the boundary lubrication of articular cartilage.^{19,20} At sufficient concentrations, it has the same lubricating ability as normal synovial fluid in vitro.²⁰ Recent studies indicate that lubricin may play an important role in controlling adhesion-dependent synovial growth,²¹ preventing protein deposition onto cartilage from synovial fluid and inhibiting the adhesion of synovial cells to the cartilage surface,^{17,22,23} in addition to providing the lubrication necessary for normal joint function.¹⁹ Lubricin has also been identified in tendons, including the surface of FDP tendon.^{17,24}

Failure of lubricin expression is present in camptodactyly-arthritis-coxa vara-pericarditis syndrome (CACP), an autosomal recessive disorder of precocious joint failure associated with noninflammatory synovio-cyte hyperplasia and subintimal fibrosis of the synovial capsule.^{22,25} A number of abnormalities in the function of tendons within tenosynovial sheaths, and tendon adhesion formation, have also been described in CACP syndrome, suggesting that lubricin is an important element necessary for normal tendon function.²⁵ Previous studies have looked at the effect of hyaluronic acid and gelatin on the gliding resistance^{14,26-28} and outcome of tendon repairs.²⁹⁻³³ The purpose of the current study was to investigate the effect of the addition of lubricin to existing tendon surface modifications on the gliding resistance of repaired flexor tendon after 1,000 cycles of tendon motion in a canine model in vitro. We hypothesized that the gliding ability of a repaired tendon would be improved with surface treatment with a combination of carbodiimide derivatized HA and lubricin.

MATERIALS AND METHODS

Specimen Preparation

Eight forepaws were obtained from four adult mongrel dogs sacrificed for other projects which had been approved by our Institutional Animal Care and Use Committee (IACUC). A total of 32 canine flexor digitorum profundus (FDP) tendons from the second, third, fourth, and fifth digits of each forepaw were used. Eight tendons were randomly assigned to each of four treatment groups. In each harvested digit, a transverse incision was made in the flexor sheath just distal to the proximal pulley (similar to the A2 pulley in humans). The tendon was marked through this incision in full digit extension. The tendon was then pulled proximally to full digit flexion, and the tendon was again marked through the previous incision. The distance between these two marks thus represented the in situ tendon excursion. In each digit, the proximal and middle phalanges, FDP tendon, flexor digitorum superficialis (FDS) tendon and FDS insertion, and proximal pulley were then harvested as a unit. The proximal interphalangeal joint was fixed in full extension with a longitudinal 1.5-mm Kirschner wire.

A complete laceration to the FDP tendon was made at a level 6 mm distal to the proximal tendon mark, in order to allow the repair site to travel the full length of the proximal pulley during normal excursion. The tendon was repaired with the modified Pennington technique^{34,35} with a 3/0 Ethibond core suture (Ethicon, Inc., Somerville, NJ), reinforced with a circumferential epitendon simple running suture of 6-0 Prolene (Ethicon, Inc.). All tendons were then tested once for initial gliding resistance (see below) and then prepared according to the various surface modification treatments for subsequent testing.

Tendon Surface Modification

Lubricin was purified from bovine synovial fluid as reported in a previous study,³⁶ and preserved at -20°C until use. The purified lubricin was diluted with a solution of 0.1 M Mes

[2-(N-Morpholin) ethanesulfonic acid] (Sigma) and 0.15 M NaCl to a 260 µg/ml concentration. The FDP tendons were randomly assigned to one of four treatment groups:

1. Saline: 0.9% NaCl, 0.1 M Mes, pH 6.0;
2. cd-HA-gelatin: 1% sodium hyaluronate (HA) (95%, 1.5×10^6 MW, Acros), 10% gelatin (Sigma), 1% 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) (Sigma), and 1% N-hydroxysuccinimide (NHS) (Pierce), 0.1 M Mes pH 6.0;
3. cd-gelatin + lubricin: 10% gelatin, 1% EDC, 1% NHS, 0.9% NaCl, 0.1 M Mes pH 6.0, 260 µg/ml bovine lubricin;
4. cd-HA-gelatin + lubricin: 1% HA, 10% gelatin, 1% EDC, 1% NHS, 0.9% NaCl, 0.1 M Mes pH 6.0, 260 µg/ml bovine lubricin.

In the cd-gelatin + lubricin and cd-HA-gelatin + lubricin groups, the tendons were first coated with cd-gelatin or cd-HA-gelatin without lubricin, and then wrapped in a smooth rubber sheet for 10 min. The excess gel was removed by gliding the tendon against pulley for five cycles of simulated flexion/extension motion. The tendon was then immersed in 260 µg/ml lubricin for 5 min. In the saline control group, the tendon was immersed in saline for 5 min and then tested.

Measurement of Frictional Force

We used a modified version of a previously described and validated testing device to measure the gliding resistance between the repaired FDP tendon and proximal pulley.^{37,38} Each digit was secured on the custom-made device with the volar side upward in a saline bath (ISOTEMP 202, Fisher Scientific, Houston, TX) at 37°C (Fig. 1). The load transducers were connected to the distal and proximal ends of the repaired FDP tendon. A 4.9-N weight was connected to the distal transducer (F_1) to maintain tension on the FDP tendon. The proximal load transducer (F_2) was connected to a custom-made mechanical actuator with a small linear slide driven by a precision gear head direct-current motor.

Based on the experience of previous studies,^{10,39} a set arc of contact, 30° and 20° between the horizontal plane and the proximal and distal transducer cables, respectively, was used to measure the gliding resistance. This method of tendon friction assessment has been well characterized since being first described by Uchiyama et al. in 1993.^{10,38,39} Briefly, the frictional force is proportional to the load, coefficient of friction, and joint angle. An arc of contact of 50° and a load of 4.9 N have become the methodological standard, and, by being held constant, allow easy comparison of the effect of changes in tendon surface on the coefficient of friction.

The tendon was pulled proximally by the actuator at a rate of 2 mm/s. Excursion was limited to the distance between the two tendon markers. Following two cycles as preconditioning, the data was collected from the third flexion/extension cycle. The force at the proximal and distal tendon ends and the tendon excursion were recorded. The friction could be obtained by $(F_{2\text{flexion}} - F_{2\text{extension}}) / 2$.⁴⁰

The data was initially recorded after tendon repair for one cycle, as representing the initial gliding resistance. After tendon surface treatment, data was recorded up to 1,000 cycles. Average and peak value of the gliding resistance was then calculated for each specimen. Since this is a repaired tendon model, the suture technique would affect the gliding resistance, therefore, the increase in average and peak gliding resistance was calculated by subtracting the initial gliding resistance after repair but before surface treatment from each gliding resistance data point.

Scanning Electron Microscopy

SEM was used qualitatively on one tendon per group. After measurement of gliding resistance, one tendon and its proximal pulley in each group were prepared for scanning electron microscopy (SEM) to inspect the gliding surfaces. We chose tendons whose gliding resistance was close to the mean for their respective groups. The selected tendon and pulley were washed in physiological saline, and fixed in a solution of buffered glutaraldehyde and osmium tetroxide. After dehydration in graded acetone, the specimen was coated with gold:palladium alloy and examined with a Hitachi 4700 scanning electron microscope at 10kV (Hitachi Scientific Instruments Inc., Pleasanton, CA).

Statistical Analysis

The increase in average and peak gliding resistance after 1,000 cycles of tendon motion was analyzed using one-way analysis of variance (ANOVA). A Tukey-Kramer post-hoc test for individual comparisons was used if there was a significant difference. A $p < 0.05$ significance level was used in all cases.

RESULTS

The means of the average and peak gliding resistance of all repaired tendons before treatment were 0.35 ± 0.06 N and 0.82 ± 0.14 N, respectively. After 1,000 cycles of tendon motion, the increase in mean gliding resistance of the repaired FDP tendons in saline, cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin groups was 0.25 ± 0.07 N, 0.00 ± 0.09 N, -0.05 ± 0.06 N, and -0.10 ± 0.06 , respectively (Fig. 2). The increase of peak gliding resistance in saline, cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin groups was 0.25 ± 0.22 N, -0.02 ± 0.13 N, -0.09 ± 0.09 N, and -0.18 ± 0.12 , respectively (Fig. 3). The increase in mean and peak gliding resistance in cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin tendons was significantly less than that of the saline control tendons after 1,000 cycles ($p < 0.05$). The increase in mean gliding resistance of the repaired FDP tendons treated with cd-HA-gelatin + lubricin was also significantly lower than that of the cd-HA-gelatin treated tendons.

The mean and peak gliding resistance of the repaired FDP tendons in the cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin groups decreased within the first 50 cycles and then increased at much more gradual rate over the 1,000 cycles (Fig. 4). In these groups, the mean and peak gliding resistance after 1,000 cycles was still lower than the initial gliding resistance before treatment, while the gliding resistance in the saline control tendons increased significantly ($p < 0.001$) over the 1,000 cycles of testing.

SEM showed that the surface of the repaired FDP tendon in the saline control group appeared roughened after 1,000 cycles. However the repaired tendon surfaces in cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin groups were still smooth, with suture materials, surface gap, and irregularities on the tendon surface still partially covered with thin layer of surface treatment (Fig. 5). It was also found that the proximal pulley surface in these three treatment groups was also smooth, while the surface in saline control appeared roughened (Fig. 6).

DISCUSSION

After flexor tendon repair, tendon rehabilitation is an important factor affecting clinical outcome.^{41,42} In safe rehabilitation, the loads applied to the repaired tendon should be large enough to induce tendon motion yet small enough to avoid creation of a repair site gap or tendon rupture. Unfortunately, many suture techniques with high breaking strength also have high gliding resistance, so that the safe zone for rehabilitation is not so much enlarged as

simply shifted to a higher force range.^{9,10,43} In addition, high friction repairs abrade the undersurface of the pulley,⁴⁴ as we observed in the control tendon in this study. Tendon surface modifications using gelatin and hyaluronic acid have been developed to reduce the gliding resistance of both tendon graft and repaired tendon.^{27,28,30} Here we investigate the effect of adding lubricin to these formulations.

EDC activates the carboxyl groups in the gelatin molecule and forms the intermediate O-acylisourea, which can chemically bind to exposed amino groups. By this rationale, it was used in this study to increase the binding of lubricin on the activated tendon surface. The carbodiimide-derivatized-gelatin used initially can also fill any gaps and/or irregularities on the repaired flexor tendon surface and this may provide a smoother surface for the lubricin binding.

In this study, the cd-HA-gelatin, cd-gelatin + lubricin, and cd-HA-gelatin + lubricin all improved the final mean and peak gliding resistance of the repaired flexor tendon significantly as compared to the saline controls. The two lubricin-treated groups had the lowest gliding resistance at every testing point. The cd-HA-gelatin + lubricin tendons were significantly better than the tendons treated with cd-HA-gelatin alone. While not significant, there was clearly a trend for improved results with cd-gelatin + lubricin, as well.

Although the canine digit is functionally different from the human finger, the anatomic structure, biological components, and mechanical properties of canine flexor tendons are very similar to human flexor tendons. We have assessed the coefficients of friction for canine and human tendons, and they are also very similar.⁴⁵ Thus, we feel comfortable in using the canine model as a proxy for human tendons.

A common program of postoperative therapy in the canine model *in vivo* is 10 cycles of flexion/extension twice per day for 6 weeks,⁴⁶ or 840 cycles. We selected 1,000 cycles to simulate this situation. Human rehabilitation programs vary in the number of cycles per day, but are typically more. For example, one of us uses an initial frequency of 10 cycles per hour, 10 times per day for the first few weeks after tendon repair clinically. In such a scenario 1,000 cycles would be achieved within 10 days. Either way, we believe that the number of cycles is clinically reasonable.

The normal frictional force between tendon and pulley is only approximately 0.09 N.¹¹ This value roughly quadruples after laceration and repair, to 0.35N. The increment of friction after 1,000 cycles with no treatment was a further 0.25N, whereas the treatment groups showed no further increase in friction after 1,000 cycles, compared to the post-repair baseline, implying that the roughness of the tendon surface in the nontreatment group after 1,000 cycles was much greater than in the treated groups (shown in Fig. 5). As the tendon glides repetitively against the pulley and sheath, the rougher tendon surface may cause more damage to the flexor synovial sheath, just as sandpaper, used repetitively, abrades the surface it contacts. This outcome has been confirmed in the changes seen in the pulley surface examined by SEM (Fig. 6), and has been reported previously in canine studies *in vivo*, comparing tendon suture constructs that differed by a similar magnitude (0.25N) gliding resistance.^{8,12} Thus, there may be an adverse cumulative effect of friction *in vivo* that is not captured in simple *in vitro* studies.

These results suggest that the lubricin surface modification can improve the gliding of repaired flexor tendons, at least as well as, and possibly better than, a carbodiimide-derivatized hyaluronic acid-gelatin treatment without lubricin. The lubricin treated specimens viewed qualitatively by SEM also appeared to have less wear after 1,000 cycles.

We believe that these results are logical, as previous studies have indicated that lubricin interacts with HA and works synergistically to provide boundary lubrication of a latex-glass bearing under increasing load,^{47,48} and that HA and lubricin in combination lowered friction coefficients further at high concentrations.⁴⁹ In the current study, the increase of average gliding resistance of the repaired tendon treated with cd-HA-gelatin + lubricin combination was the least, and significantly lower than that of the cd-HA-gelatin treated tendon. This result supports the previous study and suggests that lubricin and HA in combination would further improve the gliding of repaired tendon significantly compared to either substance individually.

The principal limitation of this study is that it was an in vitro investigation. Surface wear studies in vitro have significant limitations due to the short-term nature of the studies and the lack of a biological response. However, we believe that lubricin would have an even greater effect on repaired tendon gliding in vivo, since it also plays an important cytoprotective role by preventing cellular adhesion to the tendon surface.¹⁷ The surface modification procedure was performed based on an experimental in vitro protocol with an isolated repaired tendon that was immersed in chemical reagents. Considering the feasibility of clinical application, an exposure in vitro similar to a typical tendon repair in vivo was also performed. The tendon exposure was sufficient for the administration of this surface modification. A piece of silicone sheeting is sufficient to constrain the surface application to the tendon surface. We have begun using the same surface treatment in vivo in our canine model recently, without significant difficulty.

In this study, we used a modified Pennington technique with a two strands core suture and a circumferential epitendon simple running suture.⁵⁰ With a multiple strand suture method such as the Becker technique, the repair site may become bulky, which could impair passage through the pulley.⁵¹ Although the lubricin surface modification cannot decrease the bulk effect, the gliding of a tendon after multiple strand suture repair could be improved by enhancing the boundary lubrication between repaired tendon and its pulley.

In summary, we have shown that the addition of lubricin to a tendon surface pretreated with cd-gelatin and HA can significantly reduce the gliding resistance of the repaired flexor tendon and maintain a qualitatively smooth tendon and pulley surface after 1,000 cycles of simulated flexion/extension tendon motion compared to the carbodiimide derivatized hyaluronic acid (cd-HA-gelatin) preparation alone. These findings may have important implications for the development of tissue engineered tendon surfaces to improve the results after tendon repair.

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Figure 1. Lateral view of testing apparatus for measurement of gliding resistance between the repaired FDP tendon and its proximal pulley. F1 is the distal force transducer and F2 is the proximal force transducer.

Figure 2.

Increase in average gliding resistance of repaired FDP tendon after treatment at 1,000 cycles. Tendon was treated with saline (saline), 10% gelatin/1% HA/1% EDC/1% NHS (cd-HA-gelatin), 10% gelatin/1% EDC/1% NHS + lubricin (cd-gelatin + lubricin), and 10% gelatin/1% HA/1% EDC/1% NHS + lubricin (cd-HA-gelatin + lubricin). (*) indicates significant difference ($p < 0.05$).

Figure 4. Increase in average gliding resistance of repaired FDP tendon in the four treatment groups at different cycles of tendon motion.

Figure 5. The surface of repaired FDP tendon treated with (A) saline, (B) cd-HA-gelatin, (C) cd-gelatin + lubricin, and (D) cd-HA-gelatin + lubricin after 1,000 cycles of tendon motion. Bar = 5 μ m.

Figure 6. The surface of proximal pulley in (A) saline, (B) cd-HA-gelatin, (C) cd-gelatin + lubricin, and (D) cd-HA-gelatin + lubricin group after 1,000 cycles of tendon motion. Bar = 2 mm.