# Effect of Lactoferrin Peptide (PXL01) on Rabbit Digit Mobility After Flexor Tendon Repair

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**Purpose** Restoration of digital function after flexor tendon injuries remains a clinical challenge. Complications such as adhesion formation and tendon rupture can lead to limited hand function. The aim of this study was to compare the effects of the lactoferrin-derived peptide, PXL01, formulated in sodium hyaluronate (SH), with SH alone on joint mobility as an indirect measure of postsurgical adhesion prevention and healing strength of the tendon and to elucidate the most optimal concentration of PXL01.

**Methods** Using a rabbit flexor tendon repair model, in which the deep flexor tendon was fully transected and repaired, PXL01 in SH or SH alone was administered between the repaired tendon and the tendon sheath before closure of the surgical wound. Three concentrations of PXL01 in SH (5, 20, or 40 mg/mL) were compared to determine the lowest effective concentration. The repaired tendons were evaluated 7 weeks after surgery by measuring the proximal interphalangeal joint mobility by full range of flexion assessment and the tendon repair strength.

**Results** Treatment with PXL01 formulated in SH resulted in improved mobility of the proximal interphalangeal joint with an average of 10°, corresponding to improvement of approximately 25% to 60% of the flexion of nonoperated toes at the different measuring points compared with SH alone. The difference was statistically significant in 5 out of 6 measuring points (0.5, 1, 2, 3, and 4 N; $P < .05$). The dose-response study indicated that the lowest effective concentration of PXL01 was 20 mg/mL. There was no difference in healing strength of the tendon between the groups as assessed by load-to-failure breaking strength.

**Conclusions** PXL01 in SH significantly improved the mobility compared with the carrier SH alone, without any negative effect on healing strength, and PXL01 at 20 mg/mL was the lowest effective concentration.

**Clinical relevance** The result provides a valuable basis for a clinical trial to assess efficacy and safety of PXL01 in clinical hand surgery. *(J Hand Surg 2012;37A:2519–2525. Copyright © 2012 by the American Society for Surgery of the Hand. All rights reserved.)*

**Key words** Adhesions, flexor tendon, lactoferrin, rabbit, sodium hyaluronate.

The formation of peritendinous adhesions associated with flexor tendon injury and repair causes reduced postoperative gliding function of the tendon and constitutes a clinical challenge. Reduced mobility of the affected digit and impairment of hand function following flexor tendon repair may lead to adverse personal, social, and economic consequences.[1–5]

There is a strong incentive to develop pharmaceutical products for prevention of peritendinous adhesions.[4] One such product that has been evaluated both in ani-

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mal models and clinically is sodium hyaluronate (SH). The results from studies with exogenous administration of SH to reduce postoperative adhesions after flexor tendon surgery have been inconclusive, and the benefits of using SH have not been demonstrated.[6–14]

In recent studies, the efficacy of the synthetic peptide PXL01, with SH as a carrier, in reducing adhesions has been assessed in 2 different experimental animal models: the abdominal surgery model in rats[15] and the flexor tendon repair surgery model in rabbits.[16] In both the abdominal and the hand surgery models, PXL01, in combination with SH, significantly reduced adhesions compared with sham-operated controls.

In the present study, the effect of PXL01 formulated in SH was compared with SH alone, and the optimal concentration of PXL01 in SH was assessed on joint mobility as an indirect measure of postsurgical adhesion formation as well as healing strength of the tendon using a rabbit model of flexor tendon surgery.

## MATERIALS AND METHODS

### Product preparation

PXL01 dissolved in 0.9% sodium chloride solution was added to 2.5% SH solution (Bohus Biotech, Strömstad, Sweden) at a volume ratio of 2/5 PXL01 and 3/5 SH, to obtain 5, 20, or 40 mg/mL PXL01 in 1.5% SH. The solution was homogenized by drawing the mixtures several times through a 2.1-mm-diameter needle. To receive 1.5% SH alone, 2.5% SH was mixed with 0.9% NaCl according to the same procedure.

### Animal model

Female New Zealand White rabbits (body weight ~3 kg; HB Lidköping, Sweden) were used in the study. The regional animal ethical committee approved all experimental procedures. The rabbits were housed in single cages for a minimum of 2 weeks before surgery and had free access to water and pellets (Lactamin AB, Kimstad, Sweden) and daily fruit or carrots.

Anesthesia was induced by an intramuscular injection of medetomidin (0.3 mg/kg; Domitor Vet, Orion Pharma, Espoo, Finland) and ketamin (20 mg/kg; Ketaminolvet, Intervet, Boxmeer, Netherlands). A booster dose of ketamin (10 mg/kg) was administered 40 minutes after induction, and medetomodin (0.15 mg/kg) was administered 1 hour after induction. After the surgery, atipamezol (1.5 mg/kg; Antisedan, Orion Pharma, Espoo, Finland) was given intramuscularly. A single dose of 100-mg cefuroxime (Zinacef; GlaxoSmithKline, Mölndal, Sweden) was administered intravenously in an ear vein before surgery. An intramuscular injection of buprenorfin (0.3 mg/kg; Temgesic, Schering-Plough, Brussels, Belgium) was given for pain relief when the effect of the general anesthesia was decreasing. An additional dose was given the first evening and the next morning after surgery.

### Study design

*Part I: comparing the effect of PXL01 in SH versus SH alone.* In each animal, the third digit in 1 paw received treatment with PXL01 (20 mg/mL) in SH whereas the corresponding digit of the other paw received only the carrier, SH. The other digits were left undisturbed. There were 12 rabbits and, thus 24, paws analyzed (12 paws in each group). To compare the obtained values with nonoperated paws (negative control) and sham-operated paws (positive control; the surgery was performed in an identical manner but no treatment was administered), the data were pooled with data from a previous study performed using identical protocols[16] including: nonoperated (n = 21), sham-operated (n = 18), and additional data from PXL01-treated (20 mg/mL) paws (n = 19) from a total of 29 rabbits.

*Part II: dose response for PXL01.* In this part, 3 different concentrations of PXL01 (5, 20, or 40 mg/mL) in SH were evaluated in 24 rabbits (48 hind paws; n = 16 for each group). The third digit on each paw was used, and the other digits were left undisturbed. Owing to anesthesia-related and postoperative complications, 36 toes could be used for evaluation (5 mg/mL, n = 13; 20 mg/mL, n = 13; and 40 mg/mL, n = 10).

To obtain an overview on the dose-response part in relation to nonoperated paws (negative control), sham-operated paws (positive control; the surgery was performed in an identical manner but no treatment was administered), and SH-treated paws, the data were pooled with the data from Part I and data from a previous study performed using identical protocols[16] including: nonoperated (n = 21), sham-operated (n = 18), SH-treated (n = 12), and additional data from PXL01-treated (20 mg/mL) paws (n = 31) from a total of 41 rabbits.

### Surgical procedure

The surgery was performed as previously described.[14,16,17] The animals were anesthetized and the hind paws were shaved and cleaned with alcohol. A division of the flexor tendon at the tendon/muscle interface above the ankle was performed, resulting in a diminished tensile load of the phalangeal sections of the tendons and allowing unrestricted cage activity without immobilization of the paws after surgery.[14,18-21]

A central longitudinal incision was made in the skin on the plantar side of the proximal phalanx of the third

digit. The other digits were left undisturbed. After opening the flexor tendon sheath with a longitudinal incision between the first and the second pulleys, the superficial flexor tendon was divided and resected locally for about the length of the phalanx. The deep flexor tendon was completely divided with a sharp cut through the intermediate segment proximal to the distal joint.[13,22] The tendon ends of the deep flexor tendon were repaired with a modified Kessler suture (5-0 Prolene; Ethicon, Sollentuna, Sweden) in the core and a running suture (6-0, PDS; Ethicon, Sollentuna, Sweden) in the periphery. The pulleys were left intact. After closing the skin, no dressing or splinting was applied. The animals were housed in single cages throughout the study. This approach was selected because of the rabbits' hierarchical behavior and the risk of overloading the operated tendons while fighting or running. The rabbits were allowed unrestricted activity until death. All surgeries were performed by 1 of the authors (M.W.) under sterile conditions in an animal operating facility.

### Product administration

Surgery was conducted on both hind paws in an identical fashion. The test articles were administered through a BD Neoflon 24GA catheter (Becton, Dickinson infusion therapy AB, Helsingborg, Sweden) that was inserted into the opening of the sheath and connected to a 1-mL syringe with the formulation. The tendon sheath was closed with a running suture (6-0, PDS; Ethicon, Sollentuna, Sweden) with the Neoflon catheter still within the tendon sheath. When tightening the final sutures, 0.5 mL of the formulation was injected, the catheter was removed, and the tendon sheath closed completely. The outer diameter of the Neoflon 24GA catheter was 0.7 mm, and thus, it was feasible to perform the running suture with the catheter within the tendon sheath. The skin was closed with a running suture (5-0 Ethilon; Ethicon, Sollentuna, Sweden). In Part I (comparing PXL01 [20 mg/mL] in SH with SH alone), PXL01 in SH was administrated in 1 paw and SH only in the other paw. In Part II (comparing different concentrations of PXL01 [5, 20 or 40 mg/mL] in SH), the product was administrated in the same manner, with the paws receiving the different treatments randomized. The pharmacological formulation and the dose were blinded to the surgeon and all personnel involved in the evaluation.

### Specimen harvest

Seven weeks after surgery, the rabbits were sedated with midazolam (Dormicum, Roche) and killed by a lethal dose of pentobarbital sodium. The hind paws were separated from the rabbits at midcalf level and the toes were prepared using a dissection protocol as previously described.[23]

### Biomechanical testing

A specifically constructed biomechanical testing device consisting of a servohydraulic actuator, designed for applying controlled force or displacement, was used to study the tendon gliding by slowly increasing the force on the tendon to mimic the muscle force and thereby test the active motion. A materials testing machine (MTS; Test Star, Minneapolis, MN) servosystem and software were used to control the test sequences (Fig. 1). The maximum applied force was set to 5 N. Previous tests revealed that a complete flexion was obtained at less than 5 N, and the addition of a higher force did not produce any further flexion.[23] Range of motion and load to failure of the operated digits were analyzed as previously described.[23] For range of motion assessment, paper printouts from the recordings were obtained for 0, 0.5, 1, 2, 3, 4, and 5 N. Measurement of the proximal interphalangeal (PIP) joint angle was performed for each applied force level on the paper printouts by drawing extended lines through the metatarsophalangeal and PIP joints and the PIP and distal interphalangeal (DIP) joints, respectively, and measuring the angle with a protractor. The angles were normalized against baseline. The angle measurements for each force level were statistically compared between the groups.

After the range of motion test, the digit was fixed over the DIP joint, and the load-to-failure test was performed on each specimen. The test was stopped when the first sign of failure was detected, notably a substantial drop in force value, often accomplished by an audible crack from the specimen.

### Statistics and data analysis

Owing to the partially paired nature of the data, paired (Part I PXL01 in SH compared with SH only) and unpaired (Part I pooled data and Part II) *t*-tests were used for statistical analysis. To reveal the relation of the data to nonoperated and sham-operated toes, the data generated in the current study were pooled with measurements of toes of a different cohort of age- and weight-matched rabbits obtained using identical assessment protocols.[16] Results are presented as mean and standard error of the mean (SEM). A level of $P < .05$ was considered significant.

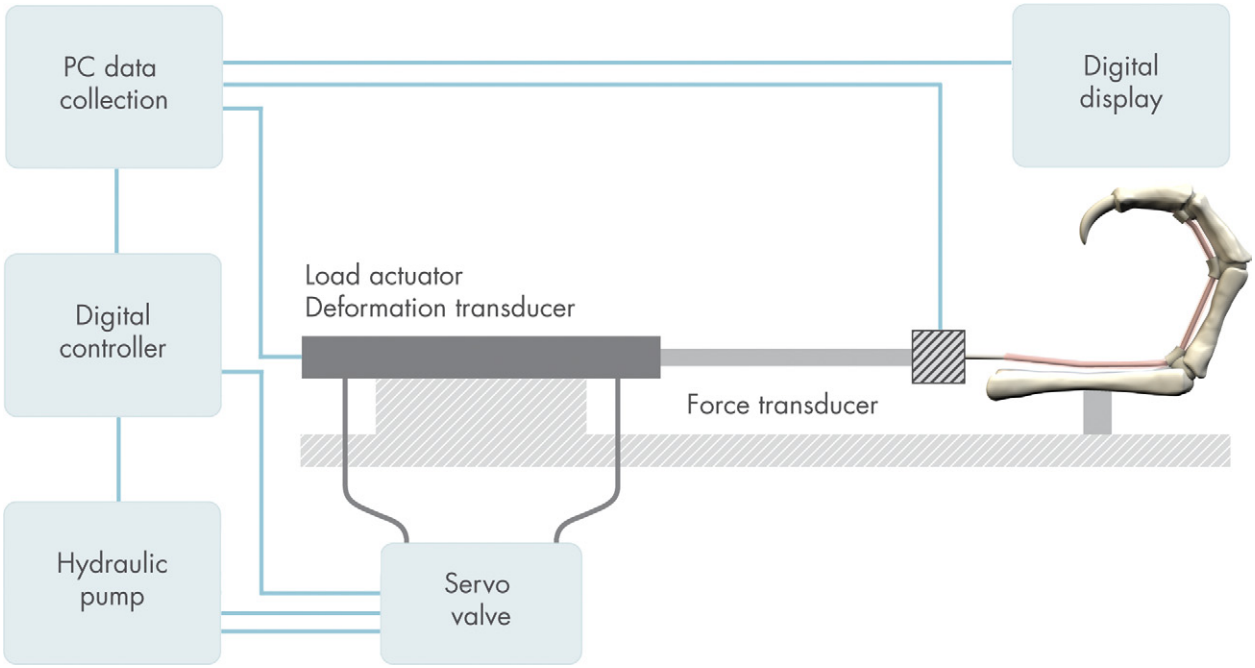


**FIGURE 1:** Schematic presentation of the biomechanical testing setup and the functional parts of the dissected rabbit toe. The specimen (right) is attached to a load actuator that comprised a built-in deformation transducer and external force transducer, mounted adjacent to the clamping device. A digital controller and a personal computer (PC) data collection unit process the transducer values, force data are collected from the force transducer unit, and length data are collected from the load actuator deformation transducer. Behind the specimen is a digital display that shows the force applied. Both the specimen and the digital display are simultaneously videotaped by the camera during the load.

## RESULTS

### Gross inspection

In total, 3 out of 36 rabbits undergoing surgery had to be withdrawn before the end of the study because the rabbits licked their wounds, causing them to open. Gross inspection of the paws after the surgery did not indicate any differences between the groups.

### Biomechanical testing

*Part I: PXL01 in SH versus SH alone.* PXL01 (20 mg/mL) in SH significantly increased the PIP joint mobility compared with SH at all measuring points 0.5 N to 4 N ($P < .05$; at 5 N $P = .058$) (Fig. 2) without affecting the tendon healing strength because no significant difference was observed in the load-to-failure assessment (PXL01 in SH: 97 ± 8N, n = 12; SH only: 91 ± 4N, n = 12).

To compare the measurements from Part I with nonoperated and sham-operated digits, the data were pooled with data collected previously.[16] PXL01 (20 mg/mL) in SH close to normalized the PIP joint mobility because there was no significant difference between nonoperated digits and treatment with PXL01 (20 mg/mL) in SH except for the 1-N measuring point (Fig. 3). The SH group was significantly different from the nonoperated digits at all measuring points 1 N to 5 N but was not significantly different from the sham-operated digits at any measuring point (Fig. 3).

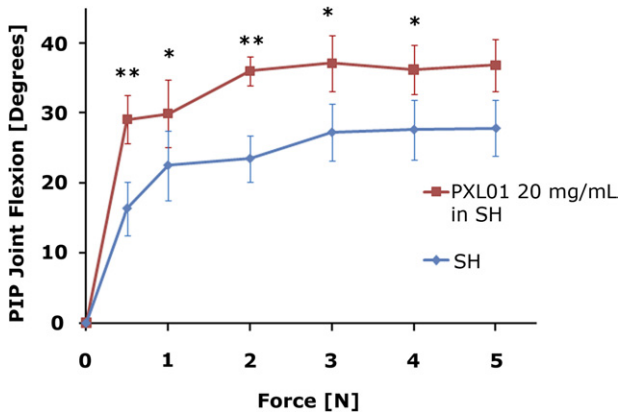


**FIGURE 2:** Comparison of the proximal interphalangeal (PIP) joint flexion after treatment with PXL01 20 mg/mL in sodium hyaluronate (SH) or SH only (part I). The angle of the PIP joint was measured at the loaded force 0.5, 1, 2, 3, 4, and 5 N. $n_{SH} = 12$; $n_{PXL01\ 20\ mg/mL\ in\ SH} = 12$. * = $P < .05$, ** = $P < .01$. Statistical test used was the paired Student *t*-test.

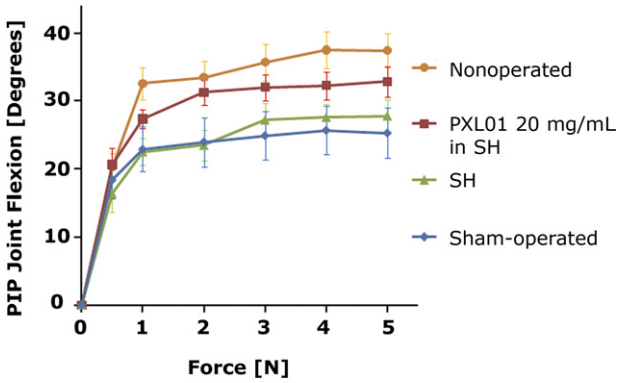


**FIGURE 3:** Pooling of the proximal interphalangeal (PIP) joint flexion data in part I with data collected previously. The angle of the PIP joint was measured at the loaded force 0.5, 1, 2, 3, 4, and 5 N. SH, sodium hyaluronate; $n_{sham\text{-}operated} = 18$; $n_{SH} = 12$, $n_{PXL01\ 20\ mg/mL\ in\ SH} = 31$; $n_{nonoperated} = 21$. Statistical test used was the unpaired Student *t*-test.

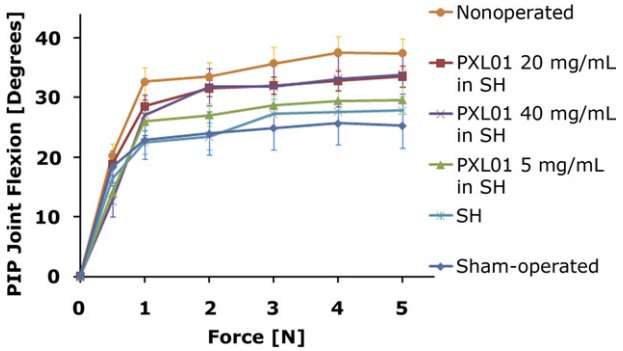


**FIGURE 4:** Pooling of the proximal interphalangeal (PIP) joint flexion data from part I and part II with data collected previously. The angle of the PIP joint was measured at the loaded force 0.5, 1, 2, 3, 4, and 5 N. SH, sodium hyaluronate; $n_{sham\text{-}operated} = 18$; $n_{SH} = 12$, $n_{PXL01\ 20\ mg/mL\ in\ SH} = 44$; $n_{PXL01\ 40\ mg/mL\ in\ SH} = 10$; $n_{PXL01\ 5\ mg/mL\ in\ SH} = 13$; $n_{nonoperated} = 21$. Statistical test used was the unpaired Student *t*-test.

*Part II: dose response.* To compare the measurements from the toes treated with PXL01 (5, 20, and 40 mg/mL in SH) with nonoperated and sham-operated digits, the results were pooled with data collected previously.[16] The highest concentration of PXL01 (40 mg/mL) did not result in any additional improvement of postsurgical PIP joint mobility compared with 20 mg/mL, whereas both concentrations improved the mobility compared with the administration of the lowest concentration, 5 mg/mL (Fig. 4). No significant difference was observed in tendon healing strength comparing the 3 concentrations, assessed by load-to-failure test (PXL01 5 mg/mL, 75 ± 7N, n = 13; PXL01 20 mg/mL, 80 ± 10N, n = 14; PXL01 40 mg/mL, 87 ± 11N, n = 10). Taken together, according to the analysis of the PIP joint mobility, 20 mg/mL of PXL01 in SH was the optimal concentration of the active compound.

## DISCUSSION

Adhesion formation between the tendon and the tendon sheath is the major cause of reduced postoperative range of active motion and functional impairment following Zone 2 flexor tendon repair, leading to disabilities for the individual.[24–26] In this study, we describe PXL01, a lactoferrin-derived peptide, for prevention of adhesions after hand surgery. We showed that a single treatment with PXL01 formulated in SH significantly improved postoperative digit mobility compared with SH alone in an in vivo model of flexor tendon surgery in rabbits and that 20 mg/mL PXL01 was the most optimal concentration.

PXL01 is a peptide derived from human lactoferrin, an iron-binding glycoprotein present in milk and mucosal secretions, that exhibits antimicrobial and anti-inflammatory properties.[27,28] Previously, we have shown that PXL01 downregulates the pro-inflammatory cytokines tumor necrosis factor-alpha (TNF-$\alpha$), interleukin-1-beta (IL-1$\beta$), IL-1-6, and the pro-inflammatory chemokine IL-8 and inhibits plasminogen activator inhibitor type-1 (PAI-1) secretion. In addition, PXL01 also exhibits a broad range of antibacterial activities, that is,. microbicidal activity against *Staphylococcus aureus, Escherichia coli,* and *Pseudomonas aeruginosa.*[15]

We have used SH as a carrier for PXL01. SH is found naturally in tendons and has been used extensively in medical applications and, therefore, is considered to have a favorable safety profile.[29] The effect of SH to prevent peritendinous adhesions has been assessed in vivo; however, the studies performed in rabbits and humans did not show any conclusive results.[6,9,29,30] In a recent study, hyaluronic acid with the addition of lubricin was evaluated in an in vivo canine model. Although the postoperative adhesion formation was reduced, the treatment also resulted in impaired tendon healing strength.[31]

In this study, the antiadhesion properties of PXL01 were indirectly assessed as a measurement of the PIP joint mobility using a previously described experimental model of flexor tendon surgery in rabbit.[14,16,17] The digit mobility, as an indirect measure of the extent of peritendinous adhesion formation, was evaluated 7 weeks after surgery using a custom-designed biomechanical setup[23] (Fig. 1). The movement of the PIP joint was considered to be the most relevant parameter to reflect reduction in mobility owing to its proximity

just distal to the tendon repair site. Moreover, the DIP joint is very closely located to the attachment of the claw in the rabbit, which complicates the assessment of DIP joint mobility. We previously reported that a single treatment with PXL01 formulated in SH nearly normalized the postoperative digit mobility without affecting the tendon healing strength, whereas sham-operated digits showed severe impaired mobility.[16] In the present study, using the same rabbit model, PXL01 in SH significantly increased the PIP joint mobility compared with SH alone, and the concentration of 20 mg/mL of PXL01 appeared optimal because it was found superior to 5 mg/mL whereas 40 mg/mL failed to show any additional increase in mobility. Administration of SH alone did not significantly increase the PIP joint mobility compared with sham-operated digits. We also demonstrated that there was no significant difference between the groups in the force needed for failure of the operated tendons.

In this study, the mechanical tests were not complemented by any histological assessment of adhesion appearance,[32–35] which is a limitation of the study. Instead, we chose to perform functional studies with an earlier published custom-made device,[23] which gives an evaluation of the digit mobility that directly reflects the functional impediment. All animals included in this paper had surgery and were analyzed according to identical protocols. However, the data were pooled from different studies separated in time, which might have increased variation and is considered a weakness of the study. The proximal tenotomy model has been described and successfully used in earlier studies.[16–19,21] Because this model induces passive unloaded motion of the repairs during movement of the rabbits in their cages, differences in rabbit activity may influence the tendon repair processes. However, in our experiment, this was true for all groups and, therefore, unlikely to have led to a bias.

The combination of the anti-inflammatory, fibrinolytic, and antibacterial properties of PXL01 with the lubricating properties of SH, which acts as an initial diffusion barrier for the fibrinogen exudates and also allows PXL01 to be slowly released,[15] therefore appears attractive and worth pursuing in clinical trials. The optimal dose of PXL01 formulated in SH defined in this experimental model should be interpreted with care regarding the human situation; however, the current study provides a valuable basis for the dose selection in patients.

## REFERENCES


1. Chow JA, Thomes LJ, Dovelle S, Milnor WH, Seyfer AE, Smith AC. A combined regimen of controlled motion following flexor tendon repair in "no man's land." Plast Reconstr Surg 1987; 79:447–455.
2. Gelberman RH, Manske PR. Factors influencing flexor tendon adhesions. Hand Clin 1985;1:35–42.
3. Manske PR. Flexor tendon healing. J Hand Surg 1988;13B:237–245.
4. Rosberg HE, Carlsson KS, Hojgard S, Lindgren B, Lundborg G, Dahlin LB. What determines the costs of repair and rehabilitation of flexor tendon injuries in zone II? A multiple regression analysis of data from southern Sweden. J Hand Surg 2003;28B:106–112.
5. Tang JB. Clinical outcomes associated with flexor tendon repair. Hand Clin 2005;21:199–210.
6. Amiel D, Ishizue K, Billings E Jr, Wiig M, Vande Berg J, Akeson WH, et al. Hyaluronan in flexor tendon repair. J Hand Surg 1989; 14A:837–843.
7. Hakansson L, Hallgren R, Venge P. Regulation of granulocyte function by hyaluronic acid. In vitro and in vivo effects on phagocytosis, locomotion, and metabolism. J Clin Invest 1980;66:298–305.
8. Miller JA, Ferguson RL, Powers DL, Burns JW, Shalaby SW. Efficacy of hyaluronic acid/nonsteroidal anti-inflammatory drug systems in preventing postsurgical tendon adhesions. J Biomed Mater Res 1997;38:25–33.
9. Salti NI, Tuel RJ, Mass DP. Effect of hyaluronic acid on rabbit profundus flexor tendon healing in vitro. J Surg Res 1993;55:411–415.
10. St. Onge R, Weiss C, Denlinger JL, Balazs EA. A preliminary assessment of Na-hyaluronate injection into "no man's land" for primary flexor tendon repair. Clin Orthop Relat Res 1980;146:269–275.
11. Thomas SC, Jones LC, Hungerford DS. Hyaluronic acid and its effect on postoperative adhesions in the rabbit flexor tendon. A preliminary look. Clin Orthop Relat Res 1986;26:281–289.
12. Weiss C. The inhibition of flexor tendon adhesions. Bull Hosp Jt Dis Orthop Inst 1986;46:193–194.
13. Wiig M, Abrahamsson SO, Lundborg G. Effects of hyaluronan on cell proliferation and collagen synthesis: a study of rabbit flexor tendons in vitro. J Hand Surg 1996;21A:599–604.
14. Wiig M, Abrahamsson SO, Lundborg G. Tendon repair—cellular activities in rabbit deep flexor tendons and surrounding synovial sheaths and the effects of hyaluronan: an experimental study in vivo and in vitro. J Hand Surg 1997;22A:818–825.
15. Nilsson E, Bjorn C, Sjostrand V, Lindgren K, Munnich M, Mattsby-Baltzer I, et al. A novel polypeptide derived from human lactoferrin in sodium hyaluronate prevents postsurgical adhesion formation in the rat. Ann Surg 2009;250:1021–1028.
16. Wiig M, Olmarker K, Hakansson J, Ekstrom L, Nilsson E, Mahlapuu M. A lactoferrin-derived peptide (PXL01) for the reduction of adhesion formation in flexor tendon surgery: an experimental study in rabbits. J Hand Surg 2011;36E:656–662.
17. Berglund M, Reno C, Hart DA, Wiig M. Patterns of mRNA expression for matrix molecules and growth factors in flexor tendon injury: differences in the regulation between tendon and tendon sheath. J Hand Surg 2006;31A:1279–1287.
18. Berglund M, Hart DA, Wiig M. The inflammatory response and hyaluronan synthases in the rabbit flexor tendon and tendon sheath following injury. J Hand Surg 2007;32E:581–587.
19. de Wit T, de Putter D, Tra WM, Rakhorst HA, van Osch GJ, Hovius SE, et al. Auto-crosslinked hyaluronic acid gel accelerates healing of rabbit flexor tendons in vivo. J Orthop Res 2009;27:408–415.
20. Loiselle AE, Bragdon GA, Jacobson JA, Hasslund S, Cortes ZE, Schwarz EM, et al. Remodeling of murine intrasynovial tendon adhesions following injury: MMP and neotendon gene expression. J Orthop Res 2009;27:833–840.
21. Oshiro W, Lou J, Xing X, Tu Y, Manske PR. Flexor tendon healing in the rat: a histologic and gene expression study. J Hand Surg 2003;28A:814–823.
22. Berglund M, Wiig M, Torstensson M, Reno C, Hart DA. Assessment of mRNA levels for matrix molecules and TGF-beta1 in rabbit flexor and peroneus tendons reveals regional differences in steady-state expression. J Hand Surg 2004;29B:165–169.

23. Olmarker K, Ekstrom L, Hakansson J, Nilsson E, Wiig M, Mahlapuu M. Model for assessment of mobility of toes and healing of tendons in rabbits. J Plast Surg Hand Surg 2010;44:266–271.
24. Strickland JW. Development of flexor tendon surgery: twenty-five years of progress. J Hand Surg 2000;25A:214–235.
25. Tang JB. Tendon injuries across the world: treatment. Injury 2006; 37:1036–1042.
26. Tang JB. Indications, methods, postoperative motion and outcome evaluation of primary flexor tendon repairs in Zone 2. J Hand Surg 2007;32E:118–129.
27. Legrand D, Elass E, Pierce A, Mazurier J. Lactoferrin and host defence: an overview of its immuno-modulating and anti-inflammatory properties. Biometals 2004;17:225–229.
28. Ward PP, Uribe-Luna S, Conneely OM. Lactoferrin and host defense. Biochem Cell Biol 2002;80:95–102.
29. Hagberg L. Exogenous hyaluronate as an adjunct in the prevention of adhesions after flexor tendon surgery: a controlled clinical trial. J Hand Surg 1992;17A:132–136.
30. Hagberg L, Gerdin B. Sodium hyaluronate as an adjunct in adhesion prevention after flexor tendon surgery in rabbits. J Hand Surg 1992; 17A:935–941.
31. Zhao C, Sun YL, Kirk RL, Thoreson AR, Jay GD, Moran SL, et al. Effects of a lubricin-containing compound on the results of flexor tendon repair in a canine model in vivo. J Bone Joint Surg 2010; 92A:1453–1461.
32. Bhavsar D, Shettko D, Tenenhaus M. Encircling the tendon repair site with collagen-GAG reduces the formation of postoperative tendon adhesions in a chicken flexor tendon model. J Surg Res 2010; 159:765–771.
33. Ozboluk S, Ozkan Y, Ozturk A, Gul N, Ozdemir RM, Yanik K. The effects of human amniotic membrane and periosteal autograft on tendon healing: experimental study in rabbits. J Hand Surg 2010; 35E:262–268.
34. Strick MJ, Filan SL, Hile M, McKenzie C, Walsh WR, Tonkin MA. Adhesion formation after flexor tendon repair: a histologic and biomechanical comparison of 2- and 4-strand repairs in a chicken model. J Hand Surg 2004;29A:15–21.
35. Tang JB, Cao Y, Zhu B, Xin KQ, Wang XT, Liu PY. Adeno-associated virus-2-mediated bFGF gene transfer to digital flexor tendons significantly increases healing strength. an in vivo study. J Bone Joint Surg 2008;90A:1078–1089.