Surface Modification with Chemically Modified Synovial Fluid for Flexor Tendon Reconstruction in a Canine Model in Vivo

Xiaoxi Ji, MD, Ramona L. Reisdorf, BS, Andrew R. Thoreson, MS, Lawrence R. Berglund, MS, Steven L. Moran, MD, Gregory D. Jay, MD, PhD, Kai-Nan An, PhD, Peter C. Amadio, MD, and Chunfeng Zhao, MD

Investigation performed at the Department of Orthopedic Surgery, Mayo Clinic, Rochester, Minnesota

Background: Functional restoration is the major concern after flexor tendon reconstruction in the hand. The purpose of the present study was to investigate the effects of modifying the surface of extrasynovial tendon autografts with carbodiimide-derivatized synovial fluid with gelatin (cd-SF-G) on functional outcomes of flexor tendon reconstruction using a canine model.

Methods: The second and fifth flexor digitorum profundus tendons from eleven dogs were transected and repaired in zone II. The dogs then had six weeks of free activity leading to tendon rupture and scar formation (the repair-failure phase). In the reconstruction phase, two autologous peroneus longus tendons from each dog were harvested; one tendon was coated with cd-SF-G and the other, with saline solution, as a control. A non-weight-bearing rehabilitation protocol was followed for six weeks after reconstruction. The digits were then harvested and evaluations of function, adhesion status, gliding resistance, attachment strength, cell viability, and histology were performed.

Results: The tendons coated with cd-SF-G demonstrated significantly lower values (mean and standard deviation) compared with the saline-solution group for work of flexion (0.63 ± 0.24 versus 1.34 ± 0.42 N-mm/deg), adhesion score (3.5 ± 1.6 versus 6.1 ± 1.3), proximal adhesion breaking force (8.6 ± 3.2 versus 20.2 ± 10.2 N), and gliding resistance (0.26 ± 0.08 versus 0.46 ± 0.22 N) ($p < 0.05$). There was no significant difference between the cd-SF-G and saline-solution groups ($p > 0.05$) in distal attachment-site strength (56.9 ± 28.4 versus 77.2 ± 36.2 N), stiffness (19 ± 7.5 versus 24.5 ± 14.5 N/mm), and compressive modulus from indentation testing (4.37 ± 1.26 versus 3.98 ± 1.24 N/mm). Histological analysis showed that tendons coated with cd-SF-G had smoother surfaces and demonstrated tendon-to-bone and tendon-to-tendon incorporation. No significant difference in viable cell count between the two groups was observed on tendon culture.

Conclusions: Modification of the flexor tendon surface with cd-SF-G significantly improved digital function and reduced adhesion formation without affecting graft healing and stiffness.

Clinical Relevance: This study used native synovial fluid as a basic lubricating reagent to treat a tendon graft in vivo, a novel avenue for improving clinical outcomes of flexor tendon reconstruction. This methodology may also apply to other surgical procedures where postoperative adhesions impair function.

Peer Review: This article was reviewed by the Editor-in-Chief and one Deputy Editor, and it underwent blinded review by two or more outside experts. It was also reviewed by an expert in methodology and statistics. The Deputy Editor reviewed each revision of the article, and it underwent a final review by the Editor-in-Chief prior to publication. Final corrections and clarifications occurred during one or more exchanges between the author(s) and copyeditors.

Flexor tendon injuries in the hand are common, especially in the young and working-age population, and they cause substantial disability and economic burden¹⁻³. Direct repair

immediately after flexor injury is standard clinical practice^{4,6}, but flexor tendon reconstruction may be needed to restore tendon function if the primary repair has failed^{7,8}. Flexor tendon

Disclosure: One or more of the authors received payments or services, either directly or indirectly (i.e., via his or her institution), from a third party in support of an aspect of this work. In addition, one or more of the authors, or his or her institution, has had a financial relationship, in the thirty-six months prior to submission of this work, with an entity in the biomedical arena that could be perceived to influence or have the potential to influence what is written in this work. Also, one or more of the authors has a patent or patents, planned, pending, or issued, that is broadly relevant to the work. No author has had any other relationships, or has engaged in any other activities, that could be perceived to influence or have the potential to influence what is written in this work. The complete **Disclosures of Potential Conflicts of Interest** submitted by authors are always provided with the online version of the article.

reconstruction also is performed if a large defect precludes direct repair of the injured flexor tendon^{9,10}. An autologous extrasynovial tendon, such as the palmaris longus or the plantaris tendon, is usually used to replace the injured intrasynovial tendon^{11,12}. Clinical and experimental studies of repair with extrasynovial tendons have shown restricted tendon gliding and reduced digital function, which are associated with the inferior surface durability of extrasynovial tendons compared with that of intrasynovial flexor tendons^{13,14}.

The intrasynovial tendon surface is covered with a thin lubricating layer, consisting mainly of hyaluronic acid (HA)¹⁵ and lubricin^{16,17}, which reduces gliding resistance between the tendon and sheath^{18,19}. In previous studies, we found that surface modification with carbodiimide-derivatized HA combined with lubricin (cd-HA-lubricin) greatly reduced tendon adhesion and improved digital function but also adversely affected tendon healing^{20,21}. In addition to HA and lubricin, phospholipids also have been found to decrease tendon gliding resistance and improve outcomes after flexor tendon repair²². All three lubricating molecules are native components of synovial fluid and are found on the intrasynovial tendon surface²³⁻²⁵. Modification of the tendon surface with use of a compound of carbodiimide-derivatized synovial fluid with gelatin (cd-SF-G) was shown to significantly improve gliding ability in vitro²⁶. Moreover, synovial fluid was found not to inhibit the proliferation of human osteoblasts in vitro, indicating that synovial fluid also may not affect tendon-to-bone healing²⁷.

The purpose of this study was to investigate the effects of cd-SF-G surface modification of extrasynovial tendon autografts for flexor tendon reconstruction using a clinically relevant canine model. We hypothesized that this modification would improve digital function and reduce adhesion formation without jeopardizing graft healing.

Materials and Methods

Study Design and Procedure

Eleven purpose-bred dogs weighing 20 to 25 kg were used. The study was approved by our Institutional Animal Care and Use Committee. Pain was managed with morphine (0.5 mg/kg, administered intravenously once before surgery), carprofen (4 mg/kg, subcutaneously, daily for one week postoperatively), and sustained-release buprenorphine (0.12 mg/kg, intramuscularly, once daily for two days postoperatively). This study model included a repair-failure phase followed by a reconstruction phase to mimic a clinically relevant scenario in which tendon grafts are used after a failed repair. For the repair-failure phase, flexor digitorum profundus (FDP) tendons were transected in the second and fifth digits at the level of the proximal interphalangeal joint of one randomly selected forepaw, followed by repair with a modified Kessler technique, as previously described²⁸. Free cage activity was allowed after repair, which caused all repaired tendons to rupture and a scar to form on the digital sheath by postoperative week 6.

For the reconstruction phase, synovial fluid was first aspirated from both knees intraoperatively. Flexor tendon reconstruction was performed in the forelimb using peroneus longus (PL) tendons as grafts, as previously described²⁸. PL tendons (approximately 6 cm in length) were harvested from both hindpaws of each dog. One PL tendon was randomly selected as the saline solution-treated control, and the other was coated with cd-SF-G, which consisted of 46% native synovial fluid, 10% gelatin (from porcine skin; Sigma Chemical), 1% 1-ethyl-3-[(3-dimethylaminopropyl) carbodiimide hydrochloride] (EDC) (Sigma), 1% N-hydroxysuccinimide (Sigma) in 0.1 M 2-(N-morpholino)ethanesulfonic acid

buffer (Sigma), pH 6.0. The previous incision was used to replace the ruptured FDP tendons with the PL tendons (treated with either cd-SF-G or saline solution). The proximal end of the tendon graft was sutured to the FDP tendon with a Pulvertaft end-to-side weave method²⁸. The distal end of the graft was sutured to the distal phalanx through a bone tunnel. To avoid weight-bearing after flexor tendon reconstruction, a high-radial neurectomy was performed through a lateral humeral approach. The operative limb was immobilized with a custom canine jacket, and modified passive synergistic rehabilitation therapy was performed daily for six weeks²⁸. After the sixth postoperative week, the dogs were killed, and the second and fifth digits of the operative and contralateral (nonoperative) paws were harvested for further examination.

Evaluation of Digital Function According to Work of Flexion

Digital function was evaluated on the basis of the work of flexion (WOF), determined using a previously established method^{28,29}. WOF data were calculated from the tendon-displacement versus tendon-loading curve during digital flexion. Data were then normalized (nWOF) by the total proximal interphalangeal and distal interphalangeal joint angles using previously established methods^{20,29}.

Evaluation of Adhesions According to Adhesion Score and Proximal Adhesion Breaking Force

After WOF testing, the adhesion status of each digit was evaluated by determining the gross adhesion score within the flexor sheath and the tendon bed in zone II. The flexor sheath was opened through an area away from the repair site. The adhesions at two sites—between the tendon and pulley/sheath and between the tendon and tendon bed—were separately graded according to previously described scoring criteria²¹. Adhesion scores at each site ranged from 0 (no adhesion) to 4 (very severe). Therefore, the total adhesion score in the two sites ranged from 0 to 8. Scores were determined by two investigators (X.J. and R.L.R.). Any disagreements were resolved by consensus.

Adhesion at the proximal repair site, between the FDP tendon and surrounding tissues, was evaluated by pullout testing using a custom testing device. The tendon graft was transected distal to the proximal repair site, without dissecting it from the surrounding tissues, and pulled proximally at a rate of 20 mm/min until the tendon was fully separated from the surrounding tissues. The tendon pullout test measured the adhesion breaking strength and stiffness of the proximal graft repair (e.g., less pullout force and stiffness indicated the presence of fewer adhesions). Because normal tendons in this area are connected to surrounding soft tissues by the loose connective tissue, pullout testing was also conducted for the intact digits in the nonoperative paw for the purpose of a baseline comparison.

Evaluation of Gliding Resistance

After evaluation of adhesion in the zone-II area, the tendon graft was further dissected for testing of gliding resistance, performed with use of a custom tendon pulley-friction testing apparatus, as previously described^{29,30}. The tendon graft was transected 15 mm proximal to the distal attachment site, and the proximal pulley and the proximal phalanx were mounted on a clamp. A 4.9-N resistance load was applied, and gliding resistance was measured between the tendon and proximal pulley.

Evaluation of Mechanical Strength at the Distal Attachment Site

The repair strength of the distal attachment was assessed with use of a previously developed protocol²¹. Briefly, the proximal 10 mm of the tendon stump was wrapped with a 3-0 silk suture (Ethicon) to improve the clamp's grip on the tendon during testing. The distal phalanx was mounted to the materials-testing machine (MTS Systems) with use of a custom grip. The tendon graft was distracted at a rate of 20 mm/min until failure³¹. Force and actuator displacement data were recorded at a rate of 50 Hz. Peak force was identified, and the stiffness was calculated from the slope of the linear region of the force-displacement curve.

TABLE I All Quantitative Measures*

Outcome Measure	Intact Tendons	cd-SF-G Tendons	Saline Solution Tendons
nWOF (N-mm/deg)	0.14 ± 0.05	0.63 ± 0.24†	1.34 ± 0.42††
Adhesion score	—	3.5 ± 1.6	6.1 ± 1.3†
Proximal adhesion strength (N)	3.5 ± 1.9	8.6 ± 3.2†	20.2 ± 10.2††
Proximal adhesion stiffness (N/mm)	2.4 ± 1.3	6.2 ± 3.1†	13.0 ± 7.0††
Tendon gliding resistance (N)	0.11 ± 0.03	0.26 ± 0.08†	0.46 ± 0.22††
Distal repair strength (N)	—	56.9 ± 28.4	77.2 ± 36.2
Distal repair stiffness (N/mm)	—	19.0 ± 7.5	24.5 ± 14.5
Compressive modulus (N/mm)	—	4.37 ± 1.26	3.98 ± 1.24

*Values are presented as the mean and standard deviation. †Significantly higher than intact tendon. ††Significantly higher than cd-SF-G tendon.

Evaluation of Compressive Properties by Indentation

A 5-mm segment of the tendon graft from the zone-II area underwent indentation testing to evaluate the effect of EDC on tendon compressive properties³². The tendon was mounted onto an electromechanical test system (ElectroForce 3200; Bose). A flat, nonporous indenter with a diameter of 3 mm was used to compress the tendon at a loading rate of 10 N/min to a maximum force of 5 N. The initial segment of the stress-strain curve, with the compressive load ranging from 0 to 0.5 N, was used in calculating the compressive modulus, which was derived from the slope of the linear segment of the curve.

Histological Analysis

Two tendons each from the intact, saline-solution, and cd-SF-G groups underwent histological evaluation of the proximal and distal repair sites. Samples were fixed in formalin, embedded in paraffin, and cut longitudinally into 7-μm sections. Sections were stained with hematoxylin and eosin (H&E) to assess tendon-to-tendon healing at the proximal site of the repair and tendon-to-bone healing at the distal site of the repair.

Assessment of Cell Viability

In order to assess whether this chemical synovial-fluid modification would affect tendon viability, in vitro tenocyte viability was tested according to the following protocol. Briefly, four additional FDP tendons were harvested from dogs used in another Institutional Animal Care and Use Committee-approved study. These four tendons were treated with cd-SF-G or saline solution and then incubated for culture for seven days. The cell viability of the tendons was

evaluated through calcein AM (acetomethoxy) and ethidium homodimer staining, as previously described²⁸.

Statistical Analysis

The sample size was justified on the basis of a previous investigation²¹, in which the major functional evaluation (nWOF) of nontreated and treated graft tendons at six weeks was 1.60 N-mm/deg (standard deviation [SD], 0.61) and 0.67 N-mm/deg (SD, 0.34), respectively. A sample size of eleven in the mechanical evaluation would be sufficient to detect a significant difference of one-half of a standard deviation with an 80% power at a level of significance of $p < 0.05$.

All of the quantitative data are presented as the mean and SD. Because the three groups (intact, saline solution, and cd-SF-G) came from the same animal, repeated-measures ANOVA (analysis of variance) was used to analyze differences in nWOF, adhesion score, proximal adhesion breaking force, gliding resistance, distal attachment strength, and compressive modulus (JMP 10 software; SAS Institute). The Tukey studentized range (honestly significant difference) post hoc test was used to evaluate the effect of cd-SF-G surface modification on each outcome variable. Significance was set at $p < 0.05$ in all cases.

Source of Funding

This study was supported by grants from the National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIH/NIAMS AR057745) and the Musculoskeletal Transplant Foundation.

Fig. 1

Digital function and adhesion by group, including mean normalized work of flexion (**Fig. 1-A**), adhesion score (**Fig. 1-B**), and proximal adhesion breaking force and stiffness (**Fig. 1-C**). cd-SF-G = carbodiimide-derivatized synovial fluid with gelatin. Asterisks indicate a significant difference ($p < 0.05$), and error bars indicate the standard deviation.

Fig. 2

Mean gliding resistance (**Fig. 2-A**), distal attachment strength and stiffness (**Fig. 2-B**), and compressive modulus from indentation testing (**Fig. 2-C**) by group. cd-SF-G = carbodiimide-derivatized synovial fluid with gelatin. Asterisks indicate a significant difference ($p < 0.05$), and error bars indicate the standard deviation.

Results

The rupture of all repaired FDP tendons was expected and confirmed during the reconstruction surgery, with scar formation evident on the tendon, pulley, and tendon bed. All surgical wounds except one in the cd-SF-G group had healed without infection by postoperative week 6. One digit receiving cd-SF-G modification showed slight superficial infection at the proximal repair site that did not affect deep tissues. No graft ruptures were detected at the proximal or distal repair sites in either repair group.

Data from all quantitative measures are presented in Table I. The cd-SF-G group showed significantly lower nWOF compared with the saline-solution group ($p < 0.001$), and both of these groups had significantly higher nWOF than the intact group ($p < 0.001$ for both) (Fig. 1-A). The adhesion score of the cd-SF-G group was significantly lower than that of the saline-solution group ($p < 0.001$) (Fig. 1-B). Tendons coated with cd-SF-G showed lower proximal adhesion breaking force and stiffness

compared with the tendons treated with saline solution ($p < 0.05$ for both). Both treated groups had higher proximal adhesion breaking force ($p < 0.001$ for both) and stiffness ($p < 0.001$ for both) when compared with the intact FDP tendons (Fig. 1-C).

Gliding resistance in the cd-SF-G group was significantly lower than that in the saline-solution group ($p < 0.05$). Both of the treated groups showed significantly higher gliding resistance compared with the intact tendons ($p < 0.001$ for both) (Fig. 2-A). Regarding strength and stiffness at the distal attachment site, differences between the cd-SF-G group and saline-solution group were not significant ($p = 0.23$ for strength; $p = 0.34$ for stiffness) (Fig. 2-B). The compressive modulus was not significantly different between the two treated groups ($p = 0.39$) (Fig. 2-C).

Similar collagen structures were observed in PL graft and native FDP tendon sections with H&E staining. The tendon grafts coated with cd-SF-G had a loose, smooth layer of paratenon covering the tendon surface, without evident adhesion

Fig. 3

Intact tendons had a smooth surface covered by a few layers of epitenon (**left panel**); tendon grafts coated with cd-SF-G (carbodiimide-derivatized synovial fluid with gelatin) had a loose, smooth layer of paratenon covering the tendon surface, without adhesions (**center panel**); and abundant adhesions appeared on the surface of tendons treated with saline solution (**right panel**) (hematoxylin and eosin).

Fig. 4

Figs. 4-A through 4-D Secure healing after grafting of treated tendons (hematoxylin and eosin). cd-SF-G = carbodiimide-derivatized synovial fluid with gelatin, and control = saline solution. **Figs. 4-A and 4-B** The proximal repair site. **Figs. 4-C and 4-D** The distal attachment site showed a solid union at the tendon-to-bone insertion site.

to the surrounding tissues. However, abundant adhesions were evident on the surface of tendons treated with saline solution (Fig. 3). The proximal repair site showed cell infiltration into the tendon graft for the cd-SF-G and saline-solution groups, although the latter had much greater cell density. Tendon grafts and native recipient tendons appeared to have secure healing at the interface, with no obvious gaps (Figs. 4-A and 4-B). Tendon-to-bone in-

corporation was seen at the distal insertion sites of both graft groups, without evident gaps (Fig. 4-C and 4-D).

Regarding the in vitro assessment of cell viability, viable cells were observed on the surface of tendons treated with either cd-SF-G or saline; cells were round and were randomly distributed. We observed no significant difference in viable cell counts between the two groups (Fig. 5).

Fig. 5

Viable cells were observed on the surface of saline and cd-SF-G (carbodiimide-derivatized synovial fluid with gelatin) tendons; cells were round and randomly distributed (calcein AM and ethidium homodimer). The viable cell count was not significantly different between the two groups.

Discussion

Intrasynovial tendons, such as the finger flexors, have a specialized, lubricated gliding surface that is not present in extrasynovial tendons. This specialized gliding surface reduces gliding resistance between the tendon and its surrounding sheath^{19,33}, and it also may serve as a barrier to adhesions^{34,35}. Extrasynovial tendons are commonly used as autografts to replace flexor tendons, owing to the lack of availability of autologous donor intrasynovial tendons. Different from intrasynovial tendons, extrasynovial tendons have an irregular surface that is covered with a multilayered paratenon and that lacks the lubricated property of intrasynovial tendons; this leads to inferior gliding performance and durability when used as a tendon graft in an intrasynovial location, compared with grafts of intrasynovial origin^{18,36-38}.

Our strategy involved the use of cd-SF-G surface modification of extrasynovial tendons to improve digital function and reduce adhesion formation without adversely affecting tendon healing. Mechanical tests showed that tendons coated with cd-SF-G had significantly lower nWOF, adhesion score, proximal adhesion breaking force, and gliding resistance compared with saline solution-treated tendons. Histological examination also showed smoother surfaces on tendons coated with cd-SF-G. We believe that the surface coating provided mechanical and biological benefits that improved gliding ability and reduced adhesion formation.

HA, lubricin, and possibly phospholipids are the lubricants in synovial fluid^{23,39,40}. Human and animal studies have shown that HA and phospholipids reduce tendon gliding resistance and adhesions, without interfering with tendon healing^{18,25,41,42}. We have previously found that HA combined with lubricin was an improvement over HA alone⁴³. Tendons coated with cd-SF-G in vitro demonstrated significantly improved gliding ability compared with coating with saline solution or synovial fluid only²⁶. The present study further validates the improvement in gliding ability and reduction in adhesions, which might be attributable to the physical barrier effect of this surface treatment.

Tendon healing, including proximal tendon-to-tendon healing and distal tendon-to-bone healing, is an important issue in flexor tendon reconstruction. A recently reported surface modification, cd-HA-lubricin, had an adverse effect on proximal tendon graft-to-host tendon healing and distal tendon graft-to-bone healing, with gaps evident at both sites²¹. This drawback might limit application of this compound in tendon grafting, despite the associated dramatic improvement in gliding ability. In our study, no ruptures occurred in either the cd-SF-G or the saline-solution group, as judged by macroscopic inspection of the proximal repair site. H&E staining showed tendon-to-bone and tendon-to-tendon incorporation, with cell infiltration in the host and tendon grafts. These findings indicate that cd-SF-G on the surface may not jeopardize tendon-to-tendon healing, at least in the short term. For the distal attachment site, mechanical testing showed that tendons coated with cd-SF-G had similar failure strength and stiffness compared with saline solution-coated tendons.

Histological images also showed a solid union between the tendon graft and bone tissue in the two groups, without visible gaps. Hence, surface modification with cd-SF-G might not interfere with tendon-to-bone healing of flexor tendon reconstruction with use of an autograft. However, neither treated group established a fibrocartilage transitional zone, a key feature of a normal tendon-to-bone insertion site.

EDC acts as a carboxyl-activating agent for the coupling of primary amines to yield amide bonds. Although EDC was shown to have little toxicity in tissue-engineering studies^{29,44}, it has the potential, with higher doses or longer exposure, to diffusely stiffen the tendon, by increasing the number of crosslinks between collagen molecules within the tendon⁴⁵. In this in vivo animal study, this potentially adverse effect of EDC on tendon stiffness was addressed. We found that surface modification with cd-SF-G did not change tendon compressive properties, which suggests that this approach might improve digital function without affecting tendon stiffness. Culture of tendon samples also showed that chemical synovial fluid modification did not affect cell viability when compared with findings for the saline-solution control group. This in vitro result was also supported by the in vivo finding that graft healing at the distal attachment site resulted in similar strength and stiffness between the two groups. This could be considered primary evidence suggesting that cd-SF-G modification does not affect tendon-to-tendon and tendon-to-bone healing. Additional investigations of cell proliferation, cell production, and cytokine changes are needed to better understand this issue.

This study had several limitations. First, only one time point (six weeks) was used to assess postoperative function. Although six-week follow-up is a common point of assessment for tendon research, it might not be long enough for the final functional evaluation of a tendon graft. Earlier time points for understanding the healing mechanisms and later time points for understanding tissue regeneration are necessary in the future studies. Second, biological analyses were not performed for cell proliferation, tenocyte production, or tenocyte markers. Thus, we were unable to illustrate cellular function in this canine model. Third, failure strength was not determined for the proximal tendon-to-tendon repair site because the tendon segment was too short after WOF testing, which was the major outcome measure of this study.

In conclusion, this study used native synovial fluid as a lubricant to improve the results of tendon grafting. Our results demonstrated that the flexor tendon surface modification with cd-SF-G significantly improved digital function and reduced adhesion formation without affecting tendon healing and stiffness in this canine in vivo model. ■

Xiaoxi Ji, MD
Ramona L. Reisdorf, BS
Andrew R. Thoreson, MS

Lawrence R. Berglund, MS
Steven L. Moran, MD
Kai-Nan An, PhD
Peter C. Amadio, MD
Chunfeng Zhao, MD
Departments of Orthopedic Surgery
(X.J., R.L.R., A.R.T., L.R.B., K-N.A., P.C.A., and C.Z.)
and Plastic Surgery (S.L.M.), Mayo Clinic,
200 First Street S.W.,

Rochester, MN 55905.
E-mail address for C. Zhao: zhao.chunfeng@mayo.edu

Gregory D. Jay, MD, PhD
Department of Emergency Medicine,
Brown University,
593 Eddy Street,
Claverick 100,
Providence, RI 02903

References

- Fetter-Zarzeka A, Joseph MM. Hand and fingertip injuries in children. *Pediatr Emerg Care*. 2002 Oct;18(5):341-5.
- Rosberg HE, Carlsson KS, Höjgård 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 Br*. 2003 Apr;28(2):106-12.
- Costilla V, Bishai DM. Lawnmower injuries in the United States: 1996 to 2004. *Ann Emerg Med*. 2006 Jun;47(6):567-73. Epub 2006 May 2.
- Strickland JW. Development of flexor tendon surgery: twenty-five years of progress. *J Hand Surg Am*. 2000 Mar;25(2):214-35.
- Tang JB, Amadio PC, Boyer MI, Savage R, Zhao C, Sandow M, Lee SK, Wolfe SW. Current practice of primary flexor tendon repair: a global view. *Hand Clin*. 2013 May;29(2):179-89. Epub 2013 Apr 3.
- Zhao C, Hsu CC, Moriya T, Thoreson AR, Cha SS, Moran SL, An KN, Amadio PC. Beyond the square knot: a novel knotting technique for surgical use. *J Bone Joint Surg Am*. 2013 Jun 5;95(11):1020-7.
- Tang JB. Clinical outcomes associated with flexor tendon repair. *Hand Clin*. 2005 May;21(2):199-210.
- Gerbin PG 2nd, Saldana MJ, Westerbeck P, Schacherer TG. Complications experienced in the rehabilitation of zone I flexor tendon injuries with dynamic traction splinting. *J Hand Surg Am*. 1991 Jul;16(4):680-6.
- Liu TK, Yang RS. Flexor tendon graft for late management of isolated rupture of the profundus tendon. *J Trauma*. 1997 Jul;43(1):103-6.
- Bertelli JA, Santos MA, Kechele PR, Rost JR, Tacca CP. Flexor tendon grafting using a plantaris tendon with a fragment of attached bone for fixation to the distal phalanx: a preliminary cohort study. *J Hand Surg Am*. 2007 Dec;32(10):1543-8.
- Aydin A, Topalan M, Mezdegi A, Sezer I, Ozkan T, Erer M, Ozkan S. [Single-stage flexor tendoplasty in the treatment of flexor tendon injuries]. *Acta Orthop Traumatol Turc*. 2004;38(1):54-9. Turkish.
- Arora R, Fritz D, Zimmermann R, Lutz M, Kamelger F, Klauser AS, Gabl M. Reconstruction of the digital flexor pulley system: a retrospective comparison of two methods of treatment. *J Hand Surg Eur Vol*. 2007 Feb;32(1):60-6. Epub 2006 Nov 28.
- Karabekmez FE, Zhao C. Surface treatment of flexor tendon autograft and allograft decreases adhesion without an effect of graft cellularity: a pilot study. *Clin Orthop Relat Res*. 2012 Sep;470(9):2522-7.
- Uchiyama S, Amadio PC, Coert JH, Berglund LJ, An KN. Gliding resistance of extrasynovial and intrasynovial tendons through the A2 pulley. *J Bone Joint Surg Am*. 1997 Feb;79(2):129-24.
- Hagberg L, Tengblad A, Gerdin B. Hyaluronic acid in flexor tendon sheath fluid after sheath reconstructions in rabbits. A comparison between tendon sheath transplantation and conventional two stage procedures. *Scand J Plast Reconstr Surg Hand Surg*. 1991;25(2):103-7.
- Jay GD. Characterization of a bovine synovial fluid lubricating factor. I. Chemical, surface activity and lubricating properties. *Connect Tissue Res*. 1992;28(1-2):71-88.
- Sun Y, Berger EJ, Zhao C, An KN, Amadio PC, Jay G. Mapping lubricin in canine musculoskeletal tissues. *Connect Tissue Res*. 2006;47(4):215-21.
- Nishida J, Araki S, Akasaka T, Toba T, Shimamura T, Amadio PC, An KN. Effect of hyaluronic acid on the excursion resistance of tendon grafts. A biomechanical study in a canine model in vitro. *J Bone Joint Surg Br*. 2004 Aug;86(6):918-24.
- Sun YL, Yang C, Amadio PC, Zhao C, Zobitz ME, An KN. Reducing friction by chemically modifying the surface of extrasynovial tendon grafts. *J Orthop Res*. 2004 Sep;22(5):984-9.
- Zhao C, Sun YL, Kirk RL, Thoreson AR, Jay GD, Moran SL, An KN, Amadio PC. Effects of a lubricin-containing compound on the results of flexor tendon repair in a canine model in vivo. *J Bone Joint Surg Am*. 2010 Jun;92(6):1453-61.
- Zhao C, Hashimoto T, Kirk RL, Thoreson AR, Jay GD, Moran SL, An KN, Amadio PC. Resurfacing with chemically modified hyaluronic acid and lubricin for flexor tendon reconstruction. *J Orthop Res*. 2013 Jun;31(6):969-75. Epub 2013 Jan 17.
- Moro-oka T, Miura H, Mawatari T, Kawano T, Nakanishi Y, Higaki H, Iwamoto Y. Mixture of hyaluronic acid and phospholipid prevents adhesion formation on the injured flexor tendon in rabbits. *J Orthop Res*. 2000 Sep;18(5):835-40.
- Schmidt TA, Gastelum NS, Nguyen QT, Schumacher BL, Sah RL. Boundary lubrication of articular cartilage: role of synovial fluid constituents. *Arthritis Rheum*. 2007 Mar;56(3):882-91.
- Uchiyama S, Amadio PC, Ishikawa J, An KN. Boundary lubrication between the tendon and the pulley in the finger. *J Bone Joint Surg Am*. 1997 Feb;79(2):213-8.
- Sun Y, Chen MY, Zhao C, An KN, Amadio PC. The effect of hyaluronidase, phospholipase, lipid solvent and trypsin on the lubrication of canine flexor digitorum profundus tendon. *J Orthop Res*. 2008 Sep;26(9):1225-9.
- Ikeda J, Sun YL, An KN, Amadio PC, Zhao C. Application of carbodiimide derivatized synovial fluid to enhance extrasynovial tendon gliding ability. *J Hand Surg Am*. 2011 Mar;36(3):456-63.
- Fuchs TF, Petersen W, Vordemvenne T, Stange R, Raschke M, Paletta JR. Influence of synovial fluid on human osteoblasts: an in vitro study. *ScientificWorldJournal*. 2007;7:2012-20. Epub 2007 Dec 18.
- Zhao C, Sun YL, Ikeda J, Kirk RL, Thoreson AR, Moran SL, An KN, Amadio PC. Improvement of flexor tendon reconstruction with carbodiimide-derivatized hyaluronic acid and gelatin-modified intrasynovial allografts: study of a primary repair failure model. *J Bone Joint Surg Am*. 2010 Dec 1;92(17):2817-28.
- Zhao C, Sun YL, Amadio PC, Tanaka T, Ettema AM, An KN. Surface treatment of flexor tendon autografts with carbodiimide-derivatized hyaluronic acid. An in vivo canine model. *J Bone Joint Surg Am*. 2006 Oct;88(10):2181-91.
- Zhao CF, Amadio PC, Berglund L, An KN. The A3 pulley. *J Hand Surg Am*. 2000 Mar;25(2):270-6.
- Zhao C, Amadio PC, Momose T, Couvreur P, Zobitz ME, An KN. Effect of synergistic wrist motion on adhesion formation after repair of partial flexor digitorum profundus tendon lacerations in a canine model in vivo. *J Bone Joint Surg Am*. 2002 Jan;84(1):78-84.
- Ikeda J, Zhao C, Chen Q, Thoreson AR, An KN, Amadio PC. Compressive properties of cd-HA-gelatin modified intrasynovial tendon allograft in canine model in vivo. *J Biomech*. 2011 Jun 3;44(9):1793-6. Epub 2011 May 6.
- Sun YL, Zhao C, Jay GD, Schmid TM, An KN, Amadio PC. Effects of stress deprivation on lubricin synthesis and gliding of flexor tendons in a canine model in vivo. *J Bone Joint Surg Am*. 2013 Feb 6;95(3):273-8.
- Schaefer DB, Wendt D, Moretti M, Jakob M, Jay GD, Heberer M, Martin I. Lubricin reduces cartilage—cartilage integration. *Biorheology*. 2004;41(3-4):503-8.
- Burns JW, Skinner K, Colt MJ, Burgess L, Rose R, Diamond MP. A hyaluronate based gel for the prevention of postsurgical adhesions: evaluation in two animal species. *Fertil Steril*. 1996 Nov;66(5):814-21.
- Momose T, Amadio PC, Zobitz ME, Zhao C, An KN. Effect of paratenon and repetitive motion on the gliding resistance of tendon of extrasynovial origin. *Clin Anat*. 2002 May;15(3):199-205.
- Noguchi M, Seiler JG 3rd, Boardman ND 3rd, Tramaglini DM, Gelberman RH, Woo SL. Tensile properties of canine intrasynovial and extrasynovial flexor tendon autografts. *J Hand Surg Am*. 1997 May;22(3):457-63.
- Leversedge FJ, Zelouf D, Williams C, Gelberman RH, Seiler JG 3rd. Flexor tendon grafting to the hand: an assessment of the intrasynovial donor tendon—a preliminary single-cohort study. *J Hand Surg Am*. 2000 Jul;25(4):721-30.
- Blewis ME, Nugent-Derfus GE, Schmidt TA, Schumacher BL, Sah RL. A model of synovial fluid lubricant composition in normal and injured joints. *Eur Cell Mater*. 2007;13:26-39. Epub 2007 Mar 6.
- Mills PC, Hills Y, Hills BA. Surface-active phospholipid (surfactant) in equine tendon and tendon sheath fluid. *N Z Vet J*. 2005 Apr;53(2):154-6.
- Akasaka T, Nishida J, Imaeda T, Shimamura T, Amadio PC, An KN. Effect of hyaluronic acid on the excursion resistance of tendon graft: a biomechanical in vitro study in a modified human model. *Clin Biomech (Bristol, Avon)*. 2006 Oct;21(8):810-5. Epub 2006 Jun 9.
- Gaughan EM, Nixon AJ, Krook LP, Yeager AE, Mann KA, Mohammed H, Bartel DL. Effects of sodium hyaluronate on tendon healing and adhesion formation in horses. *Am J Vet Res*. 1991 May;52(5):764-73.
- Taguchi M, Sun YL, Zhao C, Zobitz ME, Cha CJ, Jay GD, An KN, Amadio PC. Lubricin surface modification improves tendon gliding after tendon repair in a canine model in vitro. *J Orthop Res*. 2009 Feb;27(2):257-63.
- Duan X, Sheardown H. Dendrimer crosslinked collagen as a corneal tissue engineering scaffold: mechanical properties and corneal epithelial cell interactions. *Biomaterials*. 2006 Sep;27(26):4608-17. Epub 2006 May 19.
- Zhao C, Sun YL, Zobitz ME, An KN, Amadio PC. Enhancing the strength of the tendon-suture interface using 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride and cyanoacrylate. *J Hand Surg Am*. 2007 May-Jun;32(5):606-11.