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Review Article

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Tendon Injuries of the Hand: Current Treatment Strategies and Future Options

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Abstract

Tendons form the crucial connections linking muscles to bones, allowing movement of the axial and appendicular skeleton. Hand injuries often involve tendinous injury which may severely impair daily function. Current clinical treatment strategies for tendon injuriesare suboptimal, requiringimmobilization and prolonged rehabilitation, but regenerative medicine presents promising future treatment strategies that may expedite return of function, improving long-term patient outcomes. In this review, we discuss current treatment paradigms for upper extremity tendon injuries, as well as the potential impact that emerging regenerative medicine and stem cell related strategies may bring to improving clinical treatment.

Keywords: Tendons, Hand, Trauma, Regenerative Medicine, Stem Cells

Introduction

More than 30 million tendon injuries occur worldwide each year, affecting all age groups due to attritional degeneration or acute trauma [1]. As crucial components of the complex anatomy present in the hand, tendons allowmanipulation of everyday objects and interpersonal interactions. Tendinous injuries can thus be severely debilitating, preventing execution of daily activities.

Acute tendon lacerations and ruptures are ideally treated surgically with direct apposition of tendon ends via suture repair. However, due to retraction after injury, delayed presentation or injuries with significant tendon loss often require grafting from a donor site, creating a secondary site of injury. Even under optimal conditions with primary repair, tendinous healing requires a period of immobilization which often lasts several weeks. Immobilization and wound care lead to substantial inconvenience to the patient and result in secondary complications to uninvolved portions of the hand, commonly exemplified by stiffness of uninjured digits. The time required for rehabilitation has drastic economic impacts as patients must cease or modify employment during recovery.

Throughout recovery, adhesions of the healing tendon to surrounding tissues can hinder return of pre-injury range of motion, necessitating hand therapy and potentially operative tenolysis. In severe cases, adhesions and joint stiffness make pre-operative range of motion unattainable [2]. Even after full healing, the fibro vascular scar formed at the site of injury has inferior tensile strength compared to the native tendon, potentially predisposing higher-demand patients to subsequent re-injury [3].

Current imperfect treatment pathways imply that regeneration of native tendon could lead to ideal early recovery of tensile strength and return of motion. Here we discuss relevant histology and anatomical concepts regarding tendons of the hand, current treatment strategies for hand tendon injuries, and potential applications of regenerative medicine for such injuries.

Tendon histology and anatomy

Tendons primarily are composed of organized Type 1 collagen and elastin embedded in a proteoglycan-rich matrix.4Highly organizedcollagen forms fibers, which are bundled to form subfascicles, fascicles, and tertiary fiber bundles, which are each invested by endotenon. The outer layer of the tendon, the epitenon, is enveloped in a thin layer of connective tissue, the paratenon [4]. Tendon mostly consists of extracellular elements and is only sparsely populated by cells. Tenoblasts and tenocytesmake up to 95% of this cell population; ten oblasts are immature tendon cells which flatten and elongate over time to become tenocytes, while tenocytes respond to mechanical loads of the tendon and maintain the extracellular matrix [5]. The remaining cellular composition includes chondrocytes at points of insertion, synovial cells of the tendon sheath, and capillary endothelial cells [5]. Furthermore, evidence demonstrates the presence of resident tendon stem cells with multilineage and self-renewal potential, and their role in tendon homeostasis is under investigation [6].

Vascular supply arises from blood vessels entering at the myotendinous junction, running parallel to the tendon fibers and within the endotenon. In the flexor tendons of the phalanges, additional fibrous bands, vincula, provide additional blood supply, while the synovial sheath also provides additional dorsal blood supply [7]. Around regions of maximal tendon excursion and pulley

systems, the tendon is relatively avascular.

Innervation is provided by nerves crossing the musculotendinous junction, entering the endotenon and paratenon. The majority of these nerve fibers lie on the surface of the tendon and include specialized mechanoreceptors (Golgi tendon organs) and nociceptive fibers [8]. Notably, the tendon core is normally devoid of nerves, but after injury, neural in growth occurs and is thought to mediate the resultant inflammatory and healing response [9].

Anatomical structures of flexor and extensor mechanismsdifferbut work together harmoniously. On the extensor side, all of the fingers excluding the thumb share a common muscle belly with separate tendons for each finger -- the extensor digitorum communis. The index finger and the small finger each have an additional, separate extensor (the extensor indices proprius and the extensor digiti minimi, respectively), allowing independent extension. At the level of the proximal interphalangeal joint, the extensor mechanism divides into two lateral bands and a central slip, which have differential action on the proximal interphalangeal joint and the distal interphalangeal joint. Additionally, the intrinsic muscles of the hand (the interossei and lumbricals) also have insertions onto the extensor lateral bands (Figure 1). The thumb has two extensors, the extensor pollicis longus and the extensor pollicis brevis.

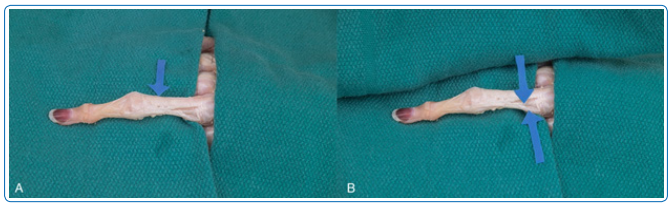

Figure 1: Anatomic specimen demonstrating the extensor tendon mechanism for the finger. At the level of the metacarpophalangeal joint, the extensor digitorum communis splits into 3 tendons. The central slip is the extension that continues past the proximal interphalangeal joint to insert onto the middle phalanx (arrow, panel A). The remaining extensions travel laterally to form the lateral bands (top arrow, panel B). With additional contributions by the hand intrinsic muscles (bottom arrow, panel B), the conjoint lateral band is formed which continues to insert on the distal phalanx

Flexor tendons of the fingers glide through distinct synovial sheaths and pulleys. From muscle bellies in the forearm, the flexor digitorum superficialis (FDS) and flexor digitorum profundus (FDP) run through the carpal tunnel toward each finger. The FDS decussates into two limbs and inserts onto the middle phalanx of each finger, while the FDP travels between the split FDS slips through Camper's chiasm and inserts onto the distal phalanx. Five annular pulleys and 3 cruciate pulleys stabilize the tendons against the phalanges, allowing linear pull of the muscles to be converted into torque, thus resulting in flexion of the finger joints [10]. (Figure 2) of these, the even-numbered annular pulleys contribute the most to prevent tendon bowstringing, with the A2 pulley classically being cited as the most important. The thumb has two annular pulleys and one oblique pulley, with the oblique pulley being the most critical to thumb motion.

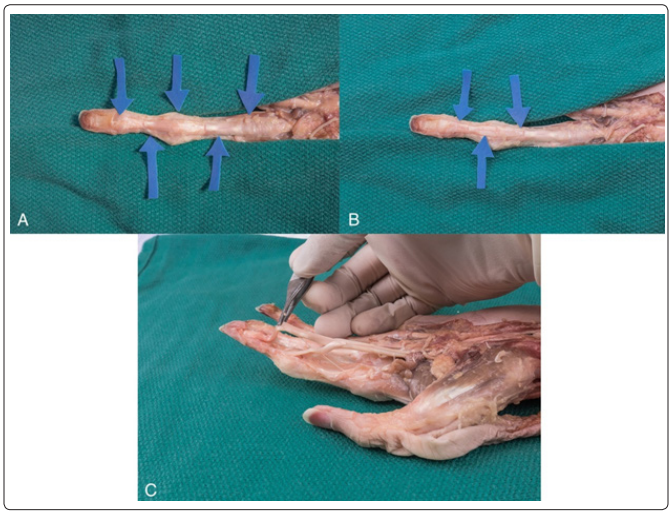

Figure 2: Anatomic specimen demonstrating flexor tendons and associated tissues. The annular ligaments (from right to left, A1-A5) are designatedin panel A. The cruciate ligaments are similarly designated in panel B. In panel C, Camper's chiasm can be seen with the profundus tendon (held in the forceps) piercing the decussation of the superficialis tendon. The vincula longus and brevis can also be seen as thin mesenteries linking the dorsal tendon sheath to the flexor tendons.

Treatment of hand tendon injuries

Similar to other areas of the body, tendon injury andrepair stimulates inflammatory, fibroblastic, and remodeling phases. These phases overlap and last 3-5 days, 3-6 weeks, and 6-9 months, respectively [11]. During the inflammatory phase, the strength of the tendon almost entirely depends on the suture repair, with only modest strength provided by fibrin clot. Strength increases with fibroblast deposition of new extracellular matrix and collagen. During the remodeling phase, collagen molecules re-align to resemble native tendon, but the tensile strength of the repaired tendon never reaches the pre-injury value [12].

It is critical to note that both extrinsic and intrinsic healing processes have crucial impacton subsequent functionand eventually create opposing forces. In the extrinsic healing response, inflammatory cells and fibroblasts from the paratenon migrate to the site of injury, leading to adhesions of the tendon to the surrounding support tissue which impair subsequent tendon gliding. Immobilization promotes the extrinsic response [10]. Conversely, intrinsic healing, guided by resident tenocytes, is promoted by motion of the repaired tendon and leads to more favorable patient outcomes.Thus, current treatment paradigms seek to balance the opposing intrinsic and extrinsic healing timelines, waiting for sufficient tendon strength to allow early motion protocols.

Technical aspects of suture repairaffect tendon healing. Apposition of tendon ends is crucial; gapping beyond 3 mm inhibits healing and also impairs range of motion in animal models [13]. Synthetic 3-0 or 4-0 braided suturesarewidely considered most effective for tendon repair in balancing suture strength and size. Furthermore, repairstrength is directly proportional to the number of core suture

strands; cadaver studies and *in vivo* observations have demonstrated that 4 core strands sufficiently withstand stresses of light active motion [14]. While more core strands may conceptually sound favorable, placement of numerous core sutures can be technically difficult and tendon bulk may not support increased core strands. Trauma introduced by excessivesurgical manipulation of the tendon also leads to adverse outcomes. Thus, four core strands are generally considered the "gold standard" for flexor tendon repair.

Other aspects of tendon repair impact functional results as well. The use of epitendinous sutures increases the strength of tendon repairs by a fraction and may prevent gapping [11]. (Figure 3) Placement of sutures within the dorsal tendon has also been shown to be superior to palmar placement, potentially due to more favorable biomechanics with motion, decreased friction against the pulley mechanisms, and differential strength within the tendon bulk [15]. Although numerous suture patterns have been advocated, those using locking sutures have been demonstrated to have higher *in vitro* pull-out strength [11]. Fewer suture knots are also preferable as the knot site is a common area of failure11. Knots placed outside the repair site lead to a stronger immediate repair, although this discrepancy equalizes over six weeks [16].

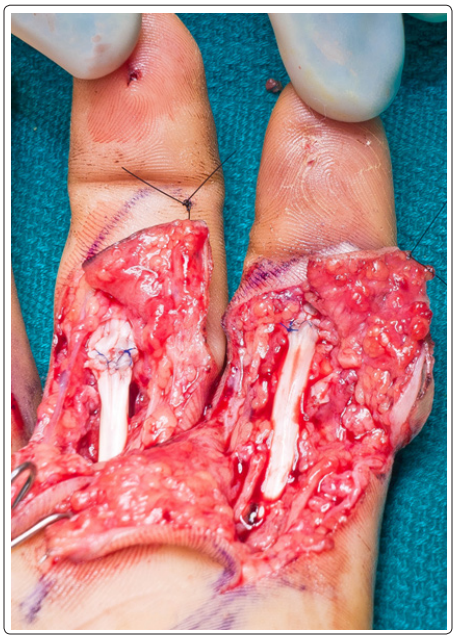

Figure 3: Example of intrasynovial tendon repair (Verdan Zone 2) in the index (right) and middle (left) fingers. These tendons were repaired with 4-0 braided polyethylene sutures in a 4-core cruciate pattern. 5-0 polypropylene running locking sutures (visible as blue stitches) were used for epitendinous repair

In contrast, there is little debate on optimal repair mechanisms for the extensor tendons. Compared to flexor tendons, extensor tendons have less excursion, and tendon ends are more easily retrieved at the time of injury [17]. Less emphasis is placed on preventing adhesions with surrounding tissues since these are more easily overpowered by the flexors, and early active motion is not emphasized. The tendon cross-section is flatter, allowing less creativity regarding suture pattern and placement during repair. Common repairs include utilizing 3-0 or 4-0 absorbable or nonabsorbable sutures in horizontal mattress configuration and post-operative immobilization. Some extensor injuries are also amenable to non-surgical care if the injured ends are still in apposition, such as a soft tissue mallet finger injury, which involves injury of the extensor tendon at the distal interphalangeal joint. However, adequate repair of the extensor tendons after injury can be of great importance as derangements in tension and integrity of the extensor apparatus can severely affect the balanced forces between intrinsic and extrinsic muscles of the hand.

Future treatment paradigms

Current treatments are limited by an imperfect balance between healing within the intrinsic tendon substance while minimizing healing to surrounding soft tissues that limit postoperative motion. Early motion aims to limit extrinsic healing and subsequent adhesion formation, yet the largely acellular structure within tendons creates less rapid healing compared to other tissues. Tendon adhesions may require subsequent surgical release and impair the final recovery of the patient, creating a costly burden to patients, employers, and society. Thus, regenerative therapies that enhance the intrinsic healing pathway and provide earlier recovery of tensile strength would be valuablein preventing extrinsic adhesions.

Supplementation of tenocytes has shown promise in existingclinical settings. When injecting patellar tendon tenocytes into the extensor tendon origin for lateral epicondylitis, Wang et al. demonstratedimproved pain scores and tendinopathy based on imaging. Skin fibroblasts, like tenocytes, are collagen producing and injection into diseased patellar tendons showed improved pain scores compared to injected plasma [18,19]. Although *ex vivo* replication of tendon stem cells and replantation is conceptually possible, clinical studies have not been performed using isolated tendon-derived stem cells [20]. Critics note the procurement of tendon-derived cells necessitates a biopsy site, which would introduce another tendon injury as part of treatment.

The use of stem cells of varying origin has also shown promise. Bone marrow derived stem cells has shown promising results *in vitro* while growing anterior crucial ligaments, demonstrating histologic similarities to tendon [21]. Mesenchymal stem cells – plentiful throughout the body – are also promising potential donors, but may form ectopic calcium deposits in the tendon after transplantation [22]. Stem cell introduction to injured tendons may lead to a synergistic healing reaction with native cells; Long et al. demonstrated that co-culture of adipocyte derived stem cells and tenocytes lead to improved cell proliferation, type 1 collagen deposition, and tenocyte migration than monoculture controls [23]. Fat grafting clinically demonstrates beneficial effects on the recovery of radiated skin, and this is theorized to be due in part to transfer of adiposity derived stem cells [24]. Thus, a clinical protocol utilizing fat autografts in tendon repair may have some future potential.

Other evidence suggests direct introduction of stem cells into tendon substance may not be required to stimulate repair and downregulate inflammation, but rather that these effects result from tissue signaling pathways as opposed to direct engraftment of stem cells. While it is assumed that stem cells promote repair through tendon engraftment and differentiation, experiments in rodents with tagged cells demonstrate that injected stem cells may not persist beyond 4 weeks after injection [25]. Alternatively, a paracrine effect of mesenchymal stem cells may stimulate native tissue healing responses [26]. Thus, the introduction of signaling molecules to mature tenocytes and resident tendon stem cells may have the same effect as introducing exogenous stem cells themselves.

Stimulation of specific transcription factors of tendon development, such as *Mkx, early growth response protein 1, smad8*, and *Scx* has been found to promote tenogenic differentiation in pre-treated stem cells [4]. The treatment of native tendon cells has also been attempted, however, this has not translated to clinically meaningful outcomes. Treatment with growth factors such as bone morphogenic protein, exogenous basic fibroblast growth factor, and platelet derived growth factor-BB have been performed *in vivo* with measurable alterations to proteins expressed and scar formation in healing tendons versus controls, but this has not translated to increased early tensile strength [27]. *TGF-B* is also a potential therapeutic target, but similar to its role in other healing pathways such as digit tip regeneration, its role in promoting tendon repair is likely spatiotemporally complex and over expression promotes excessive inflammation and fibrosis [28,29]. Further study is needed to see if isolated growth factors or specific combinations lead to clinically meaningful results.

Attempts at seeding *in vitro* constructs suggests that cell density and dynamic mechanical stress play roles in optimizing collagen structure and ultimate tensile strength of constructs [30]. Multiple cell types also show promise for seeding implantable grafts [31]. Interestingly, de-cellularized cadaveric tendon grafts, while shown to have comparable results with auto grafts in animal studies, have not gained widespread clinical use [32,33]. This may be due to the fact that donor autograft tissue is often available for hand tendon injuries (such as the palmaris longus tendon), and that there is no clear post-operative benefit regarding duration of immobilization or risk of tendon repair rupture when allograft is utilized compared to autograft. However, in specific anatomical areas such as the entheses where bony fixation is possible, allograft replacement may have a role [34]. Regardless, if engineered constructs are to become commercially successful, they must provide a healing advantage with measurable patient benefit compared to the current autograft standard.

Conclusions

Tendons, due to their innate cellular properties, are slow to heal. Favorable outcomes after tendon repair in the hand depend on early motion, which requires sufficient tensile strength to prevent rupture. Regenerative medicine and stem cell technologies may improve patient outcomes by enhancing early repair strength, enabling aggressive rehabilitation and limiting adhesion formation, and thus expediting return of meaningful function.

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