Linköping University Medical dissertations

No. 1573

Tendinosis in Trigger Finger

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Linköping 2017

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Cover picture by Michelangelo, Anna-Carin Lundin and Per Lagman
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Printed by LiU-tryck, Linköping
ISBN: 978-91-7685-535-5
ISSN: 0345-0082

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POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Det finns tecken på sjukdom i fingersenan vid triggerfinger

Triggerfinger är ett märkligt tillstånd där fingrar far upp som spända fjädrar när man försöker sträcka på dem. Man tappar saker, det gör ont och man vaknar på nätterna. Ungefär tre av hundra personer drabbas.

Sjukdomen beskrevs redan på 1800-talet som att en knöl på en av fingrets böjsenor fastnar i senskidan och ger en upphakning. Under 1900-talet började man istället anse att det var senskidan som var för trång.

Vi tyckte att många senor såg sjuka ut när vi opererade triggerfingrar, trots att de enligt den rådande teorin skulle vara friska. Vi beslöt oss för att undersöka detta.

Först tittade vi på triggerfingersenor i ljusmikroskop och fann att de såg sjuka ut och liknade vad man brukar se i onda hälsenor, hälsenetendinos. Vi undersökte detta vidare genom att titta på senornas mRNA (proteinritningarna). Man kan titta på en vävnads proteintillverkning genom att undersöka mängden mRNA för utvalda proteiner. Den förändras vid sjukdom och kan ge en fingervisning om vad för slags process som pågår. Det vi fann liknade tidigare fynd vid hälsenetendinos. I en annan av våra studier fann vi en ökad risk för triggerfinger och tendinos i axel och hälsena vid behandling med statiner (kolesterolsänkande läkemedel). Triggerfingersenorna ser alltså ut som vid tendinos, de uttrycker samma mRNAmönster som vid tendinos och reagerar på statiner på samma sätt som andra tendinoser. Triggerfinger förefaller alltså vara en tendinos.

Det här innebär att man kan pröva tendinosbehandlingar mot triggerfinger. Man kan också forska om tendinossjukdomen på triggerfingrar och på det sättet undvika en del djurförsök.

Riskökningen för tendinos vid statinbehandling är inte tidigare visad. Den var olika stor för olika typer av statiner. Risken var emellertid låg och skall inte göra att man slutar använda statiner, men kanske skall man fundera över att byta preparat hos patienter som drabbas av tendinos.

En vanlig behandling av triggerfinger är lokala kortisoninjektioner som kan ges i primärvården. Ett par injektioner innan man tar ställning till vidareremittering för operation, har visat sig vara en kostnadseffektiv strategi. Det har tidigare saknats kunskap om när effekten kommer. En information som behövs för att patienterna skall kunna planera eventuell sjukfrånvaro och läkarna skall kunna följa upp sina patienter vid rätt tidpunkt, samhället vill ha kostnadseffektiva flöden. Vi har funnit att upphakningarna upphör under de första 14 dagarna efter en injektion och berättar nu redan vid injektionstillfället för patienterna när en effekt är att förvänta.

ABSTRACT

Trigger finger is one of the most common hand conditions, with a prevalence of almost 3%. The aetiology remains unclear even though many causes have been suggested. The prevailing paradigm is that the pathogenesis of trigger finger is ascribed to primary changes in the first fibrous condensation of the tendon sheath (A1-pulley). Several studies have investigated pathology in the pulley, but few have investigated the tendon. The general aim of this thesis was to find out if there is pathology in the trigger finger tendon and to define it.

We first looked at trigger finger tendon biopsies in a light microscope, and found that they were histologically different from healthy tendons. They showed signs of micro-ruptures, collagen degradation, increased amounts of ground substance, both hyper- and hypo-cellular areas, round active cell nuclei and absence of inflammatory cells, all similar to tendinosis. The histological picture was further assessed by using a scoring system for Achilles tendinosis. The trigger finger tendons scored high, suggesting a similar histopathology.

Next, we performed a quantitative real-time polymerase chain reaction (qPCR) on trigger finger tendons. We assessed the mRNA expression of 10 genes, which have been described to be differently expressed in Achilles tendinosis (collagen 1 and 3, versican, decorin, biglycan, aggrecan, MMP-2, MMP-3, ADAMTS-5, and TIMP-3). The overall expression pattern agreed with previous studies on Achilles tendinosis, suggesting that the cellular function in trigger finger tendons is disturbed in a similar way as in Achilles tendinosis.

Recent experimental and observational research has suggested potential side effects of statin treatment on tendons, but firm evidence was lacking. We performed an epidemiological study on two large population-based cohorts. Statin use was found to increase the risk of both trigger finger and tendinosis in the shoulder and Achilles tendons, especially among men. This suggests a similar pathology in trigger finger and tendinosis.

We have also studied the time to treatment effect after a single injection of glucocorticoid in trigger finger. Our results suggest that 60-80% of patients can expect resolution of the triggering within 14 days, and half of them within seven days. This result allows correct information to be given to the patient and proper planning of follow-ups.

In conclusion, the pathology in trigger finger tendons is similar to tendinosis in other tendons.

THESIS AND SPECIFIC AIMS

Thesis:

I postulate that there is tendinosis in idiopathic trigger finger.

Specific aims:

To find out:

Paper I

if there are histological signs of pathology in trigger finger.

if the histological appearance in trigger finger differs from normal tendons.

if the histological appearance resembles Achilles tendinosis.

Paper II

if the gene expression pattern in trigger finger differs from normal tendons.

if the gene expression pattern resembles Achilles tendinosis.

Paper III

the time from glucocorticoid injection to effect, in trigger finger.

Paper IV

if statin use is associated with trigger finger.

if statin use is associated with tendinosis in the shoulder and Achilles tendon.

LIST OF PAPERS

I.

Lundin AC, Eliasson P, Aspenberg P

Trigger finger and tendinosis

J Hand Surg Eur Vol. Mar 2012;37(3):233-236

II.

Lundin AC, Aspenberg P, Eliasson P

Trigger finger, tendinosis, and intratendinous gene expression

Scand J Med Sci Sports. Apr 2014;24(2):363-368.

III.

Lundin AC, Yak R, Aspenberg P, Sebastin S

How long does it take for triggering to resolve after a single glucocorticoid injection?

Manuscript

IV.

Eliasson P, Lundin AC, Aspenberg P, Wolk A, Michaëlsson K

Statin treatment is associated with trigger finger and other forms of tendinosis

Manuscript

INTRODUCTION

Trigger finger is a disorder characterized by snapping or locking of a finger. According to the prevailing paradigm at the start of our work on this thesis, the pathology in trigger finger was ascribed to a reduced inner diameter of the proximal part of the tendon sheath, the A1-pulley, and a subsequent miss-match of diameters between the pulley and the flexor tendons[1-8]. However, there were descriptions of trigger finger in terms of tendon pathology[9-12], but we could not find any evidence for this assumption. There were many studies of pulley pathology, but the knowledge of the tendons was scant. Now, as well as some other observations, I am happy to contribute data in support of the idea that trigger finger is due to tendinosis within the flexor tendons. I have chosen to present our findings [Papers I, II, III and IV][13,14] woven into an overview of the current knowledge about trigger finger and tendinosis.

Terminology

There is a diversity of language reflecting historical disagreements within the scientific community as to the exact aetiology for the pathology in trigger finger and tendinosis.

Trigger finger

In spite of the fact that trigger finger was described over 150 years ago and much has been published in the area, the terminology is still confusing[7]. This problem affects not only scientists and physicians, but also patients[15].

Trigger finger was first thought to be a condition of inflammatory origin and consequently, the use of the suffix –itis for inflammation and terms such as tendinitis, tendonitis and vaginitis were used. Whether there is inflammation or not is unclear, but there is a lack of inflammatory cells[16,17]. In spite of this, stenosing tenosynovitis is the second most common term used today (PubMed search 20 Feb.2017).

It has also been common to name trigger finger according to the suspected occupational aetiology. The precision in terminology in this field deteriorated in the mid-1980-ies, and terms as ’repetitive strain injuries’, ’overuse syndromes‘, or ’cumulative trauma disorders‘ were introduced[1]. Trigger fingers are therefore hidden by unprecise terminology in many well-performed studies.

It is most common to name the condition based on the characteristic symptomatology, but again there are many variations such as ‘snapping finger’ and ‘springing finger’. ‘Trigger finger’ is, however, the most common denomination (PubMed search 20 Feb.2017), named after the triggering that also constitutes the diagnostic criteria. Trigger finger is used in the ‘Multidisciplinary Consensus Guideline for Managing Trigger Finger’ (supported by FESSH (Federation of

European Societies for Surgery of the Hand) and EFSHT (European Federation of Societies for Hand Therapy))[8]. I therefore regard it as the most accurate term.

This thesis deals with idiopathic trigger finger, but I do not add the prefix 'idiopathic' unless necessary.

Tendinosis and tendinopathy

Tendinopathy is the etiologically least specific descriptive term for the clinical condition characterized by a combination of pain, swelling (diffuse and localized) and impaired performance, in and around tendons[18]. Tendinopathy sometimes includes tendon ruptures. The histopathological picture is best described by the term tendinosis, which does not imply a suggested aetiology. Tendinosis is described as degeneration without inflammation, due to the paucity of intratendinous inflammatory cells[19]. Tendinitis or tendonitis, on the other hand, implies the presence of inflammatory cells[18-20]. It is however an oversimplification to regard all tendinopathies as entirely non-inflammatory, as there are recent indications of inflammation[21].

I have chosen to use tendinosis as the preferred term both for the clinical condition where there is a suspected tendinosis, and for the histological appearance.

Inflammation

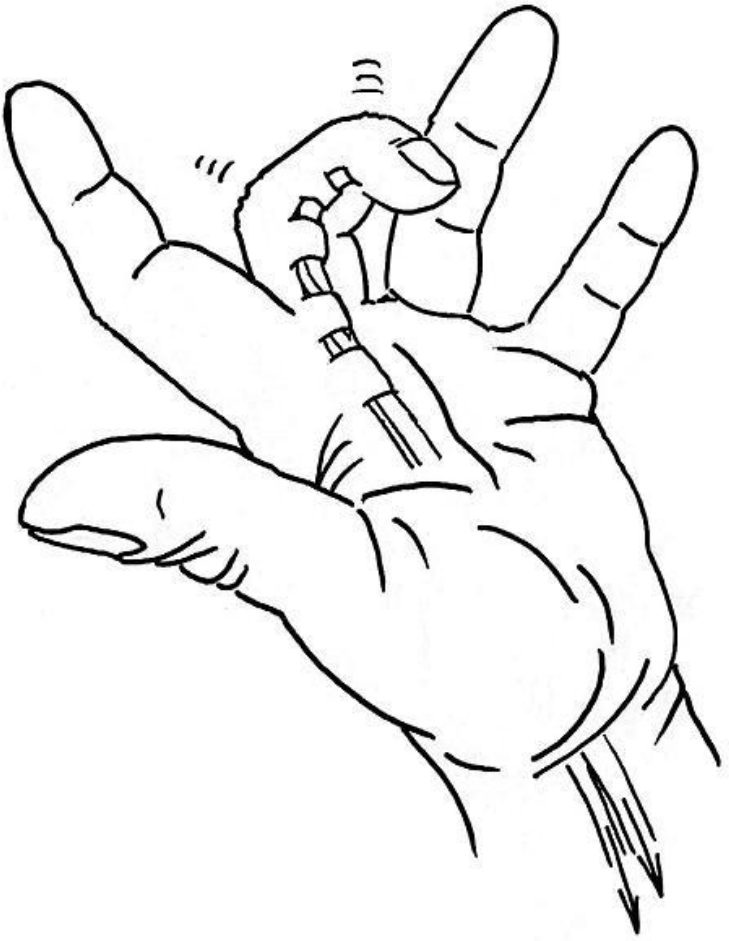
What is meant by inflammation? As early as the first century A.D., Celsus described the clinical features of inflammation as calor (heat), dolor (pain), rubor (redness) and tumor (swelling). A newer definition is that chronic inflammation is a prolonged, dysregulated and maladaptive response that involves active inflammation, tissue destruction and attempts at tissue repair[22].

Normal tendon structure and molecular biology

Tendons are tissues connecting muscle to bone. The composition and organization of the tissue is matched to their loading history[23]. There are cells scattered between the collagen fibres, connected to each other, communicating and maintaining the extracellular matrix. The cells, tenocytes and tenoblasts are poorly defined, and there is no single marker for them[24,25]. The tendon matrix is a composite of collagens constituting the reinforcing skeleton, and of various proteoglycans and glycoproteins. Fibrous collagen builds up the tendon by forming successively larger units. Three collagen molecules constitute a triple helix that forms fibrils that in turn form fibres, fascicles and tendons[26]. Type I collagen is the major component of tendons, type III is the next[24,27]. Collagen is degraded by matrix metalloproteinases (MMPs) that in general are stimulated by pro-inflammatory cytokines and inhibited by growth factors. There are other more specific inhibitors, such as tissue inhibitors of metalloproteinase (TIMPs). The non-fibrous component of the extracellular matrix is constituted mainly of proteoglycans with special tasks[28,29]. Decorin and biglycan bind to collagen and affect

fibril formation; they also bind growth factors. Versican lubricates between adjacent collagen fibrils, and aggrecan is a big molecule, binding water to build resistance to compression. Proteoglycans such as aggrecan are degraded by aggrecanases, members of the ADAMTS group (a disintegrin and metalloproteinase with thrombospondin type I motif) that are inhibited by TIMP-3[24,27].

Tendons are surrounded either by paratenon or a synovial lining within tendon sheaths, and are consequently named intra- or extra-synovial. The synovial sheath consists of a layer of parietal synovium, which lines the tendon surface and the inside of the fibrous sheath[30]. At the tendon surface the synovium constitutes the epitenon[31,32] which is specially adapted for gliding with a durable gliding surface[33]. The surface consists of lubricating elements (hyaluronic acid, phospholipids, and a lubricin) that protect the underlying collagen from abrasion and also functions as a protective barrier preventing tissue ingrowth. The coefficient of friction is similar to that of articular cartilage. Extra-synovial tendons are surrounded by an areolar parathenon external to the epitenon.



Normal finger flexor system

The finger flexor system can be regarded as a specialized joint[31]. There are two flexor tendons on the volar side of each finger (except in the thumb), the flexor digitorum profundus (FDP) and the flexor digitorum superficialis (FDS)[1-3,7,34-36]. They run within tendon sheaths that extend from the metacarpal neck to the distal interphalangeal joint (DIP). Those sheaths are thickened at five specific points in the fingers (four in the thumb[37,38]) forming strong, rigid bands of dense connective tissue: the annular ligaments- or the pulleys (the A1-A5-pulley), holding the tendons down to the underlying bones. The A1-pulley is the most proximal one. Its bands extend from either side of the volar plate of the metacarpophalangeal joint (MCP), encircling the tendons (Figure 1). The mean thickness of a normal A1-pulley is 0.48 - 0.59 mm[39] and the approximate length is 5 - 11 mm[40-42]. The sagittal tendon thickness of the middle and ring fingers at the level of the MCP is approx. 3 - 4.5 mm[10]. Female tendons are slightly thinner.

There are topographic landmarks for finding the A1-pulley; in the fingers, the distance between the digital palmar crease and the proximal interphalangeal crease corresponds to the distance between the proximal end of the A1-pulley and the digital palmar crease[41,43]. In the thumb, the proximal MCP flexion-crease corresponds to the proximal A1-pulley border[42].

Histologically, the normal A1-pulley can be divided into three layers. The innermost is an avascular, unicellular or bi-cellular gliding layer containing cartilage-like cells[44]. Next is the middle layer, also avascular, and characterized by spindle shaped fibroblasts. Externally there is a richly vascularized layer, in continuum with the membranous tendon sheath; however, the number of layers is a matter of debate. Both the thickness and stiffness of the A1-pulley increase with age[45].

The histological picture of the finger flexor tendons in general is well structured with evenly arranged and slightly waved fibres. The cell nuclei are mainly small, spindle-shaped and evenly distributed[14,46].

Blood is supplied through the vinculae vessels to the dorsal aspect of the tendons. The volar tendon aspects, the friction surfaces of the system, are less well vascularized and this, in combination with forces directed perpendicular to them, is suggested to be the explanation for occasional observation of chondrocyte-like cells[31,32,47,48].

Historic remarks

Below are some historical remarks that explain the development of the trigger finger paradigm and justify our studies. Unfortunately, on reading them one is often struck by how often the conclusions have been changed or simplified in citations in later articles.

In **1850** the French physician Notta, described for the first time the 'doigt à ressort', the trigger phenomenon:

> To straighten the ring finger the patient has to use her other hand. A cracking sound at the centre of the hand can be heard as it opens up by itself. Upon this event is observed: Firstly, a nodosity on the span of the flexor tendons located slightly above the inferior palmar crease given that the ring finger is flexed. Secondly, the nodosity disappears when the finger is extended and relocates itself at the digital palmar crease. Thirdly, the movement takes place in two steps. First there is a total resistance which then gives way and secondly there is the aforementioned sound followed by an acute protrusion at the point of the nodosity which seems to have overcome an obstacle.

This description still holds. He suggested inflammation as the cause of the condition, but he was unsure about the specific location. He also presented two hypotheses for the aetiology of the node. It could be a swollen segment of the tendon sheath or it could be a thickened area of the tendon itself. He proposed that 'pseudo membranes', such as depositions in atherosclerosis, could attach to the tendon or inside the sheath and could be the root cause of the suggested inflammation[49]. (This paper has in part been translated into English from French[50]). In later studies, inflammation was cited as the cause of trigger finger. Therefore, when no inflammatory cells were found in the tendon, tendon pathology was excluded, and when inflammatory cells were found in the pulley it was supposed to be the site of primary pathology.

In **1874**, Menzel, a German physician, tested the theories of Notta on cadavers. He hypothesized that 'a small round moveable body on the flexor tendon blocks the passage through the fibrous pulley, causing the finger to be, either permanently or temporarily, locked in flexion'. He looped a thread around a tendon to construct a node, but no triggering was achieved unless he also applied a thread around the tendon sheath and the pulley. Based on this, pulley constriction later became the explanatory model for the trigger phenomenon and swelling of the tendon secondary to it. In another experiment he introduced free bodies, hemp seeds and grains of rice, referred to as Notta's pseudo membranes, inside the tendon or into the tendon sheath. No triggering was achieved and he therefore cast doubt on the theory of tendon pathology, although it is obvious that the obstructing foreign bodies in his experiment were not adherent to tendons or sheaths, as the pseudo membranes that Notta suggested would have been. In conclusion, Menzel suggested a single mechanism behind trigger finger; contraction of the sheath, with a subsequent tumour of the tendon leading to triggering. He agreed with Notta's suggestion that trigger finger was due to inflammation, the latter

unfortunately again giving a reason for claiming a lack of tendon pathology on finding no inflammatory cells in the light microscope[50,51].

Five decades after Notta's article, in **1903**, Barnard published one of the first articles describing a surgical procedure resembling an open A1-pulley release, a surgical method still in use. He successfully resected the A1-pulley and in that way solved the problem of triggering, whatever the cause[50].

In **1944** Lipscomb presented a case series of 190 patients diagnosed with non-specific tenosynovitis (including cases of crepitating, non-crepitating and stenosing tenovaginitis) in all body locations. He retrospectively examined the pathological reports in 15 cases (all that were operated on) and found no case of tendon pathology. This is often cited as proof of lack of pathology in the trigger finger tendon. There are, however, objections; we do not know the diagnoses in the examined group and we do not know what the primary question to the pathologist was. If it was to examine for inflammation, which at the time was to look for inflammatory cells, the answer 'no pathology' would not necessarily mean that other pathological signs were missing. This article has, strangely, been cited as evidence that the trigger finger tendons are healthy (even if no one actually knows if a single trigger finger was examined) supporting the paradigm of pulley pathology and leading research efforts away from the tendon[17].

In **1951** Sperling described the only published provocative test for trigger finger, as far as we know. He performed it on himself. He repeatedly flexed the right little finger against the load of a spring, 9000 times. The little finger swelled up immediately, became tender, and a trigger phenomenon developed. He repeated the experiment on his thumb, flexed it approx. 8000 times, and it started to trigger. He concluded that 'numerous small movements, which individually are neither abnormal nor strenuous, may lead to the condition'.

Moreover, he presented in his introduction a microscopic examination of the thickening of a trigger finger tendon. It revealed an increase in fibrillar connective tissue with one or more cysts and also an increased infiltration of lymphocytes. Unfortunately he did not refer to the original histologic work, and perhaps that is the reason why we have seen no one citing this article for the histology. This is a pity as it could have increased the interest in possible tendon pathology in the 50s and led away from the narrow paradigm of pulley pathology[11].

In **1952** Lapidus and Fenton published their experiences from, and demographic facts about, 245 fingers with stenosing tenovaginitis. They described macroscopic changes of both the A1-pulley and the tendons and presented an explanatory model of primary pathology in the pulley from repeated flexions and wear from the tendons. The majority of the cases were considered work-related. Unfortunately, there is no information about the development of the pathology over time and I object that it is not possible to comment on what comes first, pulley or tendon pathology, since it was not investigated. The association with occupational exposure is interesting as it is also described for tendinosis. The description of obvious macroscopic tendon pathology is also worth noting[52,53].

In **1954**, Fahey and Bollinger concluded from macroscopic observations that Notta's node was due to a thickened A1-pulley. Secondly they presented the histopathology of the pulley, describing varying degrees of degenerative changes and fibrous tissue proliferation. Thirdly, they described the tendon histopathology, 'a purer type of collagenous degeneration and in some cases a few inflammatory cells'. They noted a difference in histological appearance between tendons from adults and children, and concluded that there was a different pathology in children and adults. They also concluded that the adult A1-pulley involvement was prominent and tendon changes minimal. There is no information about the tendons examined and again, tendon pathology was excluded due to a relative absence of inflammatory cells. This article has been cited as evidence of no pathology in trigger finger tendons in spite of histology indicating just that. We also note that their evidence for the suggested true nature of the node of Notta comprised unspecified macroscopic per-operative observations. We believe that this is the article that definitively established the paradigm of pulley pathology[16].

In **1969**, Lenggenhager, from Switzerland, discussed the controversy about the genesis of trigger finger, citing exclusively articles written in German. He stated that a mechanism involving thickening of the tendon agreed with his own experience and described a series of model experiments to substantiate his standpoint. He wound wires around the claws of a dead chicken and concluded that tremendous pressure on the flexor tendon was required to produce snapping, 'a pressure so great as to lead invariably to necrosis of the tendon in a living animal'. This was in contrast to Menzel's experiment (above), that pointed to pulley pathology. Lenggenhager wrote that 'implicating the tendon sheath as the primary factor seems to be of more theoretical than practical interest' suggesting that the thickened tendon irritated the pulley until a stadium of hypersensitivity appeared, with or without secondary swelling. He also wrote that the tendon thickening was not always possible to detect during surgery under general anaesthesia as active flexion was usually required to reveal it, thus leading to the common conclusion that there is no tendon pathology[12].

In **1972** Hueston and Wilson, presented a theoretical model for how thickening of the tendon could occur in trigger finger. They suggested an aetiology based on a stenosed A1-pulley, (similar to the eye of a needle) and a tendon-architecture with spiralling fibre bundles (similar to a twisted thread), and that the tendon thickens in the same way as a thread can bulge when it is threaded. This mechanism was suggested to lie behind all types of trigger fingers. It would be interesting to see it tested. Even if not tested, this hypothesis has been cited as evidence for primary pulley pathology[54].

In **1976**, Puddu et al. suggested tendinosis as the chosen term for degenerative lesions in the Achilles tendon. Its macroscopic appearance was described as thicker, softer and more yellowish in comparison to normal tendon and with loss of its normal lustre, just as we sometimes see in trigger fingers. They also presented histopathological findings; of focal degeneration, hyaline degeneration, reduction of the normal cell population, chondroid metaplasia, increase of ground

substance and fibrillation of collagen fibres. This is suggestive of tendon pathology similar to tendinosis, in trigger finger[11,16,17,19].

The only investigation directed primarily at trigger finger tendon histology (that I have found) is an abstract, from the 28th Annual ORS conference in**1982**, by Amadio et al. They obtained tissue from six adult patients and normal material from one. Both electron- and light-microscopy showed a disarray of collagen fibres that was not present in the normal tendon. They concluded that it may be involved in the pathophysiology of trigger finger. These results have never been published as an article[9].

In **2012** we published the first study on histopathology in trigger finger tendons[14].

In **2014** we published the first study on gene expression changes in trigger finger tendons[13].

TENDINOSIS

General remarks

Tendinosis is the most common tendon disorder[55]. At the age of 35 years and above, degenerative changes are frequent[56]. Tendinosis occurs in loaded tendons in all extremities and results in decreased exercise tolerance, pain and a reduction of function.

There are locations within the tendon that are considered to be more vulnerable, such as sites with low blood supply or the presence of focal compression[56]. Tendons with high mechanical demands, such as the supraspinatus, extensor carpi radialis brevis, patellar and Achilles tendons are more often affected by tendinosis[46], and some individuals are more susceptible, due to suggested inheritance[57]. Other factors associated with higher risk of Achilles tendinosis are age, male gender[58], inflammatory arthropathies, diabetes, hypertension, obesity, gout, and high bodyweight[59].

There is a general support for the hypothesis that impairment of extracellular matrix quality leads to tendinosis, and that proteolytic enzymes and their effects on the matrix are key factors[24,27]. The tenocytes have a central role in maintaining the extracellular matrix and in synthesizing its constituents[60-62]. Their metabolic rate is low[24,27] and hypoxia, high temperature, biochemical mediators produced by other cells, and drugs affect tenocyte activity[59].

A genetic component is implicated[57] and differences in mRNA expression pattern for 40 genes have been shown in Achilles tendon disorders compared to normal tendons[63].

Appearance and pathology

Histology

The histological picture, seen with light or electron microscopy, shows parallel fibre alignment in the normal tendon, while in tendinosis there is separation of the fibres, increased waviness, loss of fine fibre structure, and sometimes signs of hyalinization[46,64].

Normally, the tenocyte number is quite low, the nuclei are spindle-shaped and located between collagen fibres[46,64]. In tendinosis, both a reduced and an increased number of nuclei can be seen, and they are either of normal or more rounded shape. The collagen normally stains deep red with haematoxylin and eosin, but in tendinosis the stainability is often reduced. There is an increased amount of proteoglycans, sometimes seen as vacuolated lakes. In normal tendons, the vessels and nerves are few and generally run parallel to the collagen fibre bundles. In tendinosis, an increased vascularity is common and occasionally signs of vascular ingrowth from the peritendinous tissue can be found (in extrasynovial tendons). There are no signs of inflammatory cell infiltration. Calcium deposits or lipomatosis are uncharacteristic findings. Notably, there is a paucity

of knowledge about the tenocytes and tenoblasts, and it is also increasingly clear that the previously suggested absence of inflammatory cells is not the same as total absence of inflammation[25,65-68]. Macrophages, T lymphocytes, B lymphocytes[69] and granulocytes[25] can now be found with immunohistochemic methods. Nevertheless, the histopathological picture of tendinosis is still dominated by typically degenerative changes.

Histological classification of tendinosis

There are at least two scoring systems for histopathological findings in tendinosis: the Bonar and the Movin systems. They have a high correlation and assess approximately the same characteristics and variables. There are also validated modifications of the Movin system[70,71]. The Movin system was originally developed for the Achilles tendon[64] and the Bonar system for the patellar tendon[61].

The Movin score variables are 1) fibre structure, 2) fibre arrangement, 3) rounding of the nuclei, 4) regional variations in cellularity, 5) vascularity, 6) collagen stainability, 7) hyalinization, and 8) Glucoseaminoglycan (GAG) content. The variables are scored between 0 and 3, with 0 being normal, 1 slightly abnormal, 2 abnormal, and 3 markedly abnormal. Haematoxylin and eosin staining are used to assess the first seven variables and alcian blue staining is used to assess GAG-content. The total score for a given tendon can range between 0 (normal tendon) and 24 (the most severe abnormality detectable)[64]. We used a modification of this scoring system in paper I.

The Bonar score variables are 1) tenocytes, 2) ground substance, 3) collagen, and 4) vascularity. The variables are scored between 0 and 3, with 0 being normal and 3 markedly abnormal. The total score for a given tendon can range between 0 and 12[61].

Sonography

With ultrasonography, normal tendons appear as hyperechoic structures consisting of fine hyper- and hypoechoic fibrils. In tendinosis, ultrasonographic findings include focal thickening with heterogeneous decreased echogenicity. There is loss of the normal fibrillar pattern, and an appearance of fibre disorientation and collagen degeneration. There are signs of intratendinous hyperaemia associated with neovascularisation rather than inflammation[72]. The neovascularisation may be seen in, or around the tendon. Tendon sheaths can only be discriminated when distended with fluid, or if there is detectable vascularity with colour Doppler imaging[73].

Aetiology

The pathogenesis in tendinosis is not clear, and depends on the suggested primary event. Suggested pathogenetic models can be divided into at least four groups; 1) collagen disruption or tearing, 2) failed healing response, 3) tendon cell response or 4) inflammation[25,62,74].

1) The collagen disruption or tearing model explains tendinosis with cumulative damage and vascular insufficiency.

2) The failed healing response model describes a failure to repair as the main pathologic mechanism.

3) The tendon cell response model is based on tenocyte response to changes in tendon load (stress, shear or compression), i.e. either over-stimulation or underloading[61,75]. This is suggested to result in a cascade of responses, cell activation, proteoglycan expression and changes in collagen type[61]. There are indications of tenocyte activation already after two weeks of overload in animal studies, without other features of tendinosis[76]. In humans, primary tenocyte activation with cellular abnormalities is almost always present when ground substance and collagen abnormalities are seen[61]. Tendinopathy has also been reported to precede tendon rupture[56,70,77]. The tendon cell response model suggests a continuous progression of pathology, from mild reversible to severe non-reversible and also provides a base for staging; from mild with only tenocyte activation, to severe with tissue destruction[74].

4) In the inflammation model, inflammation is suggested as the key event. This model has recently received increasing attention. Increased levels of interleukin-1 and -6, cyclooxygenase-1 and -2, iso-forms of transforming growth factor-β or substance P have been presented in tendinosis[21]. There is now also evidence supporting an increased number of inflammatory cells in tendinosis[25,66,67,78], but still no evidence supporting inflammation as the primary event[74].

It is not likely that any of these models alone fully explain the pathogenesis of tendinosis[74] and my recent reading on this subject leads me to believe that a paradigm shift is under way, from the old paradigm of degeneration to something else.

Whatever the pathogenesis, tendinosis is thought to be a cell-mediated process involving remodelling and increased turnover of the extracellular matrix[24,27]. The collagen content is subnormal, the gene expression of collagen types I and III is upregulated and the composition of the collagenous matrix altered[79]. The degradation of the extracellular matrix is mediated by enzymes such as aggrecanases and matrix metalloproteinases (MMPs)[24,27]. MMP-3 has been shown to be very differently expressed between normal and pathological tendons in tendinosis[63,80]. The loss of MMP-3 activity has been suggested to account for increased levels of proteoglycans. However, there is also increased gene expression of the proteoglycan core proteins, decorin and versican[81,82] in both tendon ruptures and tendinosis[28,29], and biglycan in painful tendinopathy[81]. Furthermore, the altered metabolism of the cells, not due to genetic alterations, can lead to increased synthesis of proteoglycans, for example of aggrecan and versican[83].

There may be more genes involved, as many as 983 transcripts have been identified (with global gene expression profiling) as differently expressed in tendinopathy[84], reminding us again of the complexity.

Neovascularisation develops later than other features of tendinosis. It has been implicated in the pathogenesis of tendon pain[85]. Although this is an interesting association, no studies have shown that neovascularisation is the cause of tendon pain[61].

Drug exposure, in particular statins

Four classes of drugs have been suggested to be associated with risk of tendinosis or tendon rupture: fluoroquinolones, glucocorticoids, aromatase inhibitors, and statins. The specific pathophysiology remains unknown and the time to onset varies.

Unspecified tendon injury (tendinosis, tendon rupture and tenosynovitis) has been suggested as a potential side effect of statin use[86-94] but firm evidence for an association has been lacking.

However, we have now shown that statin use increases the risk of tendinosis of the shoulder as well as of trigger finger. There were only a few cases of Achilles tendinosis, but still, there was a tendency towards an increased risk (paper IV). Our results are based on an epidemiologic study on two large population-based cohorts. Statin use and tendon injuries were determined by individual linkage to national register information. We found a higher risk of shoulder tendinosis among men who has used statins, compared to non-users, with an adjusted hazard ratio (HR) of 1.41 (in women, HR 1.14). The risk was highest with the use of rosuvastatin and did not appear to be dose-dependent.

Statin lowers cholesterol, and hypercholesterolemia is a potential risk factor for tendinosis[92,95,96]. It can therefore be hard to distinguish between the role of the statin and the potential hypercholesterolemia that it is supposed to treat. However, statins are used also in patients without hypercholesterolemia, and our study was not limited to patients with hypercholesterolemia. Furthermore, we could only see an increased risk among current users, and the risk disappeared when statin use was discontinued. We therefore suggest that it is the statin use that increases the risk of tendinosis.

It has also been reported that tendon problems tend to recur when statin treatment is re-introduced[89,97].

Treatment

When recommending treatment, the duration of the tendinosis must be taken into consideration. In early stages with a reactive tendon, load reduction is usually recommended, alone or in combination with NSAIDs or corticosteroids[62]. In later stages, with disrepair or degeneration, load-bearing physiotherapy (with increased load) is recommended. Eccentric training has been the principal treatment for Achilles tendinopathy[98] although there is little evidence supporting the eccentric component. There is one randomized controlled trial comparing the traditional eccentric training and heavy slow resistance training[99]. Both methods yielded a positive clinical result in both short- and long-term follow-ups. There are also other treatment modalities for tendinosis e.g. sclerotherapy, surgery, acupuncture and extracorporeal shock wave therapy. However, well-conducted studies on the effects of these treatments are lacking[62,100].

Glucocorticoid injections

Glucocorticoid injections are often used in the clinic, but they are controversial. Still, there is strong evidence that injections of glucocorticoids are beneficial in the short term, but not in the intermediate and long term[101]. There is a dilemma about the biological basis for the effect as tendinosis has not been considered an inflammatory condition[20], however this will perhaps be solved with new explanatory models. One mechanism could be a change in gene expression and a subsequent change in collagen production, production of other extracellular matrix molecules, or occasional granulation tissue[102]. Another proposed mechanism is an effect on adhesions between the tendon and the surrounding peritendinous tissues[55]. The effect of glucocorticoid injections is usually measured by relief of symptoms such as pain. If pain in tendinosis is the result of stimulation of nociceptors by noxious substances from the degenerative tissue, perhaps the glucocorticoid effect on pain is an alteration of their release, their receptors or both[55]. The glucocorticoid effect could of course also be due to reduction of an inflammatory component[21]. Three general mechanisms of action for glucocorticoids have been suggested: a non-genomic activation, DNA-dependent regulation, and protein interference. Inflammatory mediators, e.g. prostaglandins, nitric oxide, cytokines (TNFα, IL-1 and IL6), and several cellular functions of the immune system are inhibited[103]. Triamcinolone hexacetonide has been shown to inhibit expression of mRNA for collagenase, HLA-DR (MHC (major histocompatibility complex) class II cell surface receptor encoded by the human leukocyte antigen complex), TIMP and complement factors C2 and C3[102]. Dexamethasone reduces substance-P mRNA[104]. However, the exact mechanism of the effect of glucocorticoids is not fully understood.

TRIGGER FINGER

General remarks

Trigger finger is a clinical diagnosis. Some patients experience pain, while others only notice a trigger phenomenon[8,105]. Even if only one digit is affected, the co-ordination of all the digits can be altered[106,107].

The onset is usually gradual[2]. Some patients experience more symptoms in the morning, but there are great variations in diurnal rhythm. The localization of pain and the occasional palpable nodule, is on the volar aspect of the metacarpophalangeal joint (MCP), at, or slightly distal to, the distal palmar crease[1,3,5]. On physical examination there are often no pathological findings, unless there is a triggering. There is sometimes pain on palpation and occasionally a nodule. No clinical tests have been recommended, and x-rays or laboratory tests add nothing to the diagnosis.

Trigger finger is more common in women than in men, and the incidence increases with increasing age, to a peak in the fifth or sixth decade of life[1,52,53]. The age distribution is often presented as bimodal, below six years of age and above 40 years, but this is slightly misleading as there are two major types of trigger finger; an adult type including idiopathic and secondary trigger finger, and a paediatric or congenital, type. The prevalence in individuals without diabetes has been reported to be between 0.7 % and 3.6 %[108-112]. We found, in a large cohort study, an incidence rate of 1.4 per 1000 person-years among women, and 1.5 per 1000 person-years among men (paper IV). A caution is that diagnoses from primary care settings were not included in this study, indicating that the true prevalence is higher.

The thumb is most frequently affected, followed by the middle and ring fingers. The condition is more frequent in the right than in the left hand and most patients suffer from a single trigger finger[1,52,53,113].

In Sweden, trigger finger patients are managed either at specialized centres for hand surgery, by orthopaedic surgeons, or conservatively by general practitioners. Trigger finger surgery is common and made up 6% of the total operated volume at the specialized hand centres during 2010 to 2015 (www.hakir.se)[114].

SECONDARY TRIGGER FINGER

Congenital trigger thumb and finger

The congenital trigger thumb is suggested to be caused by a developmental size mismatch between the flexor pollicis longus tendon and its sheath, with a typical nodule on the tendon[115,116]. The pathology is well defined, but the pathogenesis is not. Paediatric trigger fingers represent a different entity, separate from trigger thumbs[117,118]. They are generally associated with an underlying diagnosis of metabolic, inflammatory or infectious disease, but can also be due to anatomic abnormalities.

Trigger finger in rheumatoid arthritis

In patients with rheumatoid arthritis or other inflammatory systemic diseases, it is impossible to separate an idiopathic trigger finger from a triggering due to a rheumatoid manifestation[119]. A rheumatic trigger finger usually presents as tenosynovitis, and is associated with swelling and pain. The histopathological picture of tendinopathy in association with rheumatic diseases is different from the degenerative picture in idiopathic trigger finger.

Other causes of secondary trigger fingers

A secondary trigger finger can also be caused by loose bodies[120], sharp trauma with partial laceration of the tendon[121-123], blunt trauma[124], hyper-extension with a subsequent tendon nodule[125], rattlesnake bite[126] or fraying due to underlying disease[127], local depositions[128] or depositions of systemic reasons as in gout, pseudo gout[129] or amyloidosis. Amyloidosis can be dialysis-related[130-132] or familial[133]. There could be an infection as tuberculosis[17], a side effect of anti-oestrogens (letrozole and exemestane)[134] or an effect of acromegaly[135]. There might be an exostosis[136] or a soft tissue tumour, either in the tendon sheath[120] or in the tendon[137,138], at the level of the wrist[139,140], on the dorsum of the hand[141] or both[142]. It can trigger due to a chondroma[143], leiomyoma[144,145], granuloma[146], or fibroma[147]. It can trigger at other pulleys[137,148], or because of variations in anatomy, an anomalous lumbrical insertion[149,150] or an intertendinous connection[151].

IDIOPATHIC TRIGGER FINGER

Classification

There have been several attempts to classify trigger fingers over the years. In the 'Multidisciplinary Consensus Guideline for Managing Trigger Finger'[8], a treatment chart is published where duration, intensity of snapping and grade of symptoms from mild to very severe are presented and linked to advice on treatment. The study, which these guidelines have been based on, the HANDGUIDE study, states that it was not possible to find consensus among the experts for one grading system[152]. Only 30% of them used one, and there are also many different grading systems, for example the systems of Patel and Moradia, Peter et al, the Quinnell grading and the Newport classification. There is a lack of correlation between grading and outcome after injection therapy, which casts doubt on the relevance of these systems[153]. However, a simple classification can be useful, especially in research. Several authors, including us, have used the system modified by Green in 1997[153], as follows:

- Grade I, a history of catching, tenderness over the A1-pulley, pain
- Grade II, demonstrable catching and the patient can actively extend the digit
- Grade IIIA, demonstrable catching requiring passive extension
- Grade IIIB, demonstrable catching requiring passive flexion
- Grade IV, fixed flexion contracture of the PIP joint

Appearance

Sonography

High-frequency ultrasonography examination is an effective technique for imaging tendons, showing typical echo-textural patterns[154]. This technique can show pathologic abnormalities in the structure of the tendons, the A1-pulley and surrounding tissue, and can distinguish between involved and non-involved digits[155].

The tendons usually appear rounder[34], under a thickened and hyper-vascularized A1-pulley. There are also signs of tendinosis and tenosynovitis[156], as seen by loss of normal fibrillar echogenic pattern, irregularity of the tendon margin and fluid collection in the tendon sheath[10,157].

Patients experiencing problems with finger extension have larger tendon diameters, and for patients with locking fingers the margins of the tendons are blurred. Trigger finger patients with a palpable nodule can have signs of tendon sheath cysts, A1-pulley fibrosis[157], swollen tendons or a combination of swollen tendons and A1-pulley pathology[155]. Also the thickness of the volar plate appears to play a role in triggering[158,159].

A thickening of the A1-pulley is seen in 44% of the patients[157] but in approximately 30% of clinical trigger fingers there is pathology in the tendons, or the sheath without concomitant abnormality of the A1-pulley. The thickness of the A1-pulley and of the proximal A2 pulley has been linked to the severity of the trigger finger[160] and the A1-pulley stiffness measured with sonoelastography is suggested to be associated with triggering[45]. However, it should be kept in mind that the pulleys are hardly visible, with unclear sonographic margins and measurements, and findings are prone to errors[161], yet the use of high-frequency ultrasound scanner systems has contributed more precision[39].

The diameter of the flexor tendons is safer to measure and is also proportional to the severity of the triggering[157,158]. With a higher grade of trigger finger the tendon echotexture is more irregular[10]. With dynamic ultrasound it has been shown that the tendon diameter varies; it thickens before the occurrence of the snapping in the fingers, and after the snapping in the thumb[158].

A1-pulley histopathology

During surgery for trigger finger, a thickening of the A1-pulley is often obvious. Biopsies examined with light or electron microscopes reveal histological abnormalities as destruction of the fibrocartilaginous portion of the pulley, which is replaced with vascularized tissue from the membranous portion[44]. The fibrocartilage can be thinner or missing. Oedema is common, and fissures and ganglions are seen, but no signs of inflammation. Also, proliferation of fibrous tissue, degenerative changes[11,16,17,162], chondroid metaplasia, and increased glycosaminoglycan content are characteristic[52,53,162-164]. Localized amyloid deposition in the tendon sheath can be seen, but only in the middle-aged and elderly, suggesting age-associated changes[165]. The amorphous extracellular matrix, constituting the gliding surface of the A1-pulley, is often missing, which leads to exposure of the underlying collagen fibres[162,166]. Parallel with worsening of the trigger finger, the gliding surface wears, and is gradually replaced by a hyperplasia from the outer layer. However, the general histopathological picture is not correlated with trigger finger grading[44].

Classification of pulley histopathology

A histopathological grading system has been suggested[44], as follows:

- Grade I, mild abnormalities; the fibrocartilaginous gliding surface is almost intact. The margin between the fibrocartilaginous and membranous portions of the pulley is well delineated.

- Grade II, moderate abnormalities; the avascular fibrocartilaginous gliding surface is fissured and thinner. The inner layer is interrupted and replaced by fibrous tissue, with fissures that do not cross through the middle layer. There is a mild vascular network hyperplasia in the outer layer beginning to invade the fibrocartilage.

- Grade III, severe abnormalities; the fibrocartilaginous gliding surface is thin, discontinuous, or completely destroyed. The hyperplastic vascular network is excessive and reaches the synovial space of the flexor tendon sheath.

There are systems for computer-aided quantification of pulley histopathology[167]. They can be used for histopathological grading, but are perhaps of little use in clinical practice because of the lack of a correlation between the histopathological and triggering grades.

Tendon/A1-pulley histopathology

There is disorganization or breakdown of the inner gliding layer of the A1-pulley[7], and the coefficient of friction is suggested to be increased[33]. The gliding layer is suggested to be disrupted by an underlying degenerative condition of the tendon, leading to disruption of the system that maintains its gliding surface[168]. The surface is constituted of synovial fluid and lubricants, such as hyaluronic acid, phospholipids and lubricin that are bound to the tendon surface. The tenosynovium has distinct histopathological features, with hyaluronic acid-producing chondrocytoid cells and a hypo-cellular collagen matrix surrounding it. This indicates an oedematous extracellular matrix in the trigger finger tendon sheath. (Lubricants have been successfully used to treat stenosing tenosynovitis in horses but the biomechanics differ substantially[33]).

Tendon histopathology

Based on a few histopathological findings showing disarray of collagen fibres, and also based on pathology in flexor tendons from horses, degenerative changes have been suspected[9,33]. However there are, as already mentioned, huge differences between human flexor digitorum profundus and superficialis and the corresponding tendons in a quadruped[169].

We have performed a series of studies on trigger finger tendon pathology.

We found early on that even an untrained youngster can separate trigger finger tendon biopsies, dyed for ground substance, from controls without a microscope, just by their general appearance (paper I)[14].

With microscopy it was also easy to separate controls from trigger finger slides, in a blinded test (paper I)[14]. In general, trigger finger tendon histology was characterized by separated, disorganized and disrupted fibres. Collagen staining was uneven and the specimens looked pale. The cells in trigger finger biopsies were numerous, with large round nuclei, often unevenly distributed in hyper- and hypo-cellular regions. There were chondrocytes with surrounding hyalinization and indications of increased amounts of glucoseaminoglucans (GAG) in the ground substance, both around collagen fibres and between bundles. This is suggestive of tendinosis. A modified Movin score, originally designed for Achilles tendinosis, resulted in high scores for trigger finger biopsies, and low scores for controls.

Assessed with quantitative real-time polymerase chain reaction, trigger finger tendons also showed differences in gene expression, in comparison to normal tendons (paper II)[13]. Up-regulation of collagen types I and III, as well as aggrecan and biglycan, conformed to the reported histological signs of an increased turnover, with formation of new tissue reminiscent of an immature scar. The overall expression pattern in trigger finger tendons agreed with previous studies in Achilles tendinosis and suggested that the normal function in the trigger finger tendon is disturbed in a similar way as in Achilles tendinosis.

In a retrospective large cohort study, statin treatment was associated with a higher risk of developing trigger finger and shoulder tendinosis (paper IV). There was a tendency to higher risk of developing Achilles tendinosis. The exact mechanisms behind the detrimental effect of statin treatment on tendon tissue is not known[170], but similar responses to statins in these different locations also suggest a similar pathology in trigger finger as in the shoulder and Achilles tendinoses.

Aetiology

Occupational exposure

The literature contains abundant studies on trigger finger in relation to occupation, but there are no controlled studies. A Cochrane protocol has been published, but no results have been reported so far[171]. Unfortunately, as already noted, the trigger finger diagnosis has often disappeared behind diffuse definitions e.g. somewhere among 520,000 cases of 'work-related musculoskeletal disorders of the distal upper extremity' in a study on US workers[172]. However, a point prevalence among workers in Thailand of 9.5% has been presented[173], which is similar to the overall incidence rates among workers in an American meat packing plant, 9.96 cases per 100 person-years[174]. The use of hand held tools was suggested as a risk factor in the latter study, with incidence rates of 12.4 per 100 person-years for tool users compared to 2.6 for non-tool users. Still the occupational history for patients with idiopathic trigger finger is not significantly different from a local general population, suggesting that the vast majority of trigger fingers develop for reasons other than occupation[175,176].

Diabetes

About 25% of patients with trigger digits suffer from diabetes[177], and the incidence of trigger finger is reported to be higher for persons with diabetes. The presented numbers (incidence, life time incidence, prevalence, period prevalence) however, vary widely, from 1.5% to 11.6%[108,111,178-182] (among younger persons, 5% (14-38 years)[183]) and there is no firm evidence concerning the risk[184]. The considerable range in incidence and prevalence has been suggested to be due to an ethnic component[178]. The lowest number is from a large cohort study in California[111] with no registration of ethnicity. The highest number is from India[181], and in between are studies from Jordan[179], Iran[180] and Pakistan[178]. The studies

differ considerably regarding methodology, and perhaps that is the reason for the discrepancy between studies.

Over 415 million people in the world were diagnosed with diabetes in 2015, and it is believed this figure will rise to 642 million in 2040 (www.diabetesatlas.org)[185]. If the trigger finger incidence is increased in patients with diabetes, we can expect to see quite a large increase of trigger finger cases in the future.

The risk of trigger finger in diabetes is associated with high HbA1c[111], neuropathy, nephropathy and retinopathy[181], female gender, age over 60 years, long duration of diabetes and hypertension[179], and the risk for multiple trigger fingers and bilateral involvement is increased[177]. A suggested explanatory model is irreversible glycosylation of collagen. This has also been the explanation for why trigger fingers in diabetes are suggested to respond less well to treatment with glucocorticoid injections[186,187]. However, there are conflicting results concerning the latter[188] and we and others have seen no difference in response to a glucocorticoid injection, in patients with diabetes, (paper III)[188]. It is also worth noting that in one study on diabetes and trigger finger, as much as 60% of the trigger fingers were reported to recover spontaneously, raising doubt about the hypothesis of irreversible glycosylation[189].

Carpal tunnel syndrome

Carpal tunnel syndrome and trigger finger often occur synchronously[190]. A common pathological process is suggested[191]. The incidence of both carpal tunnel syndrome and trigger finger is higher in diabetes[105]. There could be another coexisting, yet unknown, predisposing disorder[105,133,192] or a local biomechanical component. Volar migration of the flexor tendons, after surgery for carpal tunnel syndrome has been suggested[193,194], but there is no evidence for an association between surgery for carpal tunnel and postoperative trigger finger[195,196].

Dupuytren's disease

Dupuytren's disease is mentioned as a possible cause of trigger finger[197], but information about concomitant disease is sparse. As for trigger finger, there is a suggested higher risk of Dupuytren's disease in diabetes, which could explain some coexistence[109]. Based on perioperative findings, two types of trigger finger in Dupuytren's disease have been described, one where vertical Dupuytren's septa constitute a compressive component, and another type where the trigger finger seems unrelated to the fascial disease[197].

Drug exposure, in particular statins

As already mentioned, we have found that statin use seems to increase the risk of trigger finger especially in men (paper IV). The risk is seen in current users (HR 1.5; 95% CI: 1.21-1.85) and disappears after the use is discontinued. The highest risk is associated with the use of rosuvastatin and appears to be dose-independent. This risk increase has previously not been described. The role of statin use in tendon pathology is a current topic of debate. The mechanism behind this increased risk is not known, but it could be due to the lowering of cholesterol, which is suggested to weaken cell membranes[198]. In vitro studies have shown that statins can influence cell proliferation and cell migration, and induce apoptosis[199,200]. Furthermore, mechanical properties are suggested to be impaired[170,201,202], perhaps through a disturbed MMP balance or reduced collagen production[170,199,203,204]. There is also a suggested correlation of trigger finger and the use of third generation aromatase inhibitors[134].

Treatment

There is a lack of randomized controlled studies on treatment of trigger finger, but there are other types of studies[205]. The most commonly used and accepted methods are orthosis, surgery and glucocorticoid injections. Less common treatment suggestions include acupuncture[206], vibration[207], hyaluronic acid injections[208] and extracorporeal shock wave therapy[209].

Orthosis

The supposed rationale for orthoses is the prevention of full range proximal glide of the tendons in the digital sheath[210]. This can be achieved by immobilizing either the distal interphalangeal or the metacarpophalangeal joint[211-213]. A period of six weeks is common Reported success rates range from 35 to 75%[1,211].

Surgery

Surgery is generally considered for patients in need of quick and definitive relief, or when treatment with conservative therapy has failed[214,215]. It is usually performed under local anaesthesia, either with adrenaline-addition or with the use of a tourniquet to reduce bleeding. The objective is to divide the A1-pulley to release the tendons. The release can extend to half of the proximal A2 pulley if necessary[216], but less than full division of the A1-pulley is not recommended, as partial division is reported to always fail[217].

Some surgeons perform a transverse skin incision, others a longitudinal or oblique incision[4]. Some surgeons perform an additional step of traction tenolysis, by bringing the FDS and FDP tendons out of the wound[218]. However, a tendency to lower postoperative total active motion and more pain is reported after this, suggesting restraint.

Open pulley release has an almost total success rate[214,217,219,220] but 1% to 41% of the patients experience minor adverse advents. Major complications are rare[215,220-222], though complex regional pain syndrome (CRPS)[223] and bowstringing[224] are seen. Pulley-preserving surgical techniques are described[225]. Male gender, sedation, and general anaesthesia are suggested to be associated with greater risk[226]; however, the definition of an adverse event varies widely[227].

There are percutaneous techniques, where division of the A1-pulley is performed with a needle or a knife blade[228]. Few complications and figures of 82% to 100% relief of triggering are reported[228-230]. Multiple techniques have been presented, with or without the support of sonography. There are indications that the postoperative pain is less in comparison to open surgery[230], and that the active range of motion is recovered faster[231], but no differences are found after the first postoperative week[228,229].

In summary both percutaneous and open techniques have high success rates, few adverse effects[214,228-232] and evidence that there is a difference between them are weak and conflicting[152].

A Cochrane protocol, Surgery for trigger finger[233], and a protocol for a randomized controlled trial of open surgery versus glucocorticoid injections, have been presented, but results have so far not yet been published[234].

Glucocorticoid injections

Despite the widespread use of glucocorticoid injections in trigger finger the biological basis, as well as systematic evidence for their effect, is inadequate[55]. There is one Cochrane review[235] and at least one high quality randomized controlled trial[152,236]. Moderate evidence has been found for the effectiveness of steroid injections in comparison to placebo in the short term (one to four weeks), but not in the mid- and long-term. Figures of 36% resolution at one week[236], 71% at three weeks[237] and 60% resolution at four weeks[238] are presented.

There are other types of studies with long-term follow-up numbers of 60% good result after five years[239], 70% after eight[240] and 45% after ten years[241]. Female patients with their first trigger finger and patients with continuous relief of symptoms after two years are most likely to maintain positive long-term results. A lower rate of success is associated with long duration of symptoms (four to six months) and with an increased number of injections[219,242,243].

Prognostic indicators of recurrence are: younger age, a history of other tendinopathies (of the upper extremity), involvement of multiple digits[244]. Insulin-dependent diabetes mellitus is considered by some to be a prognostic factor, and by others not[244,245]. After documented or presumed resolution, recurrence of triggering occurs in 30% of cases[246].

Glucocorticoid injections have better outcome than physiotherapy[247], but are less effective than A1-pulley release[188,232].

The importance of the injection site has been investigated. Glucocorticoid was mixed with contrast and injected inside or outside of the tendon sheath[248]. The true deposition site was determined with x-ray. The results suggest that intra-sheath injection offers no apparent advantage over subcutaneous injection. The same question was recently investigated again using ultrasonography instead of x-ray, leading to the same conclusion[249].

Injection of glucocorticoid in trigger finger is safe[235-238], but rare adverse effects are described; tendon rupture[250,251], a mycobacterium abscess[252], pulley rupture[253] and digital necrosis from embolus[254]. A hyperglycaemic effect in individuals with diabetes mellitus is noted, for at least five days but the rise is not considered clinically significant[7,255,256].

Injections of triamcinolone acetonide seem to be a little better than dexamethasone[7,246], with a more rapid onset, but there is no difference at six weeks[7,152,257]. After injections of glucocorticoid, there are findings of reduced thickness of the A1-pulley, volar plate[159] and tendon[258]. There is also reduced stiffness of the A1-pulley[45], parallel to the relief of the triggering.

Glucocorticoids as a treatment for trigger finger has been in use since 1953[259], but as already mentioned, little is known about the pharmacokinetics in soft tissue injections. It is known that 43% of the glucocorticoid is hydrolysed in 24 hours, in vitro (www.fass.se)[260], and that the peak depression of systemic cortisone, induced by an intra-articular glucocorticoid injection (in the knee), is at 24 hours[261]. It is not measureable after 14 days. There is a study on triamcinolone acetonide injections into rat tails that revealed a peak solubility of collagen between the second and third week after an injection, suggesting a peak effect at that time (in rat)[159,262]. This in combination with the published 60% of spontaneous trigger finger relief[189] indicates that the reported effects of glucocorticoid could include cases of spontaneous relief. As mentioned earlier, there is only evidence for effect in the short term[152].

Nevertheless, patients often ask how long it will take for the triggering to resolve after the injection, and that question has not been possible to answer until now.

We have studied the specific time when the glucocorticoid injection effect sets in. As we believe that the effect must be studied when there still is a possible biological effect in the tissue, we designed a study with short study period, a prospective observational study. We looked at the first two weeks after an injection.

Patients treated with an injection received a stamped postcard and were asked to fill in the date and return it on the day of resolution of the triggering (paper III). If there was no resolution, we asked them to return it after 14 days. With this method, we gained a reasonable and adequate control over recollection bias. At 14 days, the triggering had resolved in 55 patients (71%). Among these, the mean time to resolution was seven days. The resolution described a linear function in a Kaplan Meier diagram, suggesting approximately the same number of patients with resolution per day within the 14-day study period. So, based on our study and the information above the patient can be informed that if there is an effect of the injection, which there is in approximately 70%[237] of the cases, it will set in

during the first two weeks. If no effect is obtained after two weeks, the likelihood for resolution from the injection is small. If the symptoms are troublesome or the patient is in need of quick relief, it is time for further planning.

Current treatment concepts and aspects of choosing

As regards current treatment guidelines there is the 'Multidisciplinary Consensus Guideline for Managing Trigger Finger'[8], and also a study of what treatment members of the American Association for Hand Surgery prefer[4]. There is a British study on how to make the best choice regarding the cost[263]. Still, in the clinical situation it is never easy to decide. There is a study that tested whether there is any difference in decisional conflict between patients with trigger fingers and hand surgeons[264]. They found a low, but measurable level, pointing out the importance of including the patient in the decision. Otherwise, it does not seem that psycho-social factors play a great role in trigger finger, except for pain catastrophizing[265].

Two glucocorticoid injections before surgery, is the least expensive alternative[219,243]. A therapeutic hierarchy of three recommended methods, splinting, injections of glucocorticoid and open surgery (open trigger finger release is recommended in favour of per cutaneous), is presented in the Multidisciplinary Consensus Guideline[8]. They recommend that the severity and duration of the trigger finger (pain and grade of triggering) are the main factors when deciding on the type of treatment. Splinting is recommended for mild symptoms. With increasing symptomatology and duration first injections of glucocorticoid is recommended, second is surgery.

DISCUSSION

Our data indicate that there is tendinosis in trigger finger (papers I, II, and IV)[13,14].

The histological picture in trigger finger is a picture of tendinosis. It differs from control tendons, but is similar to Achilles tendinosis (paper I)[14]. The mRNA expression pattern is similar to what is described for Achilles tendinosis and different from healthy controls (paper II). Statin use increases the risk of trigger finger in a similar way as it increases the risk of other tendinopathies (paper IV). Altogether, this indicates that there is tendinosis in trigger finger.

There is also support in the literature for this position.

In general, tendinosis is thought to be related to over-use[24,27,74,266], compression and repetitive energy storage and release are key factors in the onset[62]. Repeated flexions have been shown experimentally to induce trigger finger[11] and trigger finger prevalence is high among workers, especially among users of hand-held tools[173,174]. The use of such tools is linked to compression and repetitive energy storage and release. Furthermore, compression of the tendon could be a consequence of swelling of the tendon within the non-yielding pulley, leading to a vicious circle[267].

Another key factor for tendinosis is hypoxia[24], which is also suggested to be a factor behind trigger finger, as the tendon pathology is located in a watershed region where the blood supply may be deficient[9,31,32].

Ultrasonography of low grade trigger finger reveals an increase in tendon diameter without signs of internal structure changes of the tendon[10]. With increasing clinical severity the picture of the tendon structure present signs of increasing pathology. This is in good agreement with the continuum model for tendinosis[62,74], describing a progress of tendon pathology from reactive tendinopathy with tendon swelling through a phase of disrepair with increasing signs of pathology, to the final stage of degeneration.

One could ask if is it correct to say that trigger finger is a form of tendinosis as there are findings of pulley pathology. I consider it correct, based on our findings that have repeatedly indicated tendinosis-like changes (papers I, II, and IV)[13,14]. However, simultaneous pulley pathology would not falsify the tendinosis concept. Compression is a patho-aetiological factor[74] and theoretically a narrow pulley could lead to tendinosis. We have not investigated that.

The surgical method we used for taking tendon biopsies is a modification of a surgical procedure used for pulley-preserving trigger finger surgery, the reduction flexor tenoplasty[268]. The modification is that only a minor tissue sample, a tendon strip 10–15 mm long and 1–1.5 mm broad, is removed. We were aware of and informed the patients about a supposed increased risk for adverse advents such as adhesions or swelling. We left no foreign material inside the tendon sheath (e.g. sutures), and all patients had an uneventful recovery at the two-week follow-up. One question is whether our control biopsies were representative, and

whether they were harvested from tendons exposed to a pulley. They might not have been subjected to perpendicular forces. If so, the difference between our trigger finger biopsies and controls could be due to site, rather than disease. We harvested the control biopsies from flexor pollicis longus tendons, through a normal access for carpal tunnel release. With maximum flexion of the thumb, a proximal tendon excursion of about 2 cm is considered normal[269,270]. This provides acceptable access to the portion of the tendon exposed to the pulley[35]. In addition, outside the pulley there is a vascular network on the volar tendon surface[31,32] but we did not notice any difference in vascularity on the surface of the control tendons in comparison to the trigger finger tendons, indicating that they were harvested from tendons that were exposed to the pulley.

A possible objection concerning the mRNA expression pattern could be that it could be due to something other than tendinosis, for example perpendicular forces. We have not studied the coupling between mRNA expression patterns and pathogenesis, as we only looked for differences in mRNA expression between trigger fingers and controls. We found a different pattern and also similarities to what at that time was representative for Achilles tendinosis. Even if the objection above is correct, the difference between trigger finger tendons and normal tendons still exists, as do the similarities with Achilles tendinosis.

Do the diagnoses of tendinosis in the Achilles tendon and the shoulder really correspond to a histologically verified tendinosis? If one is absolutely stringent in the use of terms, the answer is no. However, the histological picture of tendinopathy is by definition called tendinosis[20]. It is estimated that tendinopathies are tendinoses and that the histopathological picture does not need to be stated in each case. We agree that the terminology is confusing.

Trigger finger resolves with surgical division of the A1-pulley. This is different from other forms of tendinosis that are not as easily treated. However, the triggering is the end point here, not the histological picture, the pain or the ultrasonographic findings as for other forms of tendinosis. It is also reported that 40% of operated trigger finger patients suffer from swelling, limited motion, motion pain and scar pain after triggering has resolved[215]. Some of these symptoms are perhaps explained by the healing process, but some may indicate persistent tendinosis. Tendinosis is not always coupled to pain[19], but for Achilles tendinosis, pain and impaired function lead to contact with health care and the goal for the treatment is mainly pain relief. However, the postoperative histological picture for trigger finger is not known and further answers will be speculative.

There are few human studies on histopathology in tendinosis of short duration, and knowledge about the temporal sequence of histological changes is limited[61,62]. More knowledge about early stages would provide direction as to the aetiology of tendinosis.

Trigger finger lends itself as a good tendinosis research model. The diagnosis is distinct in comparison to other tendinopathies such as a sore shoulder, and idiopathic trigger finger is easy to diagnose with few, if any differential diagnoses. Non-idiopathic trigger fingers are rather easily excluded. Trigger finger is a

common condition and we believe that it presents earlier in its course, in comparison to other tendinoses, due to the diameter mismatch and subsequent triggering that signals the condition. Patients are often operated on and good access to invasive research is provided. Biopsies might be achieved at various stages of the disease. However, ethical aspects and risk for adverse effects from additional procedures must be taken into consideration and of course discussed with the Regional Ethical Review Board and with the patients. The 'trigger finger tendinosis research model' opens up the possibility for future research on the pathogenesis of tendinosis, thus offering an alternative to research on animals.

The largest gain with my thesis - that there is tendinosis in trigger finger - however is that it allows us to start to apply and to study what is known in tendinosis on trigger finger and conversely. This concerns both treatment methods and what is known about aetiology.

CONCLUSIONS

There are histological signs of pathology in trigger finger flexor tendons that differ from normal tendons and resemble what is described for Achilles tendinosis.

There is a gene expression pattern in trigger finger flexor tendons that is different from normal tendons and resemble what is described for Achilles tendinosis.

The time from glucocorticoid injection to effect is, for the patients that experience resolution, within the first two weeks after a single injection.

Statin use seems to increase the risk of trigger finger and shoulder tendinosis.

Our results support the notion that there is tendinosis in idiopathic trigger finger.

ACKNOWLEDGEMENTS

Many people have contributed to this thesis indirectly or directly. I am grateful to all!

My thesis was carried out at:

The Division of Orthopaedics, Department of Clinical and Experimental Medicine (IKE), Faculty of Medicine and Health Sciences, Linköping University, Sweden

During employment at:

Dept. of Hand Surg. Plastic Surg. and Burns, Linköping University Hospital, Sweden
Dept. of Hand Surg. Sahlgrenska University Hospital, Gothenburg, Sweden
Dept. of Hand and Reconstructive Microsurg. Nat. Univ. Hospital, Singapore
Capio Vårdcentral Berga AB, Linköping, Sweden
HandCenter Linköping AB, Linköping, Sweden
Johannelunds vårdcentral AB, Linköping, Sweden

To all whom I have worked or work with, 'over' as well as 'under' nurses, administrative staff, occupational therapists, physiotherapists, colleagues, transportation guys, cleaners, podiatrists, receptionists, students, tutors and those whose profession I do not remember, thank you for support and encouragement, love and laughs, and for the education, practical tips and helping out.

And thank you **Stiftelsen Börje Gabrielssons minne** for great financial support over the years.

Special thanks to:

Professor **Per Aspenberg**, my supervisor, who patiently tutored me and presented solutions, wherever I have been. Describing a renaissance man in words is difficult... so I won't. Thank You Per!

Pernilla Eliasson, co-supervisor, for your support 24/7, and for all the time you have spent with me in the lab. Thank you for sharing your knowledge, for your friendship and all the fun.

Johann Zdolsek, co-supervisor and mentor, without you, I would not be here today, would not have been in Singapore, would certainly not had become a hand surgeon or married. Thank you for always believing in me just as I am.

Göran Nylander, co-supervisor, you are a great role model, full of energy, and always with the patient in focus. I thank you for your trust in me.

Therese Andersson, **Fredrik Agholme**, **Lotta Agholme**, **Anna Fahlgren**, **Anna Eriksson** and **Olof Sandberg**, for being inspiring and for making the work in the lab a pleasure.

Sandeep Sebastin and **Ryan Yak**, we were a fantastic trio, I've never worked so hard or learned so much in such a short time, though it is the friendship I remem-

ber the most. **Mr Peng**, **Dr Chong**, **Dr Lahiri**, **the staff**, **colleagues and friends at NUH**, I thank you all for letting me be one of you, for your humble strength and high ethical level. You always put the patient and others before yourselves.

Thank you. **Aymeric Lim**, you helped me see the light when it was dark. And **Ellen Lee Yutan**, who managed to translate all my cultural blunders and mitigate my mistakes, so that I could become a part of the department, and Singapore, could become my second home.

Karl Michaëlsson, thank you for making epidemiology beautiful.

Peter Söderqvist, **Anette Molbaek, Åsa Schippert** at 'cellbiologen', who helped me out with my first 'trembling research steps'. You are all professional, inspiring and down to earth. **Åsa** you fixed a job for my son, **Anette** 'your' rice porridge we still eat. and... **Birgitta Eriksson** my first co-supervisor, you gave me strength and… **Åsa Frediksson,** my research friend became my friend for ever.

Thank you professor **Bo Nordensköld**, for your support and high morale.

Lars-Erik Karlander and **Magnus Berggren,** brilliant hand surgeons and **Märta Eggerot** family doctor, you are all fantastic role models and supervisors. You are so inspiring.

Thomas Hansson, **Anders Nilsson**, **Ola Collin**, **Olof Tegsjö**, **Constance Lövefors** and **Susanne Svärm**, former chiefs, you all made it possible to be both clinically active and to do research… and **Susanne**, you are, and have done much more!

Kristina Willner, you once brought me into family medicine and became my friend. I lost hope in research but found it again - that it is thanks to you. I am happy to work under your leadership again.

Daniel Björk Wilhelms, you understand without words. I am grateful that we met and for our friendship.

To **all my other friends**, thank you for still being there though I am 'always' 'somewhere else'. Without you, life would be boring.

To my son-in-law **Andreas,** for all good films and consideration, and thank you dear **family-in-law** and brother-in-law **John** for inspiration.

Most of all, I want to thank my patient and exuberant family.

Sister **Stina** and nephew **Alexander** 'the evil'; if you hadn't told me to do something else but research sister… I am sure that I would have done so.

My parents, **John** and **Ann-Mari**, for everything and with great respect father, I would never had become a medical doctor if you hadn't questioned it.

Thea, **Joel** and **Börje**, You are the ones that really matter.

ABBREVIATIONS

A1-pulley	the first annular ligament or pulley
ADAMTS	a disintegrin and metalloproteinase with thrombospondin type I motif
CI	confidence interval
CRPS	complex regional pain syndrome
DIP	distal interphalangeal joint
DNA	deoxyribonucleic acid
FDP	flexor digitorum profundus tendon
FDS	flexor digitorum superficialis tendon
FPL	flexor pollicis longus tendon
GAG	glucoseaminoglycan
HbA1c	glycated hemoglobin
HLA-DR	a major histocompatibility complex class II cell surface receptor encoded by the human leukocyte antigen complex
HR	hazard ratio
IL	interleukin
MCP	metacarpophalangeal joint
MMP	matrix metalloproteinase
NSAID	non steroidal anti inflammatory drug
mRNA	messenger RNA
PIP	proximal interphalangeal joint
qPCR	quantitative real-time polymerase chain reaction
RNA	ribonucleic acid
TIMP	tissue inhibitors of metalloproteinase
TNFα	tumor necrosis factor alpha

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