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Chronic Tennis Elbow

Aspects on Pathogenesis and Treatment in a Soft Tissue Pain Condition

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Abstract

Peterson, M. 2011. Chronic Tennis Elbow: Aspects on Pathogenesis and Treatment in a Soft Tissue Pain Condition. Acta Universitatis Upsaliensis. *Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine* 712. 65 pp. Uppsala. ISBN 978-91-554-8187-2.

Objectives: To study the treatment practice of chronic tennis elbow (TE) among general practitioners (GPs) and physiotherapists (PTs), the effects of a simple, graded home exercise regime versus expectation, the effects of eccentric versus concentric exercise, and the involvement of the substance P – NK1 receptor system in the peripheral, painful tissue of chronic TE patients by positron emission tomography (PET).

Materials and methods: A postal survey regarding therapeutic methods used in patients with chronic TE was sent to 129 GPs and 77 PTs, 81 subjects with chronic TE were randomly and blindly assigned to either an exercise group or a wait list group, 120 subjects were randomly assigned to either eccentric or concentric exercise and ten subjects were examined by PET and the NK1 specific radioligand [11C]GR205171.

Results: High proportions of GPs and PTs used ergonomic counselling and stretching in the treatment of chronic TE. The majority of GPs prescribed passive anti-inflammatory measures such as sick leave and anti-inflammatory medication. Many PTs prescribed dynamic, particularly eccentric, exercise. Graded dynamic exercise according to a simple low-cost protocol, has better effect on pain than a wait-and-see attitude. Adjusted for outcome affecting variables, eccentric graded exercise has quicker effect than concentric graded exercise. During PET scan with the NK1 specific radioligand [11C]GR205171, voxel volume and signal intensity of this volume was significantly higher in the affected than the unaffected arm in subjects with unilateral chronic TE.

Conclusions: GPs and PTs used many treatments to a similar extent but differed regarding the use of exercise. Chronic TE responds favourably to graded dynamic exercise aimed specifically at the painful tissue. The exercise should stress the eccentric work phase. The substance P – NK1 receptor system seems to play a part in the peripheral, painful tissue of a chronic, soft tissue pain condition such as chronic TE.

Keywords: tennis elbow, pain, chronic, soft tissue, imaging, PET, RCT, survey, treatment, exercise, eccentric, concentric, epicondylosis, epicondylitis, tendinosis, tendinitis

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Gymnastiken

är en uppfinning, som, rätt brukad, beröfvar skolungdomen en half timma af frukostlofvet. Detta är dock icke dess enda betydelse, ty gymnastiken stärker äfven blodsystemet, uppfriskar hjertverksamheten, höjer menniskan från jorden (genom trapez), och är mycket lifsfarlig.

Svensken Ling var den förste, som upptäckte att ett hastigt uppsträckande af armarne (eller evenuelt ett vridande till venster af hufvudet), är ett lifsvilkor för hvarje sundt tänkande menniska. Härefter bildades gymnastikföreningar, som vidare fortplantade denna vackra idé, hvilken för närvarande är vårt lands stolthet.

Den, som skrifvit dessa rader, har endast genom gymnastik förvärfvat den fruktansvärda kroppsstyrka, som nu gör det för honom möjligt att med en viss skadeglädje emotse hvarje försök till kritik öfver denna bok.

Fakir, F: En hvar sin egen professor

List of Papers

This thesis is based on the following papers, which are referred to in the text by their Roman numerals.

I Peterson M, Elmfeldt D, Svärdsudd K. (2005) Treatment practice in chronic epicondylitis: A survey among general practitioners and physiotherapists in Uppsala County, Sweden. *Scand J Prim Health Care*, 23:239–241.

II Peterson M, Butler S, Eriksson M, Svärdsudd K. A randomized controlled trial of exercise versus wait list in chronic tennis elbow (lateral epicondylosis). *Ups J Med Sci* in press.

III Peterson M, Butler S, Eriksson M, Svärdsudd K. A randomised controlled trial of eccentric versus concentric exercise in chronic tennis elbow (lateral epicondylosis). Submitted.

IV Peterson M, Svärdsudd K, Appel L, Engler H, Långström B, Sörensen J. PET-scan shows peripherally increased neurokinin 1 receptor availability in chronic tennis elbow - a picture of neurogenic inflammation? Submitted.

Contents

Abbreviations

AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CI	Confidence interval
CGRP	Calcitonin gene-related peptide
CNS	Central nervous system
DASH	Disabilities of the arm, shoulder, hand
e.g.	exemplia gratia (for example)
FGF	Fibroblast growth factor
fMRI	Functional magnetic resonance imaging
GP	General practitioner
GQL	Gothenburg quality of life
i.e.	id est (that is)
IGF-1	Insulin-like growth factor 1
IL-1β	Interleukin 1 beta
MME	Maximum muscle elongation
MMP	Matrix metalloproteinase
MVC	Maximum voluntary contraction
NGF	Nerve growth factor
NK1	Neurokinin 1
NKA	Neurokinin A
NMDA	N-methyl D-aspartate
NSAID	Non-steroidal anti-inflammatory drug
OSEM	Ordered subset expectation maximization
PET	Positron emission tomography
PNS	Peripheral nervous system
PT	Physiotherapist
SAS	Statistical analysis system
SEK	The Swedish Krona
SBU	The Swedish council on technology assessment in health care
TE	Tennis elbow
TENS	Transcutaneous electrical nerve stimulation
TGF-β	Transforming growth factor beta
Trk-A	Tropomyosin-receptor kinase A
TSC	Tendon stem cell
VAS	Visual analogue scale

Prologue

Early in my professional career in medicine, taking my first, sometimes rather shaky steps as a general practitioner, I was struck by the number of patients consulting me about their aches and pains from tendons, muscles and their skeletal insertions. Often these patients were quite young and the problems seemed to be the result of manual labour.

Consulting the literature left me with just about one single diagnosis, tendinitis, implying inflammatory origin, no matter how long the history of the condition was. Injection of steroids or medication with non-steroidal anti-inflammatory drugs, NSAIDs, was to be the cure. When I suggested this treatment to one of my patients, an electrician, on his return visit he gave me a doubtful look. After over a year of work-related pain from tendons he had received steroid injections several times and had taken NSAIDs until gastritis became a bigger problem than his tendon pain. Could I really not come up with anything better?

It seemed apparent to me, that a long-standing pain condition from tendons and muscle insertions could not be treated as an acute inflammatory condition, at least not in the way the textbook suggested according to the presumed pathology of tendinitis. This moment of realization led me on a long journey of extended clinical training, courses and ultimately this research project.

I hope that this thesis will shed some light on the intricacies of this common but still relatively unexplored pain condition.

Introduction

Pain

Pain is defined by the International Association for the Study of Pain as: 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [1]. This definition carefully pays thorough respect to the subjective experience of pain. Pain is an individual sensation, accompanied by individual emotions and thoughts, which leaves an individual memory and affects the future behaviour of the individual. This definition also means that the subjective experience of pain should be acknowledged even in the absence of verifiable tissue damage [1].

The sensation of acute pain is probably one of the most important aspects of survival in both the evolutionary and individual perspective [2]. In human beings, evolution has provided several upgraded and refined versions of sensory systems for pain, working alongside each other [2]. This leaves a robust and quite complex system for the sensation, regulation, processing of and reactions to acute pain. Learning in relation to the processing of pain provides an evolutionary advantage whereby situations that pose a threat of tissue damage can be avoided [3]. As a result, people adapt their behaviour to handle similar situations as they arise.

In contrast, chronic pain, defined as pain persisting beyond the normal time of tissue healing, often estimated to more than three or six months [4], constitutes an enigma from an evolutionary perspective. Is the learning aspect in relation to pain so important that a constant reminder provides an evolutionary advantage? Does chronic pain represent incomplete tissue healing? Or is it just a flaw in the human construction that the sensation of acute pain, so important for survival, sometimes fails to subside in spite of the body having finished its healing response?

Chronic pain has detrimental effects on mood, thoughts, behaviour, relationships, working life and financial status, from the individual as well as the societal perspective [5]. Prevalence of chronic pain in the population is estimated to be 20-50 percent, depending on the definitions of duration, frequency and severity [5-7]. Based on the epidemiological survey 'Pain In Europe', the Swedish Council on Technology Assessment in Health Care (SBU) estimated societal costs to 2.5 % of the annual gross domestic product [5, 8]. In Sweden in 2011, this corresponds to SEK 100 billion. Chronic pain, in other words, poses a great human and socioeconomic challenge [6].

The history of musculoskeletal pain

The sixteenth century French physician Ballonius, described a state of pain from muscles and joints, which he named 'rheumatism' [9, 10]. Rheuma means flow, and the ideas of Ballonius were based on the theories introduced by Hippocrates, later developed by Galen, of four essential fluids in the body, sanguis (blood), phlegm, chole (yellow bile) and melan chole (black bile). Illness was believed to be caused by imbalances or mismatches among these fluids. Treatment consisted, among other things, of cupping and bloodletting. The concept of 'rheumatism' evolved, and physicians in the following centuries divided rheumatism into articular rheumatism and muscular rheumatism [9]. For several hundred years and well into the nineteenth century, pain from the soft tissue of the locomotor system was generally referred to as muscular rheumatism [9].

In the nineteenth century, hypotheses evolved concerning an inflammatory rather than fluidal pathology for both articular and muscular rheumatism [9, 11]. As scientific laboratory methodology developed, the pathophysiological mechanisms underpinning articular rheumatism could successively be pinpointed and mechanism-based interventions followed. For muscular rheumatism, however, no inflammatory pathology could be detected and the general term 'muscular rheumatism' gave way to 'fibrositis' and later 'fibromyalgia' during the twentieth century [9, 11]. The latter term eventually received a definition of its own.

Soft tissue musculoskeletal pain

Musculoskeletal pain is a broad descriptive term, essentially meaning pain from the locomotor system [12]. This collective term works well for epidemiological purposes. Excluding skeletal pain from the definition, meaning the soft tissue (*i.e.* muscles and tendons) of the locomotor system, however, the definition becomes far more vague, and epidemiological data are scarce. This is probably owing to the lack of consensus regarding the terminology for soft tissue pain, which makes epidemiological definition of cases difficult. Unlike skeletal pain, where the evolution of diagnostic tools such as X-ray and sedimentation rate have allowed for diagnoses based on pathophysiological mechanisms, soft tissue pain of the locomotor system more or less lacks diagnostic tools and depends primarily on clinical examination.

Diagnoses relating to locomotor soft tissue are often merely descriptive, such as myofascial pain, myalgia, tendinopathy or lumbago, and are often categorized or explained as 'syndromes' *e.g.* 'myofascial pain syndrome', 'fibromyalgia syndrome', and 'complex regional pain syndrome'. Descriptive diagnoses often become stigmatizing owing to the lack of understanding of pathophysiological mechanisms. Whereas mechanism-based diagnoses allow for treatment aimed at affecting the mechanisms of pathology, (also known as mechanism-based treatment), descriptive diagnoses lead to empirical treatment, also known as 'trial and error'. Empirical treatment is often associated with strong beliefs in spite of an absence of scientific evidence. It is important that these treatments be scientifically evaluated. It is also important to develop scientific equipment that allows for mechanism-based diagnoses relating to the soft tissue of the locomotor system. Only then will it be possible to develop mechanism-based treatments for soft tissue musculoskeletal pain.

Tendon pain

Pain from tendons and tendinous muscle insertions is a subgroup of musculoskeletal pain. It is a common reason for consultations in all outpatient settings. There is very little epidemiological data on prevalence and incidence of tendon pain in general, due to a lack of consensus regarding the terminology of tendon pain in various locations and durations. Recently a collective term, 'tendinopathy', has been suggested [13].

Common locations for tendon pain are the Achilles tendon, patellar tendon and lateral elbow. Prevalence of pain from the Achilles tendon is estimated to 7-11% of all runners [14, 15]. In the general population, prevalence could be estimated to about half that, based on the fact that about one third of sufferers have a more sedentary lifestyle [15]. The incidence of tendon pain from the lateral elbow is 1-3% in the population [16, 17]. Peak prevalence of Achilles and lateral elbow tendon pain is between 35 and 45 years of age [15, 17]. The cause is primarily repetitive overuse with the following bio-mechanical risk factors acknowledged in sports as well as in industrial labour: excessive duration, heavy load, poor technique, poor ergonomics and poor equipment [18, 19]. Other, intrinsic, risk factors are genetic variances in collagen or glycoprotein tenascin C, metabolic diseases such as diabetes, obesity, hyperthyroidism, hyperparathyroidism and rheumatologic disorders such as rheumatoid arthritis, systemic lupus erythematosus and psoriasis. Medication with fluoroquinolone antibiotics is associated with chronic tendon pain, and an association between tendon pain and statins, as well as oral contraceptives, has been proposed [18].

Tendinitis versus tendinosis

The acute stage of tendon pain comprises prostaglandin mediated inflammatory processes and is accordingly termed tendinitis. During the first 24 hours, resident immune cells such as macrophages and mast cells predominate. Vasoactive factors and cytokines that mediate vascular leakage and migration of leucocytes, primarily neutrophils, towards the inflammatory site are released [20-23]. Prostaglandins and leukotrienes are produced and activation of the complement system occurs, as well as excitation and sensitization of sensory nerves, peripheral as well as central.

The inflammatory phase is followed by a proliferation phase, when resident fibroblasts increase their production of collagen [24]. Degradation of tissue, primarily by enzymes such as matrix metalloproteinases, is also increased, resulting in an overall increase of matrix turnover [25]. The overall tissue turnover favours anabolic processes resulting in overall increase of tendon tissue and increased mechanical strength.

The proliferation phase is followed by maturation and remodelling of the tendon tissue, which can take months or up to a year. During this time, cross-linking among collagen fibres is increased and tensile strength, elasticity and the structure of the tendon are all modified [25] These are the normal physiological stages of tendon repair as studied in experimental animal research. Many of these processes have also been confirmed in humans.

Tendon pain often persists or recurs beyond the normal time for healing [14] . Up to 20% of lateral elbow cases may persist after one year [26, 27]. In this, chronic stage (defined here as lasting more than three months), histological samples show very few inflammatory changes but instead patches of degenerative tissue consisting of calcification, mucoid tissue, lipids, fibrocartilage and disruption of the normally homogenous alignment of collagen [28]. Increased numbers of nerves and capillaries have also been noted [29]. Hence, it has been suggested that this stage of tendon pain should be referred to as tendinosis [30].

In clinical practice, however, it has been common not to distinguish between the acute and chronic stages of tendon pain. Thus treatment has generally been aimed at reducing acute, prostaglandin mediated inflammation in both the acute and the chronic stage of tendon pain. Treatment as suggested in the literature consists of rest, NSAIDs, and local injections of steroids. In fact, there is now convincing evidence that local injection of steroids only provides temporary pain relief and actually worsens clinical outcome in the long term (6-12 months) [31-34].

The pathophysiology of tendinosis

The extracellular matrix of tendinosis tendons clearly differs from that of normal tendons. The normal tendon consists of connective tissue dominated by symmetrically organized collagen, water, proteoglycans and glycoproteins. The collagen and the proteins are produced by fibroblasts interspersed in the tissue. The normal tendon can withstand considerable tensile force and its strength is reinforced by intramolecular and intermolecular crosslinks. In tendinosis the collagen orientation is irregular, interspersed with calcifications, cartilage, fibrosis, hypervascularization and increased innervation [28, 29]. The proportion of collagen type I decreases, in favour of the less durable collagen type III [25].

The fibroblasts of the normal tendon respond to stretching and deformation, known as mechano-transduction, with increased collagen turnover consisting of simultaneous synthesis and degradation, accompanied by release of tissue growth factors such as IGF-I, TGF-β and FGF along with inflammatory mediators such as prostaglandins, bradykinin, adenosine, IL-6 and IL-1β [25]. The increased matrix turnover results in a net synthesis of collagen in response to loading. This increase in tissue quantity and quality improves tissue strength and force transmission.

In contrast, decreased levels of matrix metalloproteinases such as MMP-3, impair the matrix turnover in tendinosis. The tendinosis tissue also seems to respond to loading with exaggerated production of prostaglandins [35]. In addition, there are reports in tendinosis of increased levels of neuropeptides such as glutamate, substance P, along with NMDA and neurokinin 1 (NK1) receptors [36-38] in the affected tissue, which may be part of peripheral sensitization.

The fibroblasts in tendons are supported by a pool of tendon stem cells (TSC) that differentiate into fibroblasts in response to stretching or deformation [39]. Interestingly, over-stretch of TSC and high levels of prostaglandin E2 both result in differentiation of TSC into bone, fat and cartilage cells rather than fibroblasts [39]. This may be part of the pathophysiological explanation for the degenerative findings in tendinosis.

An acute inflammatory process attracts angiogenesis along with nerve sprouting [40-42] related to release of growth factors such as vascular endothelial growth factor [43] which, in the normal healing process, subsides over time [40]. A halted inflammatory process, as suggested by the impaired matrix turnover hypothesis, may explain why the tendinosis-affected tendon contains elements of hypervascularity and hyperinnervation.

The substance P – neurokinin 1 receptor system

Sensitization of the peripheral nerves leads not only to increased excitability but also to endogenous production and subsequent release of neurotransmitters such as substance P, neurokinin A (NKA) and calcitonin gene related peptide (CGRP). Peripheral C-nociceptors may be sub-grouped into peptidergic and non-peptidergic. The peptidergic nociceptors primarily use substance P and CGRP as signalling molecules, whereas the non-peptidergic nociceptors primarily use glutamate. Substance P is an eleven amino acid long polypeptide which, along with NKA, belongs to a group of mammalian peptides called tachykinins [44]. Most of the substance P will be released by the peripheral end of the peptidergic nociceptors, where it stimulates the inflammatory cascade [45, 46].

The primary receptor for substance P is the NK1 receptor. It is widely distributed in the central nervous system but has also been identified on or in immunologic cells, fibroblasts, tenocytes, endothelial cells, synovial cells, keratinocytes and osteoclasts [37, 47, 48]. 'New' substance P-like peptides (Hemokinin 1, Endokinin A/B) have been identified in non-neural cells from immune, endothelial and placenta tissue [49]. They, too, seem to act on the NK1 receptor, which makes the cellular interaction even more intricate. NK1 receptor mRNA increases significantly, in the dorsal horn as well as in peripheral tissue, in response to peripherally induced inflammation [50].

Exercise

The Swede Per Henrik Ling (1776-1839) proposed exercise as treatment for various medical conditions and elaborated a system of medical gymnastics to promote better health. He obtained permission in 1813 to open the Royal Gymnastic Central Institute, for the training of gymnastics instructors in the treatment of various medical ailments by physical exercise, massage and manoeuvres. This was the first centre in the world for the training of physiotherapists. Ling was interested in the effects of eccentric movements (*i.e.* work during elongation of the muscle) but used the term in a different sense – eccentric meaning flaccid movements with peripheral direction [51].

Eccentric exercise as treatment for tendon pain was proposed by Stanish and Curwin [52] based on observations by Komi [53] that decelerating movements (*i.e.* eccentric loading) were particularly prone to inducing pain in individuals with tendinosis in various locations. As forces causing eccentric movements often exceeds forces in concentric and isometric movements, Stanish and Curwin hypothesized that the tendon is not of sufficient strength to meet the demands of the eccentrically applied forces [52] resulting in microruptures or gross internal tearing. To better prepare the tendon for eccentric stress they proposed a strength training programme tailored to the specific tasks required, in other words a strength training programme containing eccentric loading. In 1992 Niesen-Vertommen developed this concept into a treatment protocol for Achilles tendinosis for a randomized controlled trial. Alfredson further developed the concept and, together with various co-workers, devoted extensive effort to developing and studying the effects of eccentric exercise on tendinosis. Generally, their treatment protocols follow a pattern of eccentric exercise for twelve weeks with gradually increasing load. This pattern of graded exercise is conceptually different from, but in practice has many similarities to 'graded activity' of operant behavioural therapy [3, 54] and 'graded exposure' of cognitive behavioural therapy [55, 56]. This means that the effects may not solely be related to the tissue being exercised, but that psychological mechanisms also may be involved in the treatment effects.

Whether eccentric graded exercise is superior to conventional concentric graded exercise (i.e. lifting weights according to a graded protocol), or a combination of both, has been a matter of debate [57, 58].

Tennis Elbow

Pain from the common tendinous origin of the forearm extensor muscles on the lateral elbow, traditionally known as tennis elbow (TE) is a common location of tendon pain. The incidence rate is estimated to 1-3% per year with a peak prevalence of 6.5% between 40 and 50 years of age [17, 19]. Most of the incidents heal within three months but about one third have a more protracted course and an estimated 17% of all cases still have symptoms after one year [27]. The causal factor is primarily repetitive strain, and heavy manual labour increases the risk of being affected [17, 19].

Inflammation has been considered the causal factor with no distinction being made between the acute and the chronic stages of TE. Thus, lateral epicondylitis has been used as a synonym for TE. It has now become clear that this term should be reserved for the acute stage of TE. A preferable term for the chronic stage is lateral epicondylosis. For clarity, the term chronic TE will, however, be used in the following text. Histological samples from this chronic stage show patchy degenerative findings along with increased amounts of nerves, capillaries, neural peptides and receptors similar to other locations of tendinosis [29, 36, 59].

Treatments are traditionally aimed at reducing inflammation by rest, NSAIDs or local injections of steroid, or just based on empirical methods such as ultrasound, friction massage, braces, orthoses or injections of various substances. This wide variety of treatments is probably attributable to the lack of understanding of the pathophysiological mechanisms of TE. More than 30 different treatments for TE have been documented in the literature. Most of these have not been adequately evaluated but are based on beliefs or empiricism only.

Aims

Starting from the recognition that the acute and chronic stages of tendon pain have different mechanisms of pathology and that diagnostic terminology as well as treatment should differ between the stages, this thesis set out to: First, survey the current treatment practice of chronic TE (Paper I). Second, develop a simplified protocol for graded exercise of the forearm extensor muscles and their insertions on the lateral epicondyles, which could be performed at home without involvement of costly equipment or personnel (Paper II). Third, examine whether there are differences in treatment effects between eccentric and concentric graded exercise (Paper III) and fourth, to investigate if pathologic mechanisms related to the peripheral nervous system (PNS) possibly involved in chronic TE, such as an up-regulation of the substance P – NK1 receptor system, could be visualized by positron emission tomography (PET) (Paper IV).

Specific aims

- to study the treatment practice of chronic TE among general practitioners (GPs) and physiotherapists (PTs) in Uppsala county,
- to study the effects of a simple, graded home exercise regime versus expectation on pain, muscle strength and quality of life in chronic TE patients,
- to study the effects of an eccentric versus concentric exercise regime on pain, muscle strength and quality of life in chronic TE patients,
- to study the involvement of the substance P – NK1 receptor system in the peripheral, painful tissue of chronic TE patients by PET.

Study population and methods

Paper I

Study population

The survey was carried out in Uppsala County, Sweden, located north of Stockholm and consisting of both urban and rural areas, with the city of Uppsala as the main centre. A postal questionnaire regarding therapeutic methods used in patients with chronic TE was sent to all 129 GPs and all 77 PTs working in 35 primary health care centres within a radius of approximately 60 kilometres from Uppsala. Ninety (69.8%) GPs and 47 (61.0%) PTs returned the questionnaire. No reminders were sent to non-responders.

Methods

The recipients were asked to respond to the question 'How would you treat a patient with tennis elbow of more than three months' duration?' by ticking one or more of the following five given alternatives: ergonomic counselling, stretching, acupuncture, orthotic devices or trans-cutaneous electric nerve stimulation (TENS), and a number of open-ended alternatives where any other method(s) used could be listed. In addition, GPs were asked to indicate the use of NSAIDs, cortisone injections and prescribed sick leave.

Papers II and III

Study population

The studies were performed in the city of Uppsala, Sweden. All 150 GPs and 90 PTs at primary health care centres in Uppsala County were asked for information on subjects with long lasting TE. In addition, subjects with TE symptoms were invited to participate in the studies through advertisements in the main local newspaper in order to recruit a sufficiently large number of subjects.

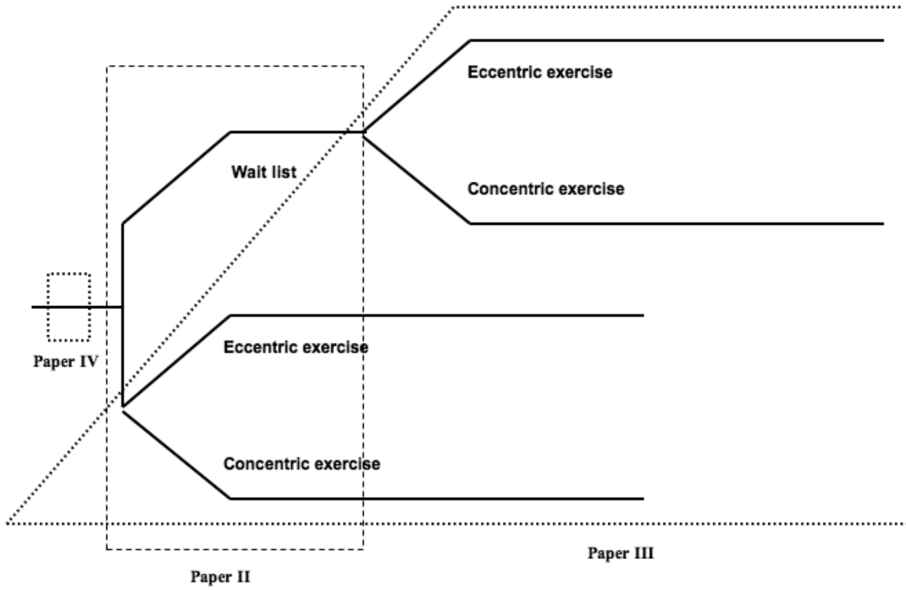

Figure 1. Graphic representation of study design in Papers II, III and IV

Inclusion criteria were age 20-75, symptoms of TE for more than three months, and a verified diagnosis. Exclusion criteria were any of concomitant supinator syndrome, compartment syndrome of musculus anconeus, rhizopathy, inflammatory joint disease, fibromyalgia, previous elbow surgery, and inability to understand Swedish. At a first appointment, the diagnosis was checked by pain on palpation, pain on stretching (Mill's test), pain on loading (maximum voluntary contraction, MVC) and Maudsley's middle finger test, by the same physician, a general practitioner and pain specialist.

Study design

The study population of Paper II was nested in that of Paper III (Figure 1). For the study of Paper III, subjects were assessed for participation from 15 October, 2003 to 18 October, 2006. From 23 December, 2004 subjects were also assessed for participation in the study of Paper II. One hundred and eleven subjects were evaluated, 30 of whom were excluded owing to incorrect diagnosis, other concomitant pain diagnoses or interfering treatment, leaving 81 as the final study population (Figure 3).

For Paper III, 173 subjects were evaluated, 53 of whom were excluded owing to incorrect diagnosis, other concomitant pain diagnoses or interfering treatment, leaving 120 subjects as the final study population (Figure 3). For Paper III an *a priori* power calculation was done based on results from previous studies of chronic Achilles tendinitis and chronic TE comparing two active treatments. For Paper II no *a priori* power analysis was done since the length of the recruitment period was determined by the power analysis of Paper III. A *post hoc* power analysis for Paper II showed 80% power for the pain variables with the actual study population size. All subjects gave written informed consent before entering the study. The Regional Research Ethics Board in Uppsala approved the study.

Randomization procedure

In Paper II the subjects were randomly and blindly assigned to either an exercise group consisting of pooled concentric and eccentric exercise (n=40) or a wait list (reference) group (n=41) by means of a random block design. The SAS 'ranuni' function, generating random numbers with equal probability distribution, was programmed so that for each consecutive four participants, two were randomly allocated to the exercise group and two to the reference group.

In Paper III the subjects were randomly assigned to eccentric (n=60) or concentric exercise (n=60) by means of a random block design similar to that of Paper II. For each four consecutive participants, two were randomly allocated to the eccentric group and two to the concentric group.

Intervention

In Paper II the reference group was informed that the condition was painful but harmless, that the arm should be used in ordinary daily activities, and the recommendation was to 'wait and see'. The exercise group received the same information except that the recommendation to 'wait and see' was replaced with a three-month daily exercise regime performed at home, with progressively increasing load on the extensor muscles of the affected forearm.

In Paper III both groups received an exercise regime to be performed at home for three months with progressively increasing load on the affected forearm extensor muscles. The eccentric exercise group was instructed to lower the weight with the affected arm and to lift it back up again with the unaffected arm, while the concentric group was instructed to lift the weight with the affected arm and to lower it back again with the unaffected arm.

In both papers the loading equipment consisted of a plastic water container with a handle. The initial load was standardized to 1 kilogram (one litre of water) for women and 2 kilograms for men. The participants sat in a chair and supported the forearm on the armrest or on an adjacent table. Holding the handle of the plastic water container with a clenched fist in pronation and

Figure 2. Photograph showing exercise set-up with the patient seated in an armchair with forearm support, holding the weight (a plastic container with a specified amount of water) in the affected arm, and performing exercise by lifting and lowering the container

the container hanging freely in front of the armchair or below the table top (Figure 2), the load was lifted or lowered in three sets of 15 repetitions, 45 in total, once daily. The load was increased weekly by one hectogram (one decilitre of water). The subjects were asked to report other competing treatments and were instructed not to use pain relieving or anti-inflammatory medication other than paracetamol. Adherence to instructions and the intervention programme was monitored. Mean participation rate in the follow-up visits was 94% (96% in the eccentric and 92% in the concentric exercise group), and mean participation rate in the exercise programme was 93% (95% in the eccentric and 92% in the concentric exercise group). The same observer did all measurements. Since the observer also gave instructions about the exercise, no blinded data collection was possible.

Data collection

In Paper II data were collected at baseline and at three follow-up appointments at one, two and three months after the baseline visit (Figure 3). In Paper III data were collected at baseline and at five follow-up appointments

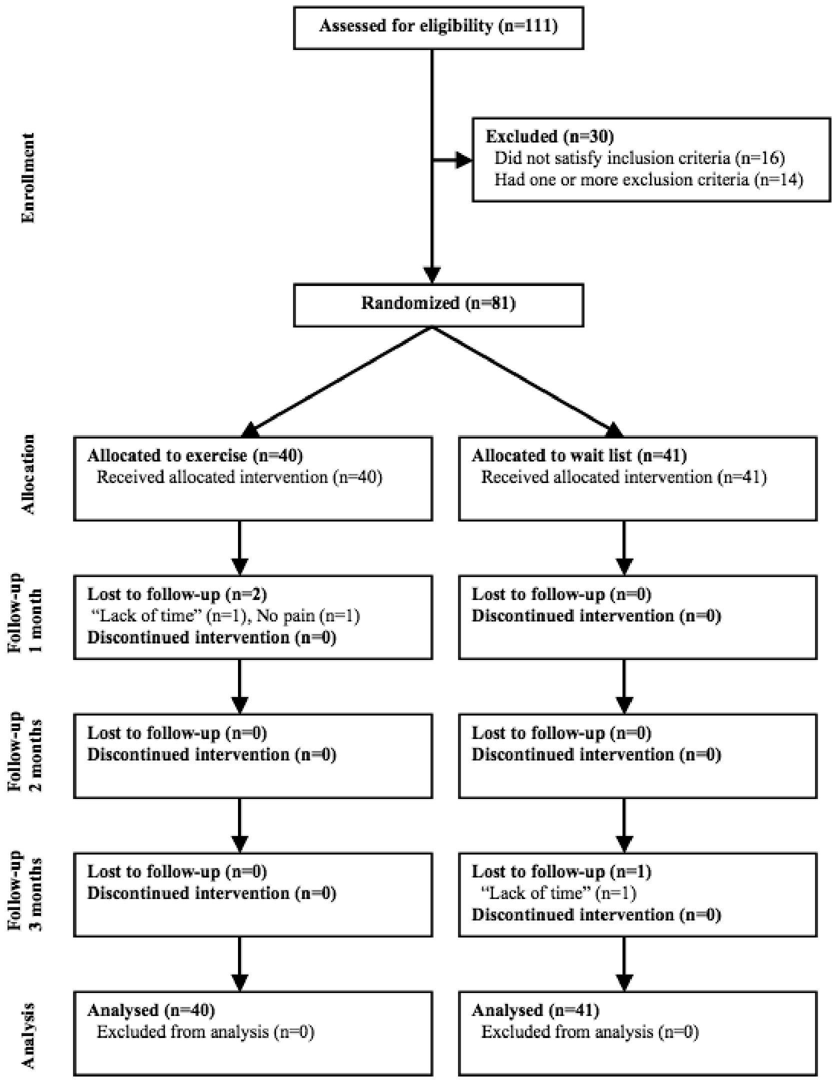

Figure 3. Flow chart of Paper II

at one, two, three, six and twelve months after the baseline appointment (Figure 4).

At baseline, information was collected regarding age, sex, educational level, marital status, smoking habits, TE history and previous treatments

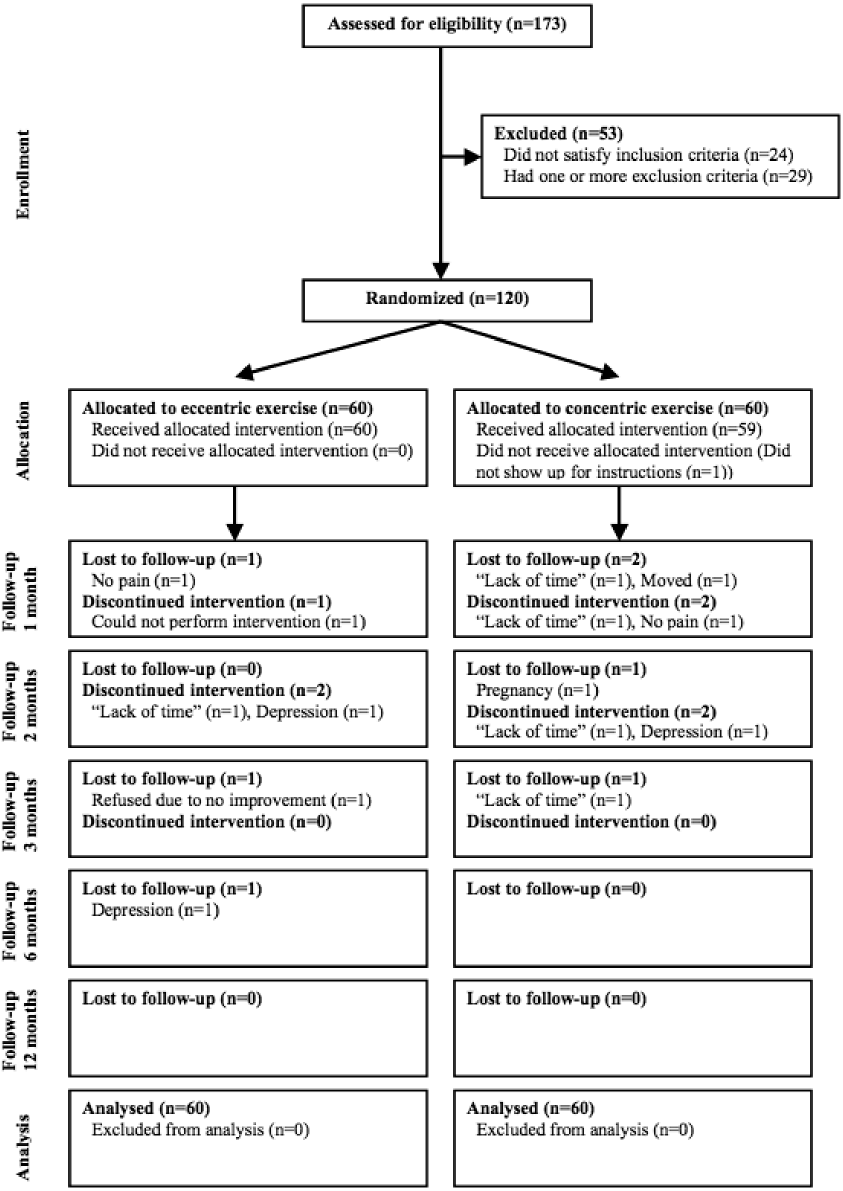

Figure 4. Flow chart of Paper III

given during the current episode. Education was classified on a four-point scale ranging from compulsory education only to college or university education. Marital status was classified as never married, married or cohabiting, divorced, or widowed. Smoking habits were classified as never smoked, exsmoker, currently smoking 1-14 cigarettes/day, 15-24 cigarettes/day, or 25 or more cigarettes/day [60]. The TE history included number of previous episodes, time since last episode, and duration of the present one. Information on previous treatments during the current episode was given in a free text format.

The primary outcome in Papers II and III, pain, was measured at all visits with two 100 millimetre Visual Analogue Scales (VAS) ranging from 'no pain' (=0) to 'worst imaginable pain' (=100). The first scale measured pain during maximum voluntary contraction (MVC) of the forearm extensor muscles (Cozen's test). The second scale measured pain during maximum muscle elongation (MME) of the extensor carpi radialis brevis and longus muscles with a load (90° abduction of the arm followed by full pronation of the forearm with a 3-kilogram dumbbell, i.e., a modified empty can test). Both pain measures were developed in cooperation with an experienced hand surgeon to simulate the most accurate pain provoking manoeuvres in TE. Based on the six measurements per subject across the study period in Paper III, the coefficient of variation for pain during MVC, adjusted for the effect of time, was 16.7%, and for pain during MME 12.5%.

The secondary outcome, muscle strength of the forearm extensor muscles, was also measured at all visits using a Chatillon MSE 100 hand-held dynamometer (arm positioned as in the MVC pain score above). An analysis of repeated muscle strength measurements in three volunteers by three observers gave a coefficient of variation of 8.2% after adjustment for observer effect, similar to previous assessments of test-retest and inter-rater reliability concerning hand-held dynamometry [61, 62].

The tertiary outcomes, general arm function and quality of life aspects, were measured at baseline, and after three months in Paper II, and at baseline and after three, six, and twelve months in Paper III, with the Disability of Arm, Shoulder, and Hand questionnaire (DASH) and the Gothenburg Quality of Life Instrument (GQL) questionnaires. DASH contains 30 questions on the ability to perform activities using a five-point Likert scale ranging from 'no problem' to 'impossible'. Responses were summarised and standardised so that the sum score, indicating overall degree of restriction, ranged from 0 to 100, low scores indicating a low degree of restriction. GQL with its three sub-scales Complaint score, Well-being score and Activity score, was used to measure quality of life aspects [63-65]. The instrument has been validated in various study populations and is widely used. The-Complaint score lists 30 general symptoms. The respondents were asked to indicate which of these they had experienced during the last three months, with possible responses 'yes' or 'no'. The Well-being sub-scale has nine items, of which self-rated health was used for this report. The response was given on a seven-point Likert scale ranging from 'very bad' to 'excellent, could not be better', with no verbal description of the intervening steps. The Activity score lists 32 specified leisure time activities and two open alternatives, covering six areas. The subjects were asked to indicate which of these activities they had performed during the last year with response alternatives 'never' (=0), 'occasionally' (=1) and 'often or regularly' (=2). The score was summed to an overall activity score, high scores indicating an active life-style.

Paper IV

Study population

The study population was recruited from that of Paper III (Figure 1). Subjects in Paper III were consecutively invited to participate in the PET study until ten had accepted. Exclusion criteria for the PET study were any of: current medication interfering with the nervous or inflammatory system, substance abuse, pregnancy, recent or planned participation in another PET study, X-ray or other significant exposure to radiation, bilateral symptoms or other pain diagnosis of the upper extremities (Figure 5). All subjects gave written informed consent before entering the study. The Regional Research Ethics Board and the Radiation Safety Committee in Uppsala approved the study.

PET examination procedure

The PET study was performed before commencement of the exercise protocol in Paper III. Prior to scanning, all participants refrained from analgesics for one day and anti-inflammatory drugs for three days. They also abstained from tobacco, alcohol and caffeine for twelve hours before, and from food for three hours before PET investigations.

Examinations were performed with the NK1 specific radioligand [11C]GR205171. The radioligand was synthesized according to standard manufacturing procedures and previously published methods [66] at the chemistry section of the Uppsala PET centre. The scanning procedure was executed with a Siemens ECAT EXACT HR+ whole body tomograph (CTI, Knoxville, TN, USA). The scanner enables acquisition of 63 contiguous planes of data with 2.46 mm plane spacing resulting in a total axial field of view of 155 mm.

Subjects were placed in prone position in the scanner with arms stretched above the head and gently fixated, so that the elbow joints of both arms were

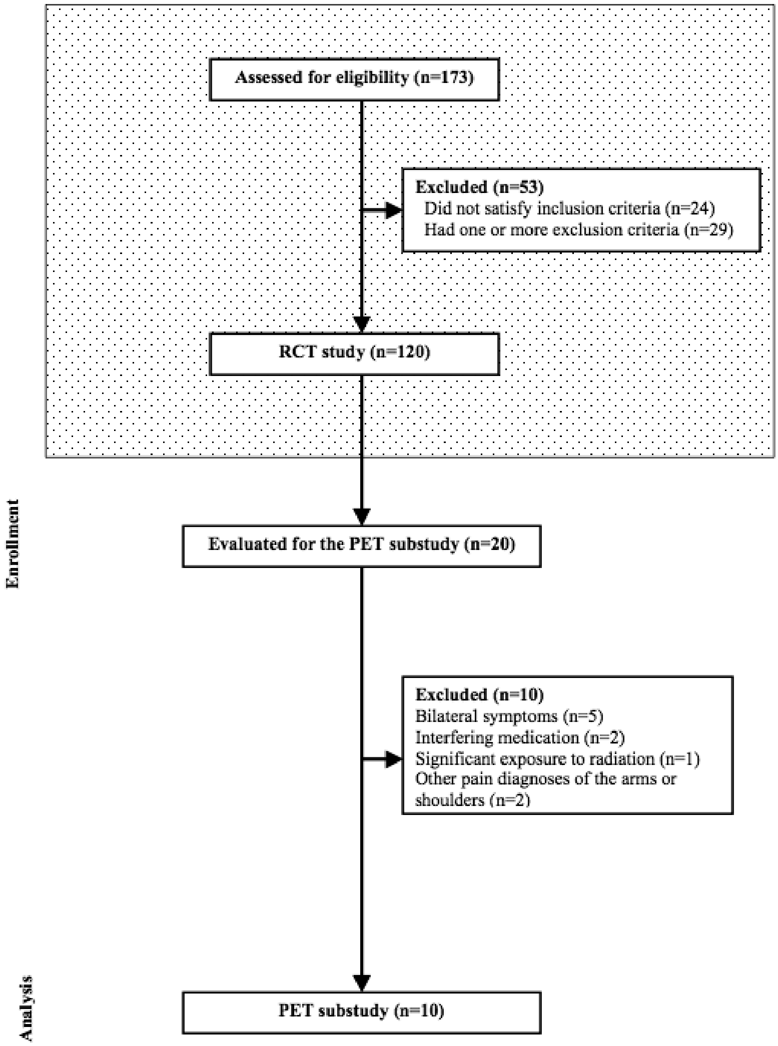

Figure 5. Flow chart of Paper IV

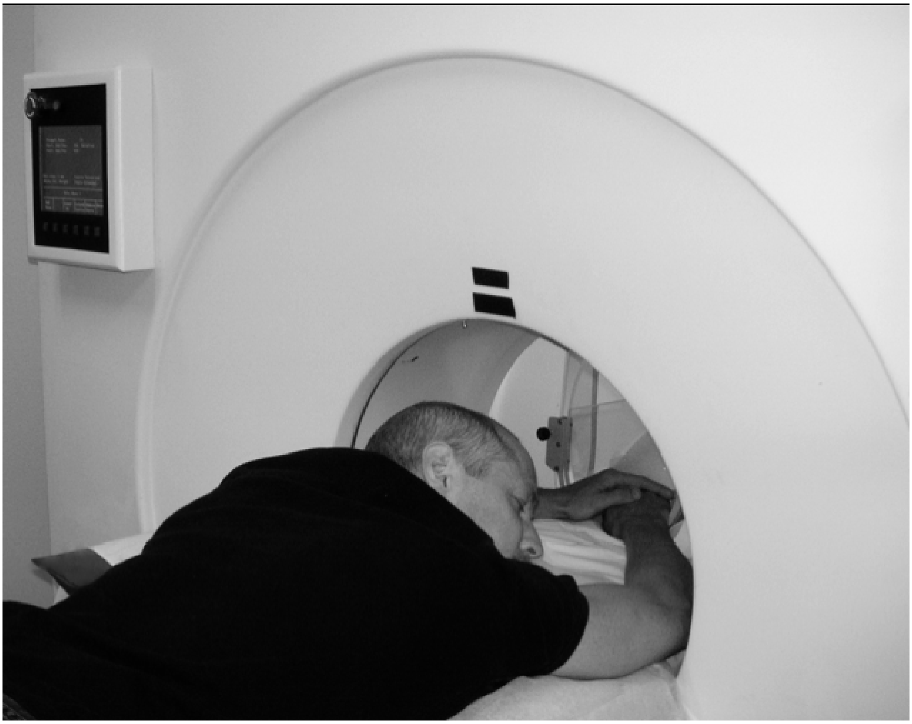

Figure 6. Position in the PET scanner

in the field of view (Figure 6). A venous catheter was inserted in the foot and a bolus of the radioligand was injected intravenously approximately 50 minutes prior to the elbow investigation. The amount of injected radioactivity was approximately 5.6 megabecquerel (MBq)/kilogram (kg) bodyweight, average dose 405 (SD 17.4) MBq. Then the imaging data was collected during a ten minute time frame. Finally, a ten-minute transmission scan was performed using three retractable ^{68}GE rotating line sources. During scanning the room was dimly lit and quiet.

Emission scans were reconstructed using an ordered subset expectation maximization (OSEM) method with six iterations and eight subsets using an eight mm Hanning filter, zoom two point five. The PET data were reconstructed to a 128x128 matrix with filtered back projection and corrected for photon attenuation, decay, scattered radiation and random coincidences according to standard procedures (Siemens ECAT Software version 7.1.1, Operating Instructions, Appendix B).

Statistical considerations

Paper I

Data were analysed using the SAS software, version 9.1. The 95% confidence intervals (CI) for the percentages of responders using the various therapeutic methods were calculated according to Clopper and Pearson [67].

Papers II and III

Data were analysed using the SAS software, version 9.1. Data loss owing to partial non-response (missing data in returned questionnaires and protocols) was 1% in Paper II and 1.3% in Paper III. Simple differences between groups in continuous variables were computed with Student's t-test and differences in proportions with the chi-square test. An intention-to-treat approach was followed whereby any missing data points were replaced with data from the nearest previous non-missing data measurement occasion (last data brought forward approach).

The statistical analysis was performed taking data at all measurement occasions into account, providing adjusted mean values for each measurement occasion and adjusted mean values across the whole study period, in order to compare temporal differences in pain regression and muscle strength improvement between the groups. Adjustments were made for differences between the groups in variables affecting outcome other than exercise, by including these as covariates in the analyses. These variables were: age, sex, smoking habits, education, marital status, number of previous TE episodes, time since last episode, duration of the present one and previous treatments (Table 2 and Table 4) and baseline differences in the outcome variable.

Pain, muscle strength, DASH score, Activity score and Complaint score, were all treated as continuous variables and multiple linear regression was used with the outcome as dependent variable and the covariates as independent variables. Since the Well-being score is an ordinal variable it was analysed with ordinal multiple logistic regression, as well as with multiple linear regression, both giving the same result. Therefore only the results from the multiple linear regression analysis are shown. To avoid analysis model overload, non-significant covariates were excluded by backward elimination. All statistical tests were two-tailed. P-values less than 0.05 was regarded as statistically significant.

As there are varying opinions as to what is a clinically meaningful pain decrease and muscle strength increase, analyses according to the cumulative proportion of responders were performed, based on percent change of pain from baseline to end of follow up [68, 69]. For each level of change, the proportion of patients that equalled or exceeded that level was calculated, plotted in Figures 7 and 8, allowing for comparisons between groups at any cut-off point desired. The difference between the graphs of the two groups represents the absolute risk reduction (ARR), which can be used to calculate the number needed to treat (NNT=1/ARR) [68].

Paper IV

The image data were analysed according to a non-observer dependent statistical approach. The original three-dimensional matrices (voxels) representing radioactivity concentration (signal intensity) and the density maps used to correct for attenuation were loaded into ImageJ, (a public domain Java image processing programme developed at the National Institutes of Health) [70, 71]. An algorithm was constructed with which the left and right arms were semi-automatically located and segmented from the density maps. Based on this segmentation, the total number of voxels, the mean signal intensity and the standard deviation (SD) of this signal intensity were calculated for each arm. The mean signal intensity of all voxels in the unaffected arm was used as reference. Then two new image matrices were created, in which the voxel data represented the SD away from reference (Z score). From each Z score image, the signal intensity of voxels in each arm >2.5 SD reference was computed. In order to obtain a composite measure of voxel volume and signal intensity, a 'Volume intensity score' was calculated by multiplying the volume of voxels with signal intensity >2.5 SD above reference in each arm, by the summed Z score signal intensity of this volume. The proportion of voxels with signal intensity >2.5 SD above reference in relation to all voxels in each arm was also computed.

The derived data were analysed using SAS software, version 9.2. Differences between the arms were computed with Student's t-test. All statistical tests were two-tailed. P-values less than 0.05 were regarded as statistically significant.

Results

Paper I

More than half of the GPs and PTs used ergonomic counselling, stretching and orthotic devices (Table 1). Acupuncture was also common, but less so among GPs than PTs. TENS was used by relatively few GPs and PTs. The open question revealed that dynamic, particularly eccentric, exercise was used by most PTs, but only by one GP. A majority of the GPs prescribed sick leave (57%) and anti-inflammatory treatment with an NSAID (73%) or cortisone injections (66%).

Table 1. *Treatment practice in chronic tennis elbow according to responses to a postal survey (Paper I). TENS=Transcutaneous electric nerve stimulation*

	General Practitioners (n=90)			Physiotherapists (n=47)		
	n	%	95% CI	n	%	95% CI
Specified alternatives						
Ergonomic counselling	81	90	82-95	44	94	82-99
Stretching	70	78	68-86	45	96	85-99
Orthotic device	63	70	59-79	24	51	36-66
Acupuncture	41	46	35-56	40	85	72-94
TENS	9	10	5-18	12	26	14-40
Open questions						
Referral to physician	2	2	0-8	2	4	1-15
Referral to physiotherapist	10	11	5-19	-	-	-
Dynamic exercise	1	1	0-6	29	62	46-75
Eccentric	1	1	0-6	25	53	38-68
Other	0	0	0-4	4	9	2-20
Deep friction massage	1	1	0-6	9	19	9-33
Other treatments	8	9	4-17	9	19	9-33

Paper II

Baseline characteristics of the study population

Mean age was 48 years, somewhat more than 40% of the participants were women, almost half had a college or university education, 88% were married or cohabitating, and 5% were current smokers (Table 2). The exercise group had an average of 1.3 previous TE episodes, range 0-20, 76 weeks on average since last episode and a mean duration of the present episode of 107 weeks. The corresponding data in the reference group was 0.8 previous episodes, 45 weeks since last episode and 96 weeks duration of the present episode.

The most common previously given treatments during the present episode were, in rank order, NSAID, acupuncture, steroid injections, stretching, orthosis or other supporting device, manual treatment, exercise, rest, and ultrasound or laser treatment. Most of the subjects had received some form of treatment. None of the baseline characteristics differed significantly between the exercise and reference groups.

Analysis of crude outcome data

Crude outcome data are shown in Table 3. The exercise group had a higher baseline level of the two pain scores and the DASH score, and lower muscle strength than the reference group, whereas the baseline levels of the Activity score, self-rated health, and Complaint score were similar. During the study period the exercise group had a larger crude decrease of pain during MVC ($p<0.01$), pain during MME ($p<0.05$), and a non-significant trend towards more muscle strength and greater decrease of the DASH score than the reference group. For the remaining outcome measures the differences in trend were small and of variable direction.

The analyses of pain during MVC and pain during MME according to the cumulative proportion of responders is shown in Figure 7 a-b. The exercise group had a higher responder rate at all levels of pain reduction, regardless of regression criteria, than the reference group. For instance, 72 percent of the subjects in the exercise group versus 44 percent in the reference group had 30 percent or more pain reduction during MVC. This represents an absolute risk reduction of 28 percent and a number-needed-to-treat of 1/0.28=4. The corresponding absolute risk reduction for MME was 15%, and number-needed-to-treat 1/0.15=7.

Table 2. *Characteristics of the study population, tennis elbow history and previous treatments during the present episode (Paper II)*

	Exercise group		Reference group		
	n	mean (SD) or %	n	mean (SD) or %	p
N	40		41		
Age, years		49.1 (8.1)		47.4 (8.6)	
Women	16	40.0	18	43.9	0.72
Educational level					0.99
Compulsory education only	3	7.5	2	4.9	
Vocational training	5	12.5	8	19.5	
Upper secondary school	12	30.0	12	29.3	
College or university	20	50.0	19	46.3	
Marital status					0.45
Never married	2	5.0	3	7.3	
Married or cohabiting	35	87.5	36	87.8	
Divorced or widowed	3	7.5	2	4.9	
Smoking habits					0.42
Never smoked	25	62.5	20	46.8	
Ex-smokers	12	30.0	19	46.3	
Current smokers	3	7.5	2	4.9	
Tennis elbow history					
Number of previous episodes		1.3 (3.91)		0.8 (2.05)	0.48
Time since last episode, weeks		76.2 (202.14)		44.6 (142.34)	0.42
Duration of present episode, weeks		106.6 (192.7)		95.6 (118.8)	0.76
Previous treatments given					
NSAID	18	45.0	21	51.2	0.58
Acupuncture	15	37.5	13	31.7	0.59
Steroid injections	14	35.0	12	29.3	0.58
Stretching	10	25.0	11	26.8	0.85
Orthosis or other fixative	10	25.0	12	29.3	0.67
Manual treatment (deep friction, massage, manipulation)	6	15.0	8	19.5	0.59
Exercise	5	12.5	5	12.2	0.97
Rest	5	12.5	2	4.9	0.23
Ultrasound or laser	4	10.0	4	9.8	0.97
Other treatments	4	10.0	2	4.9	0.38

Table 3. *Crude outcome data by measurement occasion and treatment group (Paper II). Numbers are means (standard deviation)*

	Exercise group				Reference group			
	Baseline	1 month	2 months	3 months	Baseline	1 month	2 months	3 months
Pain score, MVC (VAS)	42.2 (26.5)	30.2 (26.1)	21.3 (22.1)	19.5 (21.1)	33.9 (29.3)	30.0 (29.2)	27.3 (28.7)	27.0 (27.9)
Pain score, MME (VAS)	52.0 (21.5)	38.6 (29.2)	31.3 (26.2)	29.1 (25.9)	45.5 (27.8)	41.1 (27.9)	35.6 (27.5)	35.5 (26.7)
Muscle strength (N)	130.4 (47.9)	129.2 (44.2)	141.3 (45.6)	137.7 (38.0)	141.1 (47.9)	138.2 (43.2)	144.0 (43.1)	140.9 (43.7)
DASH score	28.7 (12.8)	-	-	18.2 (14.6)	24.6 (14.7)	-	-	18.7 (14.9)
Activity score	29.1 (7.4)	-	-	28.0 (7.4)	28.0 (6.7)	-	-	27.9 (5.7)
Well-being score	5.4 (1.3)	-	-	5.5 (1.3)	5.7 (1.3)	-	-	6.0 (1.0)
Complaint score	6.1 (4.1)	-	-	6.0 (5.3)	5.0 (5.2)	-	-	4.9 (4.6)

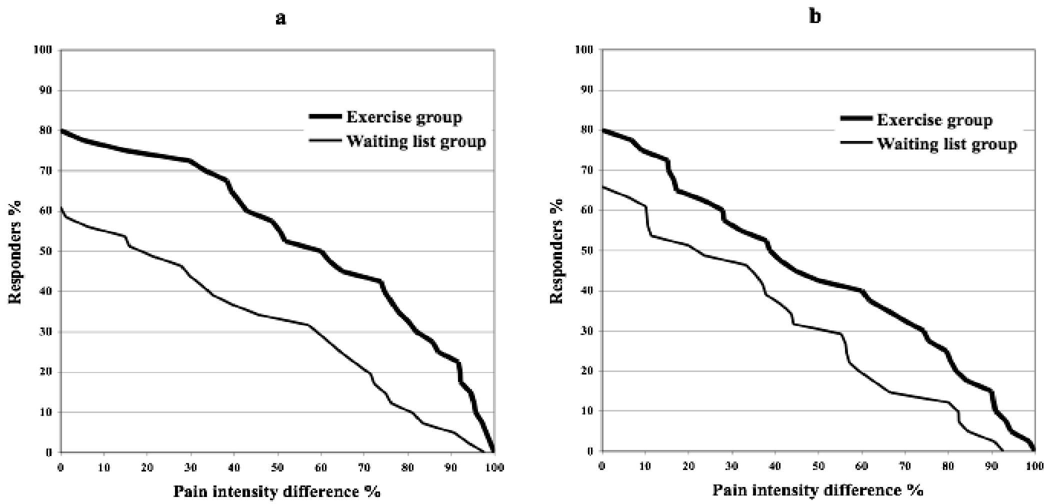

Figure 7 a-b. Graphs of the cumulative proportion of responders analyses, showing the proportion of subjects (vertical axis) that equal or exceed a specified improvement of pain (horizontal axis) in Paper II. At the three month follow-up, the exercise group had higher responder rate at all levels of change in pain score during maximum voluntary contraction (a), as well as pain score during maximum muscle elongation (b)

Analysis of outcome data adjusted for outcome affecting variables

In order to compare the change across time in the two groups in a way that includes the course of events, linear regression analyses utilizing measurements from all four measurement occasions were performed. Measured in this way the exercise group had a significantly lower level of pain during MVC (p=0.0005) as well as during MME (p=0.005) than the reference group. There was a non-significant trend towards a more favourable DASH score and muscle strength in the exercise group than in the waiting list group (p=0.30 and p=0.17 respectively). No significant differences and no clear trends regarding any of the quality of life measures were found.

Paper III

Baseline characteristics of the study population

Mean age was 47.9 years, 47.5% of the participants were women, 44.4% had a college or university education, 85.8% were married or cohabitating, and 13.3% were current smokers (Table 4). The only significant difference between the eccentric and concentric exercise groups was the proportion of women (p<0.05).

The eccentric group had an average of 1.8 previous TE episodes, range 0-20, 43.1 weeks on average since the last episode and a mean duration of the present episode of 95.3 weeks, Table 4. The corresponding data in the concentric group was 0.8 previous episodes, range 0-15, 60.8 weeks since the last episode, and 108.7 weeks duration of the present episode. None of these differences was statistically significant, although some were numerically large.

The most common previously given treatments were, in rank order, NSAID, acupuncture, steroid injections, stretching, orthosis or other supporting device, manual treatment, exercise, rest, and ultrasound or laser (Table 4). Most of the subjects had received some form of treatment, but there were no significant differences in treatments received between the groups.

Data analysis

Both groups improved regarding pain during MVC and MME as well as muscle strength between baseline and the twelve month follow-up, but the eccentric group tended to have a faster crude decrease of pain during MVC

Table 4. *Characteristics of the study population, tennis elbow history and previous treatments during the present episode (Paper III)*

	Eccentric group		Concentric group		
	n	mean (SD) or %	n	mean (SD) or %	p
N	60		60		
Age, years		48.8 (6.7)		47.0 (9.4)	
Women	34	56.7	23	38.3	0.04
Educational level					0.25
Compulsory education only	3	5.0	9	15.0	
Vocational training	12	20.0	9	15.0	
Upper secondary school	16	26.7	18	30.0	
College or university	29	48.3	24	40	
Marital status					0.22
Never married	4	6.7	3	5.0	
Married or cohabiting	48	80.0	55	91.7	
Divorced or widowed	8	13.3	2	3.3	
Smoking habits					0.17
Never smoked	55	91.7	49	81.7	
Ex-smokers	0	-	0	-	
Current smokers	5	8.3	11	18.3	
Lateral elbow tendinopathy history					
Number of previous episodes		1.8 (4.1)		0.8 (2.4)	0.10
Time since last episode, weeks		43.1 (138.1)		60.8 (179.5)	0.55
Duration of present episode, weeks		95.3 (172.9)		108.7 (159.1)	0.66
Previous treatments given	53	88.3	54	90.0	0.77
NSAID	30	50.0	26	43.3	0.46
Acupuncture	18	30.0	23	38.3	0.34
Steroid injections	21	35.0	20	33.3	0.85
Stretching	15	25.0	16	26.7	0.83
Orthosis or other fixative	14	23.3	15	25	0.83
Manual treatment (deep friction, massage, manipulation)	10	16.7	10	16.7	1.00
Exercise	3	5.0	9	15.0	0.07
Rest	6	10.0	5	8.3	0.75
Ultrasound or laser	2	3.3	7	11.7	0.08
Other treatments	5	8.3	5	8.3	1.0

and MME, as well as a faster increase of muscle strength than the concentric group (Table 5). This tendency was most striking at the two month follow-up. For the DASH score and the quality of life measures the differences in trend were small and of variable direction. However, there were no signifi-

Table 5. *Crude outcome data by measurement occasion and treatment group (Paper III). Numbers are means (standard deviation)*

	Eccentric group						Concentric group					
	Base-line	1 month	2 months	3 months	6 months	12 months	Base-line	1 month	2 months	3 months	6 months	12 months
Pain score, MVC	47.9 (26.8)	33.4 (24.9)	26.6 (22.0)	21.2 (22.9)	14.4 (21.2)	9.8 (19.5)	46.1 (27.5)	37.2 (28.4)	32.8 (28.3)	23.7 (28.2)	17.8 (23.4)	12.8 (24.8)
Pain score, MME	40.6 (27.0)	23.4 (24.9)	16.5 (20.8)	12.8 (20.8)	8.1 (20.4)	4.7 (12.4)	38.8 (28.6)	31.9 (28.0)	25.3 (26.1)	15.8 (25.6)	10.5 (22.9)	6.6 (18.9)
Muscle strength, N	119.9 (44.1)	129 (45.3)	133.8 (47.1)	127.8 (48.1)	128.7 (46.4)	128.8 (50.0)	133.7 (48.4)	142.4 (46.4)	147.3 (47.4)	135.7 (44.2)	137.1 (49.3)	138.3 (49.3)
DASH score	28.8 (18.4)	-	-	14.6 (17.9)	11.9 (17.9)	9.6 (17.8)	27.5 (17.3)	-	-	13.4 (17.2)	10.3 (16.7)	9.6 (16.3)
Activity score	28.4 (6.9)	-	-	26.3 (7.4)	25.2 (7.3)	24.9 (7.6)	27.4 (7.0)	-	-	23.9 (7.1)	23.6 (7.5)	23.0 (7.4)
Well-being score	5.3 (1.5)	-	-	5.1 (1.5)	5.0 (1.4)	5.1 (1.6)	5.5 (1.4)	-	-	5.3 (1.3)	5.1 (1.4)	5.4 (1.3)
Complaint score	6.6 (5.8)	-	-	4.5 (5.4)	4.6 (5.5)	4.2 (5.5)	6.3 (4.9)	-	-	4.6 (5.7)	4.1 (5.4)	4.9 (6.1)

cant crude differences between the groups, measured as change from baseline to end of follow up, in any of the outcome measures.

In order to compare the timing of the reduction of pain and the increase of muscle strength, linear regression analyses utilising measurements from all six measurement occasions were performed. Measured in this way, the eccentric group had a significantly lower mean level of pain during MVC ($p<0.0001$) and MME ($p<0.001$), as well as greater mean muscle strength ($p<0.05$). The eccentric group had on average a 10 percent higher responder rate at all levels of pain reduction than the concentric group for both MVC and MME (Figure 8 a-c). This represents an absolute pain reduction of 10% and a number-needed-to-treat of 1/(0.10) = 10. There were no significant differences regarding the DASH score or any of the quality of life measures.

Paper IV

Baseline characteristics of the study population

Mean age was 49 years, five of the ten participants were women, three had a college or university education and two were current smokers (Table 6). Eight stated that their work consisted of manual tasks and six suspected repetitive movement as cause of their TE condition. Five had one previous episode of TE and five had none. Mean duration of the present episode was 12 months (range 3-36). All but one had received treatment during the current episode and the majority had been treated with anti-inflammatory medication orally or by injection of steroids.

Neurokinin 1 receptor availability

Results from the analysis of the voxel data are presented in Table 7. The number of voxels in the field of view was similar in both arms of each indi vidual. The number and volume of voxels with signal intensity > 2.5 SD above reference were significantly higher in the affected than in the unaffected arm. The mean signal intensity of this voxel volume, measured as SD above reference, was also significantly higher in the affected than the unaffected arm. The Volume intensity score was, consequently, also significantly higher. These results are illustrated by PET image in Figure 9.

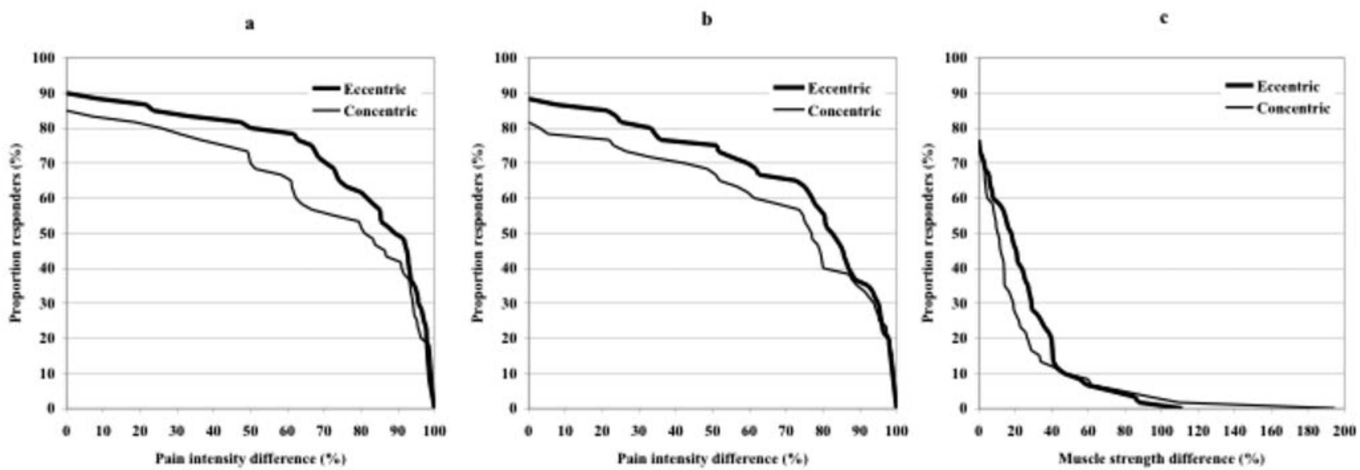

Figure 8 a-c. Graphs of the cumulative proportion of responders analyses, showing the proportion of subjects (vertical axis) that equal or exceed a specified improvement of pain (horizontal axis) in Paper III. At the twelve month follow-up, the eccentric group had a higher responder rate at all levels of change in pain score during maximum voluntary contraction (a), and pain score during maximum muscle elongation (b). The responder rate in muscle strength was higher in the eccentric group up to 40 % muscle strength difference (c).

Table 6. *Baseline characteristics of the study population (Paper IV)*

	n	mean (SD) or %
N	10	
Age, years		48.7 (8.5)
Women	5	50
Educational level		
Compulsory education only	2	20
Vocational training	4	40
Upper secondary school	1	10
College or university	3	3
Marital status		
Never married	1	10
Married or cohabiting	9	90
Smoking habits		
Never smoked	5	50
Ex-smokers	3	30
Current smokers	2	20
Lateral epicondylosis history		
Duration of present episode, weeks		52.0 (42.9)
Previous treatments given		
NSAID	4	40
Acupuncture	4	40
Steroid injections	3	30
Stretching	4	40
Orthosis or other fixative	3	30
Massage	1	10
Rest	1	10
No previous treatment	1	10

Table 7. *Data on volume and signal intensity of the neurokinin 1-specific radioligand [11C]GR-205171 (Paper IV)*

Subject and arm		Examined voxels (No.)	Mean intensity (Bq) (SD)	Voxels >2.5 SD above mean of unaffected arm				
				Voxels (No.)	Volume (ml)	Proportion (%)	Mean intensity (Bq) (SD)	Volume intensity score (ml*SD)
1	Unaffected	11675	2086 (1371)	26	1.7	0.2	2.9	5.0
1	Affected	11495	2999 (1858)	1709	110	15	3.7	406.5
2	Unaffected	9825	4664 (3748)	4	0.26	0.04	2.8	0.7
2	Affected	9626	5952 (4699)	475	30.5	4.9	3.7	112.6
3	Unaffected	9811	1837 (804)	0	0	0	0	0
3	Affected	10274	3137 (2483)	2895	186	28.2	5.2	970.1
4	Unaffected	20009	5316 (2404)	492	32	2.5	3.3	106.2
4	Affected	17661	5658 (2382)	495	31.8	2.8	3.3	104.7
5	Unaffected	15012	1432 (647)	0	0	0	0	0
5	Affected	15139	3174 (4802)	3275	211	21.6	12.4	2616.5
6	Unaffected	16525	1956 (663)	0	0	0	0	0
6	Affected	19007	2537 (1696)	3050	196	16	5.4	1064.1
7	Unaffected	12373	2953 (1844)	6	0.4	0.04	3.7	1.5
7	Affected	15185	6573 (6433)	4954	318	32.6	5.6	1773.6
8	Unaffected	13718	3056 (1118)	3	0.2	0.02	2.7	0.5
8	Affected	15010	4501 (3109)	3138	202	20.9	5.3	1072.2
9	Unaffected	13512	1715 (916)	0	0	0	0	0
9	Affected	13118	2023 (1466)	1388	89	10.6	3.5	314.8
10	Unaffected	15999	2907 (1073)	6	0.4	0.04	3.3	1.3
10	Affected	16734	3301 (1889)	1912	123	11.4	4.0	487.8
Mean								
	Unaffected	13846	2792 (1459)	54	3.5	0.3	1.9	11.5
	Affected	14325	3985 (3082)	2329	149.7	16.4	5.2	892.3
	p	0.74	0.08	<.0001	<.0001	<.0001	0.003	0.003

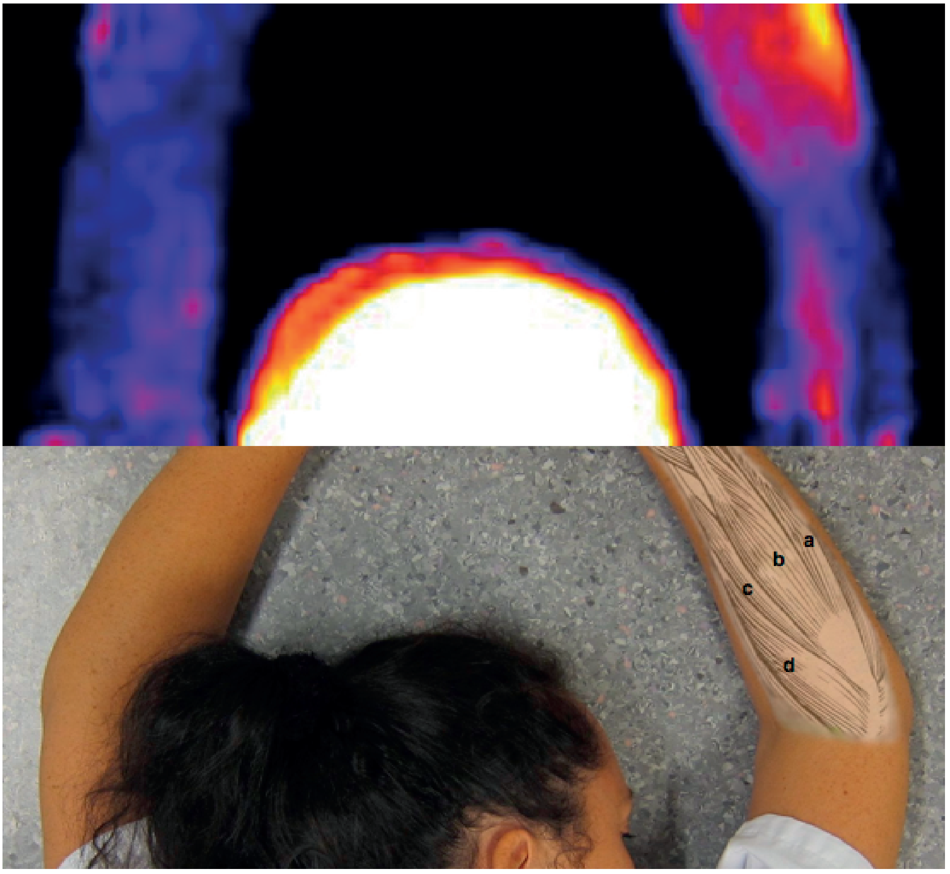

Figure 9 a. PET image showing maximum intensity projection of NK1 receptor radioligand [11C]GR-205171. Forearm muscles from top to bottom: a) m. extensor carpi ulnaris, b) m. extensor digitorum communis, c) m. extensor carpi radialis brevis, d) m. extensor carpi radialis longus.

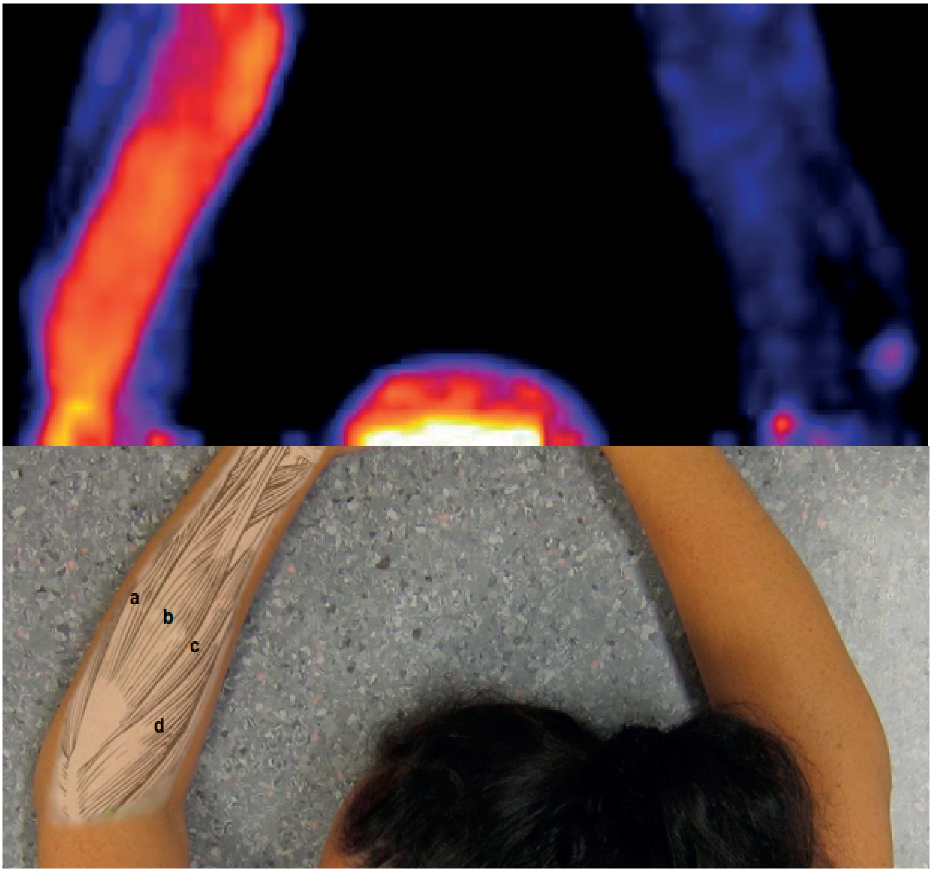

Figure 9 b. PET image showing maximum intensity projection of NK1 receptor radioligand [11C]GR-205171. Forearm muscles from top to bottom: a) m. extensor carpi ulnaris, b) m. extensor digitorum communis, c) m. extensor carpi radialis brevis, d) m. extensor carpi radialis longus.

Discussion

In the survey, high proportions of GPs and PTs used ergonomic counselling and stretching in the treatment of chronic TE. The majority of GPs prescribed passive anti-inflammatory measures such as sick leave and anti-inflammatory medication. Many PTs prescribed dynamic, particularly eccentric, exercise as treatment for chronic TE. Graded dynamic exercise (pooled concentric and eccentric) according to a simple low-cost protocol, has better effect on chronic TE than a wait-and-see attitude. Adjusted for outcome affecting variables, eccentric graded exercise has quicker effect than concentric graded exercise on pain in chronic TE. During PET scan with the NK1 specific radioligand [11C]GR205171, voxel volume and signal intensity of this volume was significantly higher in the affected than the unaffected arm in subjects with unilateral chronic TE.

Paper I

The extent to which various treatments for chronic TE were actually used in clinical practice was mainly unknown in 2004, and no report on this subject was found in a bibliographic search. Thus, the survey provided new and interesting information.

The results of the survey must be interpreted with some caution considering a number of circumstances. Since the survey was limited to a specific geographical area of Sweden, with a response rate of 70% among GPs and 61% among PTs, the results should not uncritically be generalized. The questionnaire was intentionally made as simple as possible in an attempt to achieve the best possible response rate. This may have led to some under-reporting of treatments other than those explicitly asked about. However, this is not likely to explain the differences observed between the two groups of health professionals. The survey gives information about the proportion of GPs and PTs who used a certain treatment, but says nothing about how often they were actually used. Neither does it tell us about the use of combination therapies, although it is likely that both GPs and PTs used combinations of treatments in individual cases.

A majority of the GPs prescribed sick leave, NSAID and cortisone injections. Sick leave may allow rest for the affected tissues, which may be of value in the acute inflammatory stage of epicondylitis, but will do little good in the chronic state. In cases where work cannot be continued because of pain, great effort should be invested in activating and rehabilitating the patient. As there is virtually no inflammation present in the chronic stage, the use of anti-inflammatory treatment is questionable [30].

Dynamic exercise, particularly eccentric exercise, was used by a majority of the PTs. From 1998 until the time of the survey, graded eccentric exercise received attention as treatment for chronic Achilles tendinitis owing to promising reports by Niesen-Vertommen and Alfredson. A pilot study on a combination of therapies, including stretching, eccentric exercise and ice by Svernlov [72] popularized its use among Swedish PTs even for chronic TE. In fact, however, there was very little evidence to support the effects of graded eccentric exercise on chronic TE in 2004 and no study had been performed comparing graded eccentric exercise with graded concentric exercise or with combinations thereof.

Papers II and III

The study population in Papers II and III was recruited from among chronic TE patients in primary health care. Although this was not a random population sample, it may be regarded as fairly representative of this type of patient in the general population. The same observer did all measurements, thereby avoiding inter-observer variation. The monitoring was intensive, resulting in a high participation rate. Data loss in the trial was low. Moreover, the intention-to-treat analysis strategy was used, thereby minimising the risk of selection bias. Pain scoring using VAS has previously been validated [73, 74]. The scoring has considerable inter-patient variability, but intra-patient variability in repeated measurements, like those used in these studies, is low. Muscle strength measurements with a hand-held dynamometer have reliable reproducibility in test-retest and between-day measurements [61, 62]. The DASH questionnaire has been recommended by the American Academy of Orthopedic Surgeons' Outcomes Research Committee and the Institute for Work and Health, and both the English and Swedish versions have been tested for reliability and validity [75, 76]. The GQL instrument is a validated and extensively used measure of general health and well-being [63-65].

Pain provocation measures often used to document symptoms in TE, such as pain during grip testing or pain at rest, are non-specific for the muscles affected in TE, and validity is low. Specific movements that put stress on the affected muscles, tendons and their insertions, provoke pain in TE, as in many other soft tissue pain conditions. The outcome measures for pain used in these studies were developed in cooperation with an experienced hand surgeon to be specific for the muscles affected in TE. MVC of the forearm extensor muscles (Cozen's test) puts maximum stress on the muscles involved in TE, *i.e.*, extensor carpi radialis brevis, extensor carpi radialis longus and extensor digitorum communis, which also connect to the tendinous insertion on the lateral elbow epicondyle. MME with a three-kilogram dumbbell (a modified Empty-can-test) simulates the manoeuvre most often described by TE patients as provoking everyday pain, such as lifting a frying pan or pouring out of a pot.

Complete blinding, as in drug trials, was not possible in the type of intervention used in Papers II and III. A potential bias in Paper II may be related to differences in expectations. As in all active treatment versus wait list studies, subjects given active treatment may be presumed to have higher expectations of the treatment effects than wait listed subjects, the latter perhaps having high expectations of the treatment-to-come, but not of any wait list effect. In Paper III, however, the observer monitored the adherence to the exercise procedure at baseline and the first follow-up visit, but during the following four follow-up visits, involving 480 appointments, no group allocation data were available, and it was, in practice, more or less impossible for the observer to keep track of the group allocation.

The two pain variables, which were evaluated by the subjects themselves, showed the largest differences between the groups in both studies, while differences in muscle-strength, which required observer participation, were smaller. The DASH measure was also subject-evaluated, but the difference between the groups was non-significant. The latter was unexpected, but in the context of a limited functional impairment such as TE, DASH may be a somewhat insensitive measure. In Paper II, the quality of life variables, especially self-rated health, may be more prone to expectation effects than pain or muscle strength. The fact that an effect on pain but not on quality of life was found favours the view that the treatment effects is not caused by differences in expectations to any major extent.

The results of Paper II should be interpreted with some caution considering the small sample size and the relatively moderate differences in average pain reduction between the groups. However, irrespective of the definition of improvement on the pain VAS, the exercise group had a more favourable course than the reference group. The lack of long-term follow-up in Paper II prevents firm conclusions on long-term efficacy. It is likely that the differences between the exercise and the reference group would have evened out in a long-term follow-up just as they did in the study by Smidt et al. [34] but the quicker improvement of pain seen in the exercise group would still be as obvious.

To gain maximum effect of the exercise, the starting weight should be individually tailored, for instance as percentage of one repetition maximum (1RM), the weight an individual can endure to lift once only [77]. To simplify clinical application, the starting weight in both studies was standardized to one kilogram for women and two for men. This may have had the effect that the load, and accordingly the stimulus, in some individuals was smaller or greater than what would be required for optimum gain. Therefore, the effects of the exercise regime may have been underestimated.

The exercise group in Paper II had significantly greater and faster recovery, in terms of pain during MVC and pain during MME, than the reference group. There was also a non-significant trend towards less restricted arm activity and arm muscle strength in the exercise group. In Paper III both the eccentric and concentric exercise groups improved significantly regarding pain and strength, but the crude difference was not significant between the groups at the twelve month follow-up. Adjusted for effect-modifying factors and for changes over time, however, the eccentric exercise group had significantly faster recovery from pain during MVC and MME, and muscle strength as compared with the concentric group. There were no significant differences between the groups either in Paper II or in Paper III regarding physical functioning and quality of life aspects.

Paper IV

Until now, the radioligand [11C]GR205171 has in human beings only been used for studying the CNS, where it has high affinity for the NK1 receptor and displays very slow dissociation [66]. Sex and age affect NK1 receptor presentation in the CNS. It has been a matter of discussion whether [11C]GR205171 can be displaced by endogenous substance P [66, 78]. It seems reasonable to assume that these phenomena occur similarly in peripheral tissue as in the CNS and similarly in both of arms of an individual. The method of scanning radioligand emission by PET is standard clinical and laboratory procedure today.

For interpretation of PET data it is common to define a region of interest (ROI) in one or a few of the available tomography planes, where signal intensity is measured and compared with a reference region. This allows only for a limited three-dimensional evaluation of the acquired scanner data. The extensor muscles of the forearm, as well as their tendinous insertions on the lateral epicondyle, represent an extended three-dimensional tissue volume, which makes it difficult to capture by ROI analysis. In ROI analysis, the observer defines the region or volume to be compared, which also makes the method subject to observer bias. The analysis method of comparing the number, volume, and signal intensity of all voxels above a pre-set threshold of signal intensity presented here, is less subjective. This method is well suited for statistical analysis but it does not provide information on the location in the tissue. Data analysis needs to be accompanied by images to obtain this information.

The PET scans revealed a high degree of unilateral and localized allocation of the radioligand [11C]GR205171. The specificity of [11C]GR205171 on NK1 receptors has been documented [66]. It is unlikely that the allocation could be explained by locally increased blood flow, since the examined TE elbows were in the chronic stage, when acute inflammation and its concomitant increase of blood-flow has subsided [79-81]. Although minor differences in blood flow between the two arms of each patient cannot be ruled out, this possibility cannot fully explain the one-sided findings. The allocation of [11C]GR205171 is therefore interpreted as locally increased presentation of NK1 receptors. As there is no evidence of NK1 receptors on peripheral nerve cells, the allocation of [11C]GR205171 most likely represents NK1 expression on non-neural cells such as immune and tissue cells. Immune cells known to express NK1 receptors are macrophages, mast cells and lymphocytes [48]. Tissue cells known to express NK1 receptors are fibroblasts, endothelial cells and synovial cells.

General discussion

Among physicians today it is still common not to distinguish between the acute and chronic stage of tendon pain, either in terms of diagnosis or treatment. Thus treatment is often aimed at reducing acute, prostaglandin-mediated inflammation in both acute and chronic stages of tendon pain. This was confirmed in Paper I. In the chronic stage anti-inflammatory treatment will at best have symptomatic effects. The effects will not be curative and a number of studies now support that it actually has negative effects. Adverse events in the cardiac, gastrointestinal and renal systems accompanying treatment with NSAID are well documented [82]. Injection of corticosteroids only provides temporary relief from pain [31, 34]. Anabolic processes are negatively affected, which inhibits maturation and remodelling of tendon tissue and increases the risk of tendon rupture [32]. PTs are alert and quick to pick up new treatments in clinical use, sometimes even before there is substantial evidence to either support or refute their use. This was also confirmed in Paper I regarding the use of graded eccentric exercise for chronic TE.

In addition to medical rationale, 'cultural' factors may be part of clinical decision making. These factors include traditions in the education and training of staff, health care organization, availability of equipment and other resources, and patients' expectations. Indeed, cultural factors seem important explainations of why medical staff select certain treatments, and why treatment guidelines may differ considerably between countries [83, 84, 85]. Differences in cultural factors may also explain some of the differences between GPs and PTs observed in Paper I.

Enhanced communication between these professional groups, who often work alongside each other, often with the same patients, could harmonize treatment practice to the benefit of both patients and health care staff. GPs could gain insight into new treatment options from PTs, who are often quick to pick up new trends in treatment. PTs, on the other hand, could benefit from discussing the evidence base of treatments with GPs, who often have a more conservative treatment approach.

In the last decade there has been growing interest in exercise as a treatment for tendinosis [15, 26, 86], and in spite of some methodological weaknesses a number of studies now support the effects of this treatment [15, 26, 33, 35, 57]. Paper II is a more straightforward exercise versus wait list trial than used in previous studies and supports the idea that exercise is more effective than expectation in chronic TE. The additional cost of active physiotherapy measures as compared with expectation has been questioned [34], and a simplified exercise protocol for TE has been requested [87]. The suggested exercise protocol used in Papers II and III is of a simple, low-cost kind that can be performed at home with a plastic container and an armchair. It does not require costly measures such as assistance from health care staff or specific exercise machines. Whether eccentric is more effective than concentric graded exercise has been a matter of debate [57, 58]. A previous small-scale study of short duration found no significant differences between eccentric and concentric exercise in chronic TE [88]. In Paper III, eccentric exercise reduced pain faster than concentric exercise in chronic TE. This supports previous studies on Achilles tendinosis showing eccentric exercise to be superior to concentric exercise [89, 90].

Exercise induces reorganization of the CNS [77] and may thus affect central sensitization. It is possible that some of the difference seen in Paper III is attributable to better and more effective reorganization in the CNS in response to eccentric than to concentric exercise. But the difference may also be attributed to effects on peripheral tissue. Exercise has anabolic effects on muscle and tendon cross-sectional area [91, 92]. It is well known that eccentric exercise has superior anabolic effects on muscle synthesis as compared with concentric exercise [91, 92]. The fibroblast activity in tendons, however, responds to loading in an either/or fashion [25, 91]. This makes it somewhat of a surprise that one mode of exercise would be better than another for chronic tendon pain.

Tendons and muscles work as functional units. The extra-cellular matrix of tendons and muscles share a similar structure of collagen scaffolding governed by fibroblasts [25]. It may be that the pain in TE is not solely related to the tendon but also to the muscles, where eccentric exercise has greater anabolic effects [91, 92]. Alternatively, since eccentric exercise induces greater and faster quantitative changes in muscles, it may also be that in the long run this puts more stress on the tendon, encouraging greater stimulation for collagen synthesis and matrix reorganization.

The implications of these findings are that a chronic soft tissue pain condition such as chronic TE should not be treated with rest but with graded exercise. This is in line with other studies [26, 57, 93] and with findings of pain psychologists, who point out the negative effects of inactivity and associated fear-avoidance behaviour and suggest graded activity or graded exposure as a means of overcoming this problem [3, 94, 95]. In addition to these psychological effects and the exercise-induced reorganization in the CNS, graded exercise, directed specifically towards the painful tissue, will have direct effects on that tissue [58, 91, 96]. These anabolic effects will positively affect matrix turnover and may directly or indirectly affect pain-associated processes related to halted matrix turnover and to chronic, neurogenic inflammation [25].

During PET scan with the NK1 specific radioligand [11C]GR205171, both the voxel volume and the signal intensity of this volume were significantly higher in the affected than the unaffected arm in subjects with unilateral chronic TE. Increased expression of NK1 receptors is known to occur as part of acute inflammation [50]. To my knowledge, however, this is the first time increased expression of NK1 receptors in peripheral tissue has been visualized in a chronic pain condition. The true nature of such a condition is still uncertain.

Central sensitization is well documented and probably part of the cause [97]. Based on the findings in Paper IV as well as in other studies, it seems likely that peripheral sensitization also takes place [36, 37, 98]. This sensitization may be at least partly explained by chronic neurogenic inflammation consisting of tripartite interaction among the immune cells, tissue cells and nerves. It is different from acute inflammation, which is dominated by inflammatory cells, local oedema and increased blood flow [80, 81], but shares the feature of pain. The endogenous production and release of substance P and other neurotransmitters from peripheral nociceptive neurons creates the prerequisites for a vicious circle, which may at least partly explain the longevity of the condition. Neurogenic inflammation does not, however, exclude other simultaneous mechanisms or up-regulation of other receptor systems in the peripheral painful tissue.

Despite promising results in rodents, systemic blockade of NK1 receptors in human beings has not shown any convincing analgesic effect [99]. Transient presentation of the NK1 receptor has been suggested as one possible explanation, supported by evidence that the NK1 receptor can be internalized [100, 101]. Overlapping pathways for signal transduction in the nerve system of human beings may be another explanation of why blockade of only one path does not have any significant effect [99]. In human beings there are several overlapping systems for pain signalling, which seem to be part of the phylogenetic evolution of a robust sensory system. This may in part explain the better effect in rodents.

There will always be a balance between blockade of a mediator so central in action that there is a risk of hazardous side effects, *e.g.* blockade of TNF-α, and blockade of mediators so peripheral in action that no effect is obtained. If the NK1 receptor is a key receptor in neurogenic inflammation, systemic blockade may affect chronic inflammatory conditions [48, 102].

Clinical studies of NK1 receptor blockers that failed to deliver analgesic effects in human beings were mostly done on models of acute pain, not on inflammatory pain [102]. If overlapping signalling pathways dilute the analgesic effect of systemic treatment, local treatment remains to be investigated. Combination therapy aimed at NK1 receptors and other receptor systems, *e.g*. opioid receptors, also remains to be studied [103, 104]. Treatments affecting the substance P – NK1 system may, in other words, not completely have played out their role [105].

PET scan has potential as research tool for physiological processes associated with pain, not only in the CNS but also in peripheral tissue. The NK1 specific radioligand [11C]GR205171 can be used to study the substance P – NK1 system, but other tracers may be developed to study other receptor systems such as glutamate–NMDA/AMPA, NGF–TrkA or CGRP–CGRP-receptor. The combination of PET and functional magnetic resonance tomography (fMRI) provides a tool for detailed anatomical mapping along with the study of physiological processes.

Conclusions

A large number of treatment methods for chronic TE were used by GPs and PTs in Uppsala county. None of the methods used was properly evidence-based at the time of the survey and some were even known to be ineffective. GPs used passive measures such as sick leave and anti-inflammatory medication to a large extent. GPs and PTs used ergonomic advice and stretching to similar extents, but differed regarding the use of exercise, which was used by many PTs but only by one GP. Enhanced communication between these professional groups could improve treatment for patients as well as professional satisfaction and scientific evolution.

A musculoskeletal pain condition such as chronic TE responds favourably to graded dynamic exercise aimed at the painful tissue, even if it is performed according to a simple, standardized, low-cost, home exercise protocol. The exercise should be specifically designed to put load on the affected tissue, be performed regularly with gradually increasing load, have a minimum of two months duration, and should stress the eccentric work phase.

The substance P – NK1 receptor system seems to play a part in the peripheral, painful tissue of a chronic, soft tissue pain condition such as chronic TE. The increased NK1 receptor availability may represent neurogenic inflammation and may be part of tripartite interaction among the peripheral nerve endings, the immune system and the tissue.

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Sammanfattning på svenska

Kronisk smärta är ett stort problem med avsevärda samhällsekonomiska kostnader och stort lidande för den enskilda individen. De samhällsekonomiska kostnaderna beräknas till cirka 2,5 % av bruttonationalprodukten årligen i direkta och indirekta kostnader, vilket i Sverige 2011 motsvarar cirka 100 miljarder kronor. Den vanligaste typen av smärta är relaterad till rörelseapparaten, s.k. muskuloskeletal smärta och utgör den vanligaste orsaken till konsultation i primärvården. Smärta från rörelseapparatens leder och skelett kan med hjälp av röntgen och blodprover effektivt diagnostiseras och behandlas med metoder och läkemedel riktade mot bakomliggande patofysiologiska mekanismer. Smärta från rörelseapparatens mjukdelar, d.v.s. muskler, senor och ligament saknar däremot i stor utsträckning metoder för diagnostik och därigenom effektiva behandlingsmetoder riktade mot bakomliggande patofysiologiska mekanismer. Behandlingar är idag ofta empiriska och ofta undermåligt utvärderade.

Tennisarmbåge är ett vanligt tillstånd med smärta från rörelseapparatens mjukdelar. Traditionellt har man betraktat detta som ett inflammatoriskt tillstånd, s.k. epikondylit (eller tendinit), oavsett om smärtan är i akut eller kroniskt skede (definierat som smärta mer än tre månader). Analys av vävnadsprover har dock visat att den inflammation som uppstår i akuta skedet saknas i det kroniska skedet. Följaktligen borde både diagnos och behandling vara annorlunda i detta, kroniska, skede. En utveckling av metoder för avbildning och analys av blodmarkörer vore av stort värde, både för att kartlägga patofysiologiska mekanismer och för att bidra till utvecklingen av diagnosmetoder.

Delarbete 1: Peterson M, Elmfeldt D, Svardsudd K: Treatment practice in chronic epicondylitis: a survey among general practitioners and physiotherapists in Uppsala County, Sweden. *Scand J Prim Health Care* 2005;23(4):239-41.

Syftet med delarbete 1 var att undersöka vilka behandlingsmetoder som idag används av läkare och sjukgymnaster i primärvården vid behandling av kronisk tennisarmbåge. En enkät skickades till alla 129 allmänläkare och 77 sjukgymnaster vid 35 vårdcentraler inom 6 mils avstånd från Uppsala. De ombads svara på frågan ”Hur behandlar du en patient som haft tennisarmbåge i mer än tre månader?” genom att kryssa i ett eller flera av sex fasta och ett öppet svarsalternativ där man kunde ange andra behandlingsmetoder.

Enkäten besvarades av 70 % av allmänläkarna och 61 % av sjukgymnasterna. Behandling med ergonomisk rådgivning, stretching och ortos var vanligt och användes i liknande utsträckning av läkare och sjukgymnaster. Akupunktur var också vanligt men mindre bland läkare än bland sjukgymnaster. TENS användes av ganska få i båda grupperna. Det öppna svarsalternativet visade att dynamisk träning, fram för allt excentrisk träning, användes av många sjukgymnaster men endast av en enda läkare. Majoriteten av läkarna ordinerade sjukskrivning och anti-inflammatorisk behandling med tabletter eller kortisoninjektion. Slutsatsen av enkätstudien var att ett stort antal olika behandlingar användes. Alla metoder hade vid enkätens genomförande otillfredsställande evidens för sin effekt och en del av dem var dokumenterat utan effekt. Användningen av passiva metoder riktade mot inflammatorisk smärta kan ifrågasättas i det kroniska skedet.

Delarbete 2: Peterson M, Butler S, Eriksson M, Svardsudd K. A randomized controlled trial of exercise versus wait list in chronic tennis elbow. *Ups J Med Sci* 2011; In press.

Syftet med delarbete 2 var att undersöka om graderad träning med stegvist ökande belastning enligt ett enkelt hemträningsprotokoll kunde ha bättre effekt än den för tillfället rekommenderade åtgärden aktiv exspektans, dvs att vänta och se. Patienter med kronisk tennisarmbåge rekryterades från primärvårdsmottagningar i Uppsala län samt via annons i en lokaltidning. Efter att diagnosen verifierats randomiserades 81 personer till antingen träning eller väntelista under tre månader. Träningsgruppen instruerades att träna de smärtande musklerna och deras senfäste på armbågens utsida genom att antingen lyfta, eller sänka, en plastdunk med vatten under de tre månader som studien pågick. För varje vecka ökades vikten genom att fylla på vatten. Väntelistgruppen informerades att smärtan vid tennisarmbåge är ofarlig, att de kunde använda armen som vanligt och att smärtan kan gå över av sig själv. Under studien minskade smärtan vid belastning av de smärtande musklerna och deras muskelfäste signifikant mera och snabbare i träningsgruppen jämfört med väntelistgruppen. Skillnaden var tydlig efter två månader. Slutsatsen blev att graderad träning har bättre och snabbare effekt på smärta än aktiv exspektans. Med ett enkelt hemträningsprotokoll som inte kräver aktivt deltagande av en sjukgymnast eller behandling med träningsmaskiner blir detta en kostnadseffektiv behandling.

Delarbete 3: Peterson M, Butler S, Eriksson M, Svardsudd K. A randomized controlled trial of eccentric versus concentric exercise in chronic tennis elbow (lateral epicondylosis). Submitted.

Syftet med delarbete 3 var att undersöka om excentrisk träning, där man sänker en vikt och muskeln förlängs, har bättre effekt på smärta än koncentrisk träning, där man lyfter en vikt och muskeln förkortas. Patienter med kronisk tennisarmbåge rekryterades från primärvårdsmottagningar i Uppsala län samt via annons i en lokaltidning på samma sätt som i delarbete 2. Efter att diagnosen verifierats randomiserades 120 personer till antingen excentrisk eller koncentrisk graderad träning enligt samma träningsprotokoll som i delarbete 2. Träningen pågick under tre månader men uppföljning skedde även efter sex och tolv månader. Smärtan minskade och muskelstyrkan ökade med båda träningssätten men excentrisk träning gav snabbare och större effekt än koncentrisk. Slutsatsen blev att ett graderat träningsprogram kan innehålla både excentrisk och koncentrisk träning men att den excentriska träningsfasen är effektivare och bör betonas.

Delarbete 4: Peterson M, Svardsudd K, Appel L, Engler H, Långström B, Sörensen J. PET-scan shows peripherally increased neurokinin 1 receptor availability in chronic tennis elbow - a picture of neurogenic inflammation? Submitted.

Syftet med delarbete 4 var att, med en bilddiagnostisk metod, undersöka perifera nervsystemets eventuella engagemang i den perifera, smärtande vävnaden vid kronisk tennisarmbåge. Tio personer med ensidig kronisk tennisarmbåge, konsekutivt rekryterade från studiepopulationen i delarbete 2 och 3, undersöktes med positron emissions tomografi (PET) över den smärtande armbågen med den besvärsfria armbågen som referens. En radioaktiv markör för signalreceptorn neurokinin 1 (NK1) injicerades i blodbanan och, efter att ha cirkulerat genom kroppens vävnader, avlästes signalintensiteten med PET. NK1 är den primära signalreceptorn för substans P, en av nervsystemets signalsubstanser. Bildmaterialet analyserades med en observatörsoberoende, analysmetod baserat på antal bildpunkter, s.k. voxlar, med signalnivå över ett tröskelvärde, definierat som 2,5 standarddeviationer över medelnivån i den friska armen. Undersökningen visade att de smärtande armbågarna hade signifikant fler voxlar med signalnivå över tröskelvärdet och signifikant högre signalintensitet i dessa voxlar. Detta tolkas som en ökad biotillgänglighet av NK1-receptorer. Slutsatsen blev att signalsystemet substans P-NK1 förefaller vara engagerat i den perifera, smärtande vävnaden vid kronisk tennisarmbåge.

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