Carpal Tunnel Syndrome and Diabetes. Surgical outcome and nerve pathology

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Carpal Tunnel Syndrome and Diabetes
Surgical outcome and nerve pathology

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Cover illustration: Light microscopy image from a posterior interosseous nerve fascicle of a patient with idiopathic carpal tunnel syndrome.

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To my family

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ABBREVIATIONS

ATF3	Activating transcription factor 3
AGEs	Advanced glycation end products
BCTQ	Boston carpal tunnel questionnaire
CTS	Carpal tunnel syndrome
HNPP	Hereditary neuropathy with liability to pressure palsy
HRQL	Health-related quality of life
IENFD	Intraepidermal nerve fibre density
PIN	Posterior interosseous nerve
SF-36	Medical outcomes study 36-item short-form health survey
VEGF	Vascular endothelial growth factor

LIST OF PUBLICATIONS

This thesis is based on the following papers, which will be referred to by their Roman numerals:

I   **Clinical outcomes of surgical release among diabetic patients with carpal tunnel syndrome: A prospective follow-up with matched controls.**
Thomsen NOB, Cederlund R, Rosén I, Björk J, Dahlin LB.
J Hand Surg Am. 2009 Sep;34(7):1177-87.

II   **Health-related quality of life and disease-specific assessment of diabetic patients with carpal tunnel syndrome.**
Thomsen NOB, Cederlund R, Björk J, Dahlin LB.
2009, Submitted.

III   **Neurophysiologic recovery after carpal tunnel release in diabetic patients.**
Thomsen NOB, Rosén I, Dahlin LB.
2009, Submitted.

IV   **Intraepidermal nerve fibre density at wrist level in diabetic and non-diabetic patients.**
Thomsen NOB, Englund E, Thrainsdottir S, Rosén I, Dahlin LB.
Diabet Med 2009. In press.

V   **Biopsy of the posterior interosseous nerve: A low morbidity method for evaluation of peripheral nerve disorders.**
Thomsen NOB, Mojaddidi M, Malik RA, Dahlin LB.
Diabet Med 2009;26:100-104.

VI   **Reduced myelinated nerve fibre and endoneurial capillary densities in the forearm of diabetic and non-diabetic patients with carpal tunnel syndrome.**
Thomsen NOB, Mojaddidi M, Malik RA, Dahlin LB.
Acta Neuropathologica 2009 Jul 30. Epub ahead of print.

THESIS AT A GLANCE

Paper I

Aim: Compare the clinical outcomes after surgical carpal tunnel release in diabetic and non-diabetic patients
Method: Patients were examined independently, by the same occupational therapist, prior to and 6, 12 and 52 weeks after surgery.
Evaluation methods: Sensory function (Semmes-Weinstein and static two-point discrimination test). Motor function (abductor pollicis brevis muscle strength, grip strength, key- and lateral-pinch). Pillar pain, scar allodynia, cold intolerance and patient satisfaction.

> **Conclusion:** Patients with diabetes have the same beneficial outcome after surgical carpal tunnel release as non-diabetic patients. Only cold intolerance was relieved to a lesser extent in the diabetic patients.

Paper II

Aim: Assess health-related quality of life (HRQL) in diabetic and non-diabetic patients with carpal tunnel syndrome.
Method: Preoperatively, 6, 12 and 52 weeks after surgical carpal tunnel release outcome questionnaires were administered to the patients.
Evaluation methods: Medical Outcomes Short-Form 36 Health Survey (SF-36) and disease-specific Boston Carpal Tunnel Questionnaire (BTCQ). SF-36 population norms obtained from the Swedish database for population norms.

> **Conclusion:** Generic HRQL is impaired in diabetic patients with carpal tunnel syndrome (CTS) compared to non-diabetic patients with CTS and population norms. However, diabetic patients experience similar disease-specific, symptomatic and functional improvements after carpal tunnel release as non-diabetic patients.

Paper III

Aim: Describe nerve conduction results prior to and after carpal tunnel release in diabetic and non-diabetic patients.
Method: Nerve conduction studies were performed preoperatively and at the 52 weeks follow-up.
Evaluation methods: Median and ulnar nerve, distal motor latency, motor conduction velocity, compound muscle action potential, orthodromic sensory conduction velocity and action potentials. Median nerve, antidromic sensory conduction velocity across the carpal tunnel segment. Sural and peroneal nerve measurements to diagnose peripheral neuropathy.

> **Conclusion:** Marked neurophysiologic impairment or signs of peripheral neuropathy does not preclude significant recovery after carpal tunnel release in diabetic patients.

Paper IV

Aim: Evaluate if quantification of intraepidermal nerve fibre density (IENFD) at wrist level can detect signs of subclinical small nerve fibre neuropathy in diabetic patients.
Method: Punch biopsies from glabrous and hairy skin at wrist level were obtained in conjunction with surgical carpal tunnel release.
Evaluation methods: Biopsies immunostained with anti-protein gene product 9.5. The IENFD was quantified using manual counting by light microscopy.

Conclusion: At wrist level, IENFD is not different between diabetic and non-diabetic patients. However, IENFD was higher in females and more abundant in hairy compared to glabrous skin.

Paper V

Aim: Establish if biopsy of the posterior interosseous nerve (PIN) at wrist level would be a feasible and low morbidity method to assess neuropathy in the forearm.
Method: PIN biopsy was performed on Type 2 diabetic subjects and compared to post-mortem samples with no history of diabetes, carpal tunnel syndrome or neuropathy.
Evaluation methods: Light microscopy and digital imaging to measure fascicular area, myelinated nerve fibre density, endoneurial capillary density and subperineurial space.

Conclusion: The PIN biopsy procedure fulfils the criteria for nerve biopsy and is well tolerated by the patients. A reduction in myelinated nerve fibre density was demonstrated in diabetic patients.

Paper VI

Aim: Compare pathology in the non-compressed posterior interosseous nerve (PIN) between diabetic and non-diabetic patients with carpal tunnel syndrome.
Method: PIN biopsy was performed in conjunction with surgical carpal tunnel release. As a comparator we used PIN biopsies from subjects with no history of diabetes, carpal tunnel syndrome or neuropathy (post-mortem and biopsy samples taken during elective wrist surgery).
Evaluation methods: Light microscopy and digital imaging to measure fascicular area, myelinated nerve fibre density, endoneurial capillary density and subperineurial space.

Conclusion: Reduction in myelinated nerve fibre and capillary densities may predispose patients to carpal tunnel syndrome and this is further accentuated in diabetes.

"Pathology, being practically the last synthesis of a large number of coordinated and subordinated factors, must actually be studied before these other factors have been cleared up, and as a result pathology must be more or less descriptive; but insofar as it is descriptive it must not claim more for that description than the evidence warrants"

Letter from Theobald Smith to Simon Flexner, dated June 1, 1920. From the Flexner papers in custody of the American Philosophical Society Library, Philadelphia

INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common entrapment neuropathy in the upper extremity, with a lifetime risk of approximately 10% [4]. It presents with paresthesia and/or pain in the median nerve innervated part of the hand. As documented, in the Rochester Epidemiology Study, the annual incidence of CTS is gradually increasing from 258 per 100,000 in 1981-85 to 376 per 100,000 in 2001-2005 [66, 168]. The economic and social costs of CTS are high due to lost working days, change of occupation and the need for surgical intervention [60]. In 1995, it was estimated that 400,000 to 500,000 patients underwent carpal tunnel release, annually, in the United States, with economic costs of more than 2 billion dollars [135]. The rates for carpal tunnel release in the UK are reported between 45 and 73 per 100,000 per year [26].

Diabetes mellitus is a chronic metabolic disorder, which is characterised by persistent hyperglycaemia with resultant morbidity and mortality in relation to its micro- and macrovascular complications. The total number of people worldwide with diabetes, was estimated to increase from 171 million in 2000 to 366 million in 2030, with subsequent enormous human and economic costs [190]. "*The diabetic hand*" is a term used to describe pathological hand manifestations that are more commonly found in diabetes [85]. It represents the following musculoskeletal disorders; limited joint mobility, Dupuytren's contracture, flexor tenosynovitis and carpal tunnel syndrome [31, 149]. The lifetime risk of symptomatic CTS in type 1 diabetes, has been estimated to be as high as 80% [162].

Combined occurrence of CTS and diabetes has been acknowledged for many years [120]. However, it was not until 1980 that the first case report on surgical carpal tunnel release in four patients with diabetic neuropathy was published [186]. So far, results after carpal tunnel release in diabetic patients have been sparsely investigated. The two studies existing are vitiated with methodological concerns and reached opposing results [118, 130]. In contrast to our clinical experience, it has been declared in the literature that the results of surgical carpal tunnel release in diabetic patients are variable, and that it does not particularly benefit muscle wasting or sensory loss [20, 59]. The present thesis was undertaken with these two immediate questions in mind: 1) Does diabetic patients with CTS have the same benefit from carpal tunnel release as non-diabetic patients. 2) Why do diabetic patients show increased susceptibility to CTS?

BACKGROUND

Carpal tunnel syndrome

Sir James Paget, in 1854, was the first to describe the clinical features of median nerve compression at the wrist of a patient with a sustained distal radius fracture. In 1913, based on cadaver findings, Marie and Foix provided a comprehensive histopathologic and anatomic study of non-traumatic median nerve compression, which included a description of the "hourglass" configuration [138]. In 1924, approximately 70 years after Paget's first description, Galloway performed what may have been the first surgical carpal tunnel release. In spite of improvement of sensation in the hand, the patients developed chronic pain due to injury of the palmar cutaneous nerve branch [6]. The term "*carpal tunnel syndrome*" was first used by Phalen and associates in the 1950's, when they publish a series of landmark articles providing the basis for the understanding of symptoms, diagnosis and treatment of CTS, which we have today. After many years of experience, Phalen came to the conclusion that: "There are few operations that are as successful and rewarding as the operation for carpal tunnel syndrome" [139].

Prevalence

In the general population of southern Sweden, 14.4 % reported sensory symptoms in the median nerve distribution of the hand. When confirmed clinically and neurophysiologically, the prevalence of CTS was estimated to be around 2.7% [8]. It is commonly agreed that CTS is more frequent among women. The female:male ratio is estimated to be about 3:1. In a Dutch study from a general practice, the incidence of CTS in 2001 was 280 per 100,000 for women and 90 per 100,000 for men [18]. The incidence of CTS for women increases with age and reaches a peak between 50 and 59 years where after it declines. For men, a bimodal pattern has been documented with peak incidences between 50 to 59 years and again between 70 to 79 years [117].

Incidence rates depend on several factors, such as diagnostic criteria and the socio-demographic characteristics of the population under study. However, over time, the general pattern points to a steady increase. In Siena (Italy) the crude incidences of CTS had increased by 8% for women and 74% for men between 1991 and 1998 [117]. In a surveillance study

from Canterbury and Huddersfield (UK), performed between 1992 and 2001, the number of cases increased approximately with 90% in women and 145% in men [17]. Similar to the increased incidence of CTS, it has been documented that personal risk factors for CTS, such as obesity and diabetes, have increased considerably [128, 190]. In patients with diabetes the prevalence of CTS has been estimated to be around 15%, and increases up to 30 % in the presence of diabetic peripheral neuropathy [137]. Further studies are necessary to elucidate the reasons as to why diabetic patients have an increased susceptibility to local nerve entrapment.

Symptoms

The primary symptoms of classic CTS involves numbness and tingling with or without pain in at least two of the median nerve innervated fingers [89]. Symptoms are often aggravated during sleep and at daytime caused by static or repetitive hand function. Patients typically experience alleviation of symptoms by shaking their hand or by keeping the hand in a neutral position using a splint. However, patients with CTS may in fact experience quite variable sensory symptoms and pain, even outside the typical median nerve distribution. In a study of 1039 patients with neurophysiologic verified CTS, the classic distribution pattern was demonstrated in only 13% of the hands affected [127]. Clinical involvement of the little finger without neurophysiologic ulnar nerve abnormality, were found in 48-56% of the patients [159, 167], with "glove" distribution in 5%. Paresthesia and pain may extend proximal to the wrist in nearly 40%, whereas predominant involvement of the dorsum of the hand has been reported to occur in 11% of the cases [167]. Gender differences exist, with men presenting later, and having more pronounced symptoms than women. This could be attributed to a general difference in response to symptoms [132], or differences in aetiology, such as multiple wrist trauma or vibration exposure.

The degree of neurophysiologic abnormality has been shown to reflect symptom distribution [28, 132]. Less severe median nerve dysfunction presenting diffuse symptoms, while notably pronounced nerve deficits provide more classic symptoms. Interestingly, patients with sensory CTS, involving all fingers, have evidence of enlarged hand representation in the sensory cortex [175].

Aetiology

The vast majority of cases of CTS are either idiopathic or spontaneous, presenting bilateral symptoms in over 60% of the patients [133]. Personal risk factors for idiopathic CTS include female gender, obesity and increase of age.

Numerous conditions are associated with CTS. High energy wrist trauma, such as fracture of the distal radius or carpal fracture dislocation, are frequent causes of acute CTS [61]. Failure to recognise, and treat elevated compartment pressure within the carpal tunnel, can lead to permanent median nerve dysfunction. In a recent study, distal radius fracture translation of more than 35% was determined as the most important risk factor for development of acute CTS [51].

Endocrine disorders, such as diabetes mellitus and hypothyroidism are regular causes of chronic CTS. In diabetic patients, neurophysiologic evidence of subclinical CTS was demonstrated in 20-30% of the cases, while symptomatic CTS was found in no more than 8% [4, 49]. The reason as to why CTS is more common in diabetes is unknown. It has been suggested that a nerve, with already established endoneurial hypoxia caused by diabetes, may be more susceptible to focal compression [103, 120]. Additional contributory mechanisms may arise from increased levels of advanced glycation end products (AGEs), as well as myofibroblasts in the surrounding connective tissue which lead to synovitis, stiffening of the flexor retinaculum and hence enhanced compression due to a decrease of the volume of the carpal tunnel [5, 149].

Other conditions related to CTS are pregnancy, rheumatoid arthritis, anomalous carpal tunnel structures and occupational factors such as repetitive motion or exposure to vibrating tools. It is agreed that familial occurrence of CTS exist as a rare but genetically distinct disorder [70]. However, in a study of patients with prior carpal tunnel surgery it was found that nearly 40% had a positive family history [144]. CTS occur in connection to autosomal dominant disorders, such as the demyelinating hereditary neuropathy with liability to pressure palsy (HNPP) [32]. A study on mono- and di-zygotic twins suggested that up to half of the liability to CTS in women were genetically determined. This estimate was unaffected after adjustments for age, body mass index, physical activity and hormonal factors [77].

Pathophysiology

The carpal bones and intercarpal ligaments shape the medial, lateral and posterior borders of the carpal tunnel. The anterior border is formed by the flexor retinaculum which consists of three parts. The deep antebrachial fascia represents the proximal part, the transverse carpal ligament the middle part, and the aponeurosis between the origin of the thenar and hypothenar muscles represents the distal part. It is believed that median nerve compression occur either at the proximal edge of the transverse carpal ligament, or where the carpal tunnel is narrowest at the level of the hook of the hamate.

Pressure in the carpal tunnel has been measured through an endoscopically placed catheter [65, 129]. In patients without CTS, the average carpal tunnel pressure with the wrist in neutral position was determined to be 14.3 mmHg. Of patients with CTS, the pressure averaged 43 mmHg and declined to 6.2 mmHg after surgical carpal tunnel release. A four to five fold increase in pressure was registered during active grip, or with full flexion, or extension of the wrist. After isolated carpal tunnel release, even pressure in Guyon's canal, as well as ulnar nerve symptoms were demonstrated to decline [1, 159].

Nerve compression syndromes involve peripheral nerve dysfunction due to localized interference of microvascular function, and structural changes in the nerve [146]. An experimental model, using miniature inflatable cuffs, showed disturbance of intraneural microcirculation after application of 20-30 mmHg of pressure, impairment at 40-50 mmHg, and at pressures of 80 mmHg, all blood flow ceased [153]. Similarly, axonal transport representing the communication system necessary for axon integrity and function, are inhibited at 30 mmHg [41]. Presumably, due to blockage of retrograde axonal transport, peripheral nerve compression leads to structural and biochemical alterations of the nerve cell body, with upregulation of various neuropeptides and induction of transcription factors such as activating transcription factor 3 (ATF3), the later associated with survival and regeneration of neurons [82]. In short, the cascade of peripheral nerve changes due to compression includes impaired microcirculation with increased vascular permeability, decreased venous return causing oedema, and subsequent increased endoneurial fluid pressure. In persistent cases, structural changes with segmental demyelination, fibrosis and Wallerian degeneration develop [146].

No animal model accurately or completely simulates human entrapment neuropathy. For obvious reasons, the possibility to study compressed nerve material from humans is limited. In a case report on superficial radial nerve entrapment, the findings were thickening

of the walls of the microvessels, epi- and peri-neurial oedema and marked thinning of the myelin [104]. A direct study of pathology in the compressed median nerve of human material, are limited to a case report of a patient who prior to death had neurophysiologic verified slowing of median nerve conduction velocity and increased latency. Pathology revealed loss of myelinated nerve fibres and extensive demyelination, particularly at the site of compression. In addition, there was marked swelling of the nerve proximal to the carpal tunnel ligament [177].

So far, no morphological studies on human nerve material exists providing information with regard to the pathogenesis for CTS.

Neurophysiology

Different neurophysiologic tests have been used for diagnosis of CTS. Classic measurement of median nerve distal motor latency has a high specificity (0.98) for the diagnosis of CTS, but the sensitivity (0.63) is moderate. In milder forms of CTS, fast conduction in the proximal and distal segment of the median nerve masks slowing in the segment within the carpal tunnel [94]. At present, measurement of antidromic wrist-palm sensory conduction velocity (specificity 0.98, sensitivity 0.85) is considered as the standard technique in the neurophysiologic diagnosis of CTS [83].

Assessment of CTS is the most frequent source of referral to neurophysiologic laboratories. However, its value as an additional diagnostic tool, when compared to clinical history and examination, has been questioned [71]. In addition, it has not been possible to demonstrate a relationship between nerve conduction results and clinical outcome measures after carpal tunnel release [119, 158]. Comparing neurophysiologic data between different studies, it is important to be aware that results are dependent on several factors; temperature variation, age, gender, height as well as weight of the patient [148]. Standardization becomes difficult as each neurophysiologic laboratory has its own specific "reference values". In spite of this, neurophysiology provides the most objective, non-invasive assessment of myelinated nerve fibre dysfunction, and has an important complimentary function in cases with atypical clinical presentation, or when other underlying causes such as neuropathy are suspected.

In non-diabetic patients with idiopathic CTS, significant neurophysiologic recovery of sensory conduction velocity, and distal motor latency, develops early on after carpal tunnel release [68, 98], whereas normal values are only regained in patients with minor nerve conduction abnormalities [119, 131]. In diabetes, impaired conduction in non-compressed

nerves develops early on in the disease, at which time it can still be reversed by strict metabolic control [74, 93, 150, 161]. In the presence of diabetic neuropathy, structural nerve changes such as segmental and paranodal demyelination, may cause a decrease in nerve conduction velocity, as well as reduced myelinated nerve fibre density might lead to decreased nerve action potential [14]. Neurophysiologic recovery, after carpal tunnel release in diabetic patients with peripheral neuropathy has not been studied.

Outcome assessment

Outcome assessment after carpal tunnel release has traditionally been based on physician-defined measures of success such as sense of touch, pinch or grip strength. Even though precautions are taken, all clinical examinations are at risk of examiner's bias. In published studies, clinical diagnostics and examination protocols are often not described in detail or lacks standardization [84]. Comparison of results across studies is therefore difficult. Generally, patients seek treatment because of the combined severity of symptoms and its impact on functional status. Consequently, the patient's evaluation of treatment outcome may not always be in accordance with the examiner or surgeon's judgment.

Self-administered questionnaires on Health-related quality of life (HRQL) have proven a valuable tool to assess impact of disease and outcome of intervention seen from the patients' perspective. The specific choice of an outcome measure is primarily determined by what one may wish to assess. Generic measures of quality of life, such as the Medical outcomes study 36-item short-form health survey (SF-36), allow a comparison between different diseases, and with the general population. This has been recommended in studies on both diabetes and CTS and provides a high internal reliability and validity [7, 9, 187, 193]. Disease-specific instruments such as the Boston Carpal Tunnel Questionnaire (BCTQ), have the potential of being more sensitive to detect clinical changes when they have occurred (responsiveness) [13]. The combined use of generic and disease-specific instruments to assess quality of life is therefore suggested as a comprehensive outcome measure after surgical carpal tunnel release [7, 9, 88]. Other self-administered questionnaires do exist, e.g. the region-specific disability of the arm, shoulder and hand (DASH) questionnaire [81]. DASH is a useful score across the upper limb, particularly in patients with multiple upper limb joint involvement [33, 64].

It is recognised that diabetes, its long-term complications such as peripheral neuropathy, retinopathy and cardiac disease, adversely, affect quality of life [39, 182, 187]. However, the

impact of CTS, and its surgical treatment, on generic health-related quality of life in diabetic patients has not been studied.

Diabetic neuropathy

Diabetes mellitus is a group of metabolic disorders characterised by hyperglycaemia. Type 1 diabetes (insulin-dependent or juvenile-onset diabetes) which accounts for 10% of those with diabetes, are caused by cellular-mediated autoimmune destruction of β-cells of the pancreas, leading to absolute insulin deficiency. Type 2 diabetes (non-insulin-dependent or adult-onset diabetes) includes subjects with relative insulin deficiency and insulin resistance. Diabetic neuropathy is the most common long-term complication of Type 1 and Type 2 diabetes, affecting approximately 10% within a year of diagnosis to 50% of subjects with diabetes for more than 25 years [58]. However, diabetic neuropathy associated with Type 1 diabetes tend to be more frequent, and develop more rapidly than in Type 2 diabetes [48]. The primary risk factor for the development of diabetic neuropathy is related to duration and severity of hyperglycaemia. Other risk factors include hypertension, hypercholesterolemia, obesity, age and height [2, 179].

Classification

Diabetic neuropathy is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after exclusion of other causes" [20]. It affects somatic as well as autonomic neurons of the peripheral nervous system. Several different classification systems exist based on either symptoms or topographical location. The variation probably reflects that the general understanding of the precise pathogenesis underlying diabetic neuropathy is incomplete. Diabetic neuropathies can be classified into three groups: 1) Length dependent polyneuropathy including distal sensorimotor polyneuropathy and autonomic neuropathies. 2) Focal and multifocal neuropathies such as cranial and truncal neuropathies. 3) Neuropathies that are more common in diabetes such as pressure palsy including CTS [20].

Distal sensorimotor polyneuropathy

This is the most common clinical presentation of neuropathy in diabetes, with dying-back of myelinated and unmyelinated nerve fibres. Initial symptoms include numbness and tingling in the feet, which progresses proximally in the lower leg, and may eventually reach the distal

part of the upper limb leading to a classic "glove and stocking" involvement. Sensory neuropathy, with numbness in the feet, is considered an important factor in the development of foot ulceration and lower extremity amputation. The disorder is commonly associated with small nerve fibre neuropathy (myelinated Aδ and unmyelinated C fibres) which causes burning pain, allodynia, abnormal temperature sensation, altered tissue blood flow and diminished sweating. In more advanced cases, muscle wasting may appear although motor weakness is unusual [20, 154].

Autonomic neuropathy

Diabetic autonomic neuropathy may present in different organ systems and contribute greatly to the morbidity, mortality and reduced quality of life in subjects with diabetes [192]. Cardiovascular symptoms consist of a resting tachycardia and orthostatic hypotension. Gastrointestinal neuropathy may cause delayed gastric emptying with constipation and diarrhoea. Bladder atony may lead to urinary retention and/or incontinence. Erectile dysfunction is a frequent complication in male patients with diabetes [154].

Focal and multifocal neuropathies

These neuropathies are more common in elderly Type 2 diabetic patients. They have an acute onset, tend to be self-limiting and endoneurial ischemia is considered to be an underlying cause. Cranial neuropathies typically involve the 3rd, 4th and the 6th cranial nerve and may lead to ophthalmoplegia. Truncal neuropathies are usually unilateral with pain and dysaesthesias as the predominant symptoms [20].

Neuropathies more common in diabetes

These neuropathies include the subject of this thesis – the carpal tunnel syndrome.

Pathogenesis

Interactions of pathogenic metabolic and vascular factors are responsible for the development of diabetic neuropathy. These complex mechanisms are not fully understood.

Metabolic factors

In hyperglycaemia, shunting of excessive glucose through the polyol pathway leads, via the enzyme aldose reductase, to formation of sorbitol and fructose at the expense of other

osmolytes such as myoinositol. Due to low membrane permeability the accumulation of sorbitol may lead to increased intracellular osmotic load, while the accumulated fructose stimulates non-enzymatic glycation. Depletion of myoinositol results in decreased levels of protein kinase C, which is necessary for activation of neural Na^+/K^+-ATPase activity. The activated polyol pathway causes depletion of NADPH and nitric oxide promoting oxidative stress and increased vascular tone, respectively [73, 160]. The enhanced non-enzymatic glycation of glucose on protein amino groups and lipids leads eventually to formation of irreversible advanced glycation end products (AGEs). The glycation of cytoskeletal and myelin proteins contributes to slowing of axonal transport, axonal atrophy and segmental demyelination [194]. Increased AGEs, redox imbalance due to increased aldose reductase activity and mitochondrial overproduction of superoxide are factors responsible for the induction of oxidative stress. The relative overproduction of reactive oxygen species contributes to diminished vascular blood flow, nerve conduction deficits and impaired nerve regeneration due to reduced neurotrophic support [141, 194]. Recently, is has been demonstrated that insulin and C-peptide have a stimulating effect on Na^+/K^+-ATPase and endothelial nitric oxide. As these factors are depleted in Type 1 diabetes, it may explain the differing severity of neuropathy in Type 1 and Type 2 diabetes [52, 161].

Vascular factors

Microangiopathy is a fundamental abnormality of the vasa nervorum in diabetic neuropathy. Endothelial dysfunction, measured by vascular reactivity and biochemical markers for endothelial injury, appear to precede the onset of frank hyperglycaemia in patients with impaired glucose tolerance as well as in subjects with a parental history of diabetes [27]. Indirect support for the importance of hypoxia in nerve dysfunction has been demonstrated, as exercise induces increased nerve conduction velocity in normal subjects but not in diabetic patients with neuropathy [176]. Furthermore, neurophysiologic dysfunction as in peripheral neuropathy develops in patients with chronic obstructive pulmonary disease [106]. In diabetic patients, endoneurial microangiopathy is already evident before the development of overt neuropathy, and the severity of morphologic changes correlate to the degree of neuropathy [67, 107, 178]. The ultra-structural changes demonstrated in human sural nerve biopsies include perivascular basement membrane thickening and endothelial cell hyperplasia [57, 107].

The endothelial cells, which line the internal wall of all vessels, have an important function in producing chemical messengers responsible for vascular tone, inflammatory

changes, and maintaining blood fluidity and haemostasis [29]. Nitric oxide is considered the most important vasodilator that is released from the endothelium [136]. With hyperglycaemia, impaired synthesis of nitric oxide is related to metabolic depletion of NADPH by aldose reductase, and its action is inactivated by oxidative stress [46, 141]. The rheologic properties of erythrocytes in diabetes are changed, shown by decreased erythrocyte deformability, increased membrane microviscosity and erythrocyte aggregation [124].

Diabetes also involves macrovascular complications. The common underlying factor of macrovascular complications, such as in stroke and myocardial infarction is accelerated atherosclerosis, which is triggered by insulin resistance and elevated lipid levels [38].

Neurophysiology

Measurement of sensory and motor nerve conduction velocity is important for identification and quantification of neuropathy in diabetic patients and to document the clinical course of treatment [23]. Guidelines and recommended protocols for neurophysiologic diagnosis of sensory peripheral neuropathy include; studies of sural sensory, ulnar sensory, and median sensory nerves, and peroneal, tibial, median and ulnar motor nerves. Minimum criterion for neurophysiologic confirmation of the diagnosis is defined as abnormality of any attribute of nerve conduction in two separate nerves, one of which must be the sural nerve [55].

It is generally assumed that reduced endoneurial blood flow together with metabolic factors, such as accumulation of polyols and decreased Na^+/ K^+-ATPase activity, is responsible for the abnormality in nerve conduction. These metabolic factors lead to axonal swelling, reduced nodal Na^+ current, and disruption of the paranodal ion-channel barrier [80, 115, 161]. In humans, treatment with aldose reductase inhibitors has in some studies shown improvement of nerve conduction velocity [80, 115].

Small nerve fibre neuropathy

Epidermal nerve fibres are predominantly unmyelinated C-fibres, which originate from the dorsal root ganglion, and are responsible for conveying thermal and nociceptive painful sensation [142]. Small nerve fibres degenerate early in the course of diabetic neuropathy, and are perhaps even affected in patients with impaired glucose tolerance [102, 123, 172]. Nerve conduction studies and assessment of vibration thresholds are useful to detect large nerve fibre dysfunction or damage. An accepted method to evaluate small nerve fibre pathology is quantification of intraepidermal nerve fibre density (IENFD) [99], using immunostaining with

the cytoplasmatic neuronal marker protein gene product 9.5 (PGP 9.5). In accordance with recommendations from the European Federation of Neurological Societies (EFNS), the majority of studies report results from the lower extremity [99]. It is generally believed that IENFD decreases with age, while the influence of gender seems controversial [69, 184]. In healthy subjects, as well as in asymptomatic diabetic patients, a length dependent reduction of IENFD has been demonstrated [112, 183]. Measurement of IENFD, as opposed to neurophysiology and quantitative sensory testing, was the most sensitive measure of neuropathy change during one year of lifestyle intervention for pre-diabetic neuropathy [163]. However, several reports indicate that a reduction in IENFD among diabetic patients may primarily be related to those suffering severe neuropathy symptoms associated with small fibre neuropathy [92, 143, 166].

Small nerve fibres can also be assessed from a sural nerve biopsy. However, the biopsy procedure may cause long-term discomfort for the patient [40] and evaluation requires access to electron microscopy. A study, where patients underwent skin as well as sural nerve biopsy, concluded that IENFD measurement in the skin was more sensitive than sural nerve biopsy to identify small fibre neuropathy [78].

Studies of IENFD in the upper extremity are sparse and have shown divergent results. They have been based on patients with neuropathy of different origin, lacking an age and gender matched control group, or performed to establish normative data but applying different techniques [36, 91, 126, 140]. Whether quantification of IENFD at the wrist level is able to establish signs of subclinical small nerve fibre neuropathy in diabetic and non-diabetic patients has not been investigated.

Large nerve fibre neuropathy

For many years sural nerve biopsy has been the method of choice to undertake neuropathological assessment for the diagnosis of peripheral neuropathies of unknown cause [50]. Recently, practice parameters from the American Academy of Neuromuscular and Electrodiagnostic Medicine found nerve biopsy to be most valuable in mononeuropathy multiplex or suspected vasculitic neuropathy [54]. It is not a technique which should be employed solely to diagnose diabetic neuropathy. However, much insight can be gained into the underlying pathology and pathogenesis of nerve damage. Several papers have reported high complication rates following sural nerve biopsy; wound infection, persistent pain at the biopsy site, dysaesthesia of the affected skin, persistent sensory loss and patient

dissatisfaction with the procedure [40, 63, 152]. The increased risk of wound infection is particularly relevant in diabetic patients with impaired tissue blood flow and delayed wound healing. Therefore, it has been recommended that the procedure should be restricted to carefully selected cases, and performed by experienced surgeons, at centres with a special interest in peripheral neuropathy [164].

From evaluation of sural nerve biopsies, it is known that the principal pathological lesions in human diabetic neuropathy are axonal degeneration and regeneration with loss of large myelinated nerve fibres, and segmental demyelination [189]. Myelinated nerve fibre density has proven a reliable indicator of neuropathy in diabetic patients, correlating with clinical findings as well as to nerve conduction studies [105, 109, 173]. Furthermore, a low myelinated fibre density may predict future nerve fibre loss and progression of neuropathy with time [179].

With progression of disease, diabetic neuropathy may also affect the upper limb, in particular the mononeuropathies. Due to morbidity of a nerve biopsy, as well as the length-dependent nature of diabetic neuropathy, only a few publications describe morphology of nerves in the upper limb. These results are provided from post-mortem subjects or amputated limbs [47, 147]. A low morbidity method to assess nerve pathology in the upper limb, which fulfils the criteria for nerve biopsy, has not been described. Furthermore, human morphologic studies to investigate the link between diabetes and the increased susceptibility to CTS have not been undertaken.

AIM OF THE THESIS

The general aim is to compare the outcomes of carpal tunnel release in diabetic and non-diabetic patients with carpal tunnel syndrome (CTS), and based on a new nerve biopsy method to investigate the background for increased susceptibility to CTS in diabetes.

Specific aims are to:

- compare clinical outcome after carpal tunnel release in diabetic and non-diabetic patients.
- assess health-related quality of life (HRQL) in diabetic and non-diabetic patients with CTS.
- describe nerve conduction results prior to and after carpal tunnel release in diabetic and non-diabetic patients.
- evaluate if quantification of intraepidermal nerve fibre density (IENFD) at wrist level can detect signs of subclinical small nerve fibre neuropathy.
- establish if biopsy of the posterior interosseous nerve (PIN) at wrist level will be a feasible and low morbidity method to assess neuropathy in the forearm.
- compare pathology in the non-compressed PIN between diabetic and non-diabetic patients with CTS.

PATIENTS

The study was approved by the Regional Ethical Review Board at Lund University (LU 508-03). All patients gave informed consent to participate.

Paper I-IV

From 2004 to 2007, consecutive patients with diabetes referred to our outpatient clinic with symptomatic CTS during at least six months were invited to participate in the study. Included were 36 consecutive diabetic patients with CTS and 36 age and gender matched non-diabetic patients with idiopathic CTS. The diagnosis of CTS was based on clinical history and symptoms, and confirmed by median nerve conduction studies. The exclusion criteria were; previous carpal tunnel release in the hand under study, clinical signs of focal nerve entrapment other than CTS, cervical radiculopathy, inflammatory joint disease, renal failure, thyroid disorders, previous wrist fracture on the affected side, daily long-term exposure to vibrating tools, pregnancy or age under 18 years. Signs of peripheral neuropathy demonstrated in the nerve conduction study were an exclusion criterion for the non-diabetic patients with CTS, but not for the diabetic patients with CTS.

After screening, one patient was excluded from the diabetic group due to the diagnosis of thyroid dysfunction. In the non-diabetic group, three patients were excluded due to diagnosed diabetes (oral glucose tolerance test) and two were excluded because the nerve conduction studies demonstrated signs of peripheral neuropathy of unknown origin. Thus, the patients under study consist of 35 diabetic patients with CTS (median age 54 years [range 31-73]) and 31 non-diabetic patients with CTS (median age 51 years [range 35-77]). Se papers I-IV and VI for furthers details.

Paper V

From a prospective health screening programme in the city of Malmö, Sweden [56], ten out of 23 patients with Type 2 diabetes since 1991 underwent a biopsy of the posterior interosseous nerve (PIN), and one of these patients underwent a PIN as well as a sural nerve biopsy (Fig.1). Median age (range) was 75 years (73-79). As a comparator, six PIN biopsies taken post-mortem from male cadavers with no history of neuropathy, CTS or trauma were evaluated (median age 59 years [50-72]) [170].

Paper VI

This study encompasses the same 35 diabetic and 31 non-diabetic patients as described for Papers I-IV. Furthermore, as controls, PIN biopsies from 13 subjects with no history of diabetes, CTS or neuropathy were included (10 PIN biopsies taken post mortem from male cadavers and 3 biopsies taken at the time of elective wrist surgery [170]).

Figure 1. Performing a posterior interosseous nerve biopsy.

METHODS

A more detailed description of the various methods is found in the individual papers.

Clinical examination

Clinical examination was performed prior to surgery and 6, 12 and 52 weeks after surgical carpal tunnel release. The examinations, performed by the same occupational therapist, included perception of touch with the Semmes-Weinstein monofilament [15], tactile gnosis with the static two-point discrimination test [116], strength of median nerve innervated abductor pollicis brevis muscle [22] and overall measure of grip strength, key- and lateral-pinch [111]. Visual analogue scales were used for the patient to rate pillar pain, after applying standardised pressure on to defined point in the palm of the hand, and to provide their subjective evaluation of scar allodynia and cold intolerance.

Self-administered outcome assessment

The generic medical outcomes study 36-item short-form health survey (SF-36) and the disease-specific Boston Carpal Tunnel Questionnaire (BTCQ) were administrated and completed by the patients' at all follow-up times.

The SF-36 includes one multi-item scale to measure eight health domains; physical functioning, role limitations because of physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations because of emotional problems, and general mental health [171, 188]. The response within each domain is translated into a score ranging from 0 (poor health) to 100 (optimal health).

The BCTQ consists of two multi-item scales [10, 100]. The symptom severity scale include 11 items (severity of nocturnal pain, frequency of nocturnal awakening due to pain, severity of daytime pain, frequency of daytime pain, duration of daytime pain, severity of numbness, severity of weakness, severity of tingling, severity of nocturnal numbness/tingling, frequency of nocturnal awakening due to numbness/tingling, difficulty in gripping small objects) with response categories from 1 (no symptoms) to 5 (severe symptoms). The functional status scale consists of 8 items (difficulty- writing, buttoning clothes, holding a book, gripping of a telephone handle, opening jars, performing household chores, carrying of grocery bags, bathing and dressing) with answers rated from 1 (no functional impairment) to 5

(cannot perform the activity at all). Accordingly, a higher score indicates more severe symptoms or dysfunction.

Nerve conduction studies

The nerve conduction study was performed using a Viking Select electromyograph (Viasys Inc., Madison, WI, USA). Studies were conducted with surface electrodes (skin temperature kept above 30°C); additional needle electromyography was not performed. All investigations were performed by the same technician and evaluated by the same neurophysiologist.

Measured were; median nerve distal motor latency, motor conduction velocity, compound muscle action potential, orthodromic sensory conduction velocity and action potentials from digits I and III, and fractionated antidromic sensory conduction velocity over the carpal tunnel segment. The later was our primary nerve conduction parameter for the diagnosis of CTS. Ulnar nerve measurements included; distal motor latency, motor conduction velocity, compound muscle action potential, sensory conduction velocity and sensory nerve action potential.

To diagnose peripheral neuropathy all patients underwent measurement of sural nerve sensory conduction velocity, sural sensory nerve action potential and peroneal nerve motor conduction velocity. Criterion for peripheral neuropathy was detection of abnormal values in both the sural and the peroneal nerve [55].

Carpal tunnel release

All operations were performed by the same surgeon under a regional intravenous nerve block. A short, palm only, incision was made between the distal wrist crease and Kaplan's cardinal line. The transverse carpal ligament was divided sharply and the distal one cm of the deep antebrachial fascia was split. No additional procedures were performed.

Skin biopsy

Skin biopsies were performed in conjunction with surgical carpal tunnel release using a 3 mm disposable circular needle (Dermal Biopsy Punch; Miltex, Inc, PA, USA). A sample of glabrous skin was taken from the palm, 2 cm distal to the distal wrist crease, being midpoint of the planned incision for open carpal tunnel release. On the extensor side, a hairy skin sample was taken 4 cm proximal to the distal wrist crease, centred between the radius and the ulna.

The biopsies were immediately fixed in 4% formaldehyde for 12- 24 hours, dehydrated, and subsequently paraffin-embedded. Three sections (thickness 5 μm, distance between sections 15 μm), were mounted on ordinary glass slides for routine staining and on positively charged glass slides for immunohistochemical staining. The sections were dewaxed, rehydrated and microwave pre-treated in 10mM citrate buffer for 19 minutes at 750 W for antigen retrieval. Immunohistochemical staining with an antibody against PGP 9.5, (Ultra Clone, Isle of Wright, England) at a 1:3000 dilution was performed with an automated immunostainer (TechMate 500 Plus, Dako, Glostrup, Denmark).

All nerve samples had been blinded in order to prohibit identification of individuals and diagnosis during the manual nerve counting using light microscopy (Olympus BX 50; magnification 10x40). Individual PGP 9.5 – stained nerve fibres were assessed and counted as one unit when crossing the dermal-epidermal junction. Secondary branching within epidermis was not counted [99]. However, due to the thinness of the 5 μm samples, well defined intraepidermal nerve fibres not visibly crossing the basement membrane were encountered. Such isolated nerve fibres were counted as one unit. Mean IENFD, expressed as number of nerve fibres per mm, was calculated for each biopsy and used for the further analysis.

Posterior interosseous nerve biopsy

At the level of the lateral epicondyle the radial nerve divides into the superficial sensory branch following the course of the brachioradial muscle, and the deep branch - the posterior interosseous nerve (PIN). The PIN enters and passes between the superficial and the deep head of the supinator muscle and divides into several branches supplying the superficial and the deep extensor muscles. After innervating the extensor pollicis longus and extensor indicis proprius muscles the distal part of the PIN becomes purely sensory and passes deep to the interosseous membrane in the radial part of the fourth compartment. The PIN is accompanied by the dorsal branch of the anterior interosseous artery which penetrates through from the volar side of the interosseous membrane along the pronator quadratus muscle [134]. At the level of the radiocarpal joint, the PIN splits up to innervate the central two-thirds of the dorsal wrist joint capsule. It is believed to essentially carry afferent nerve fibres from wrist joint mechanoreceptors, with no cutaneous afferent fibres or motor efferent fibres [62, 76, 181].

The biopsy procedure was carried out under local anaesthesia. On the dorsal side of the forearm a 3-4cm long straight-line incision was made 1cm proximal to the ulnar head centred exactly between the radius and ulna (Fig.2). The fourth extensor compartment was identified

containing the musculotendinious junctions of the extensor indicis proprius and extensor digitorum communis. Using blunt dissection the posterior interosseous nerve and adjacent interosseous artery, together with its venae comitantes, were identified on the interosseous membrane. A 3-4cm long nerve biopsy was harvested.

The nerve tissue was fixed in 2.5% glutaraldehyde. Semi-thin (0.5µm) sections were stained with thionin and counter-stained with acridine orange. Each fascicle was photographed (magnification x 200) using Vickers and Leica light microscopes. Digital images were captured of all fascicles from sections of each biopsy. The Image Pro Plus 4.1 image analysis system was employed to measure fascicular area (mm^2) and subperineurial space (mm^2). Endoneurial capillaries and myelinated nerve fibres were counted directly from the images. Endoneurial capillary and myelinated fibre densities (no./mm^2) were obtained by dividing the number of endoneurial capillaries and myelinated nerve fibres, respectively, by the fascicular area [108]. All fascicles were examined in each nerve and mean values were derived. The nerve samples from the CTS patients were blinded as to whether they originated from a diabetic or a non-diabetic patient.
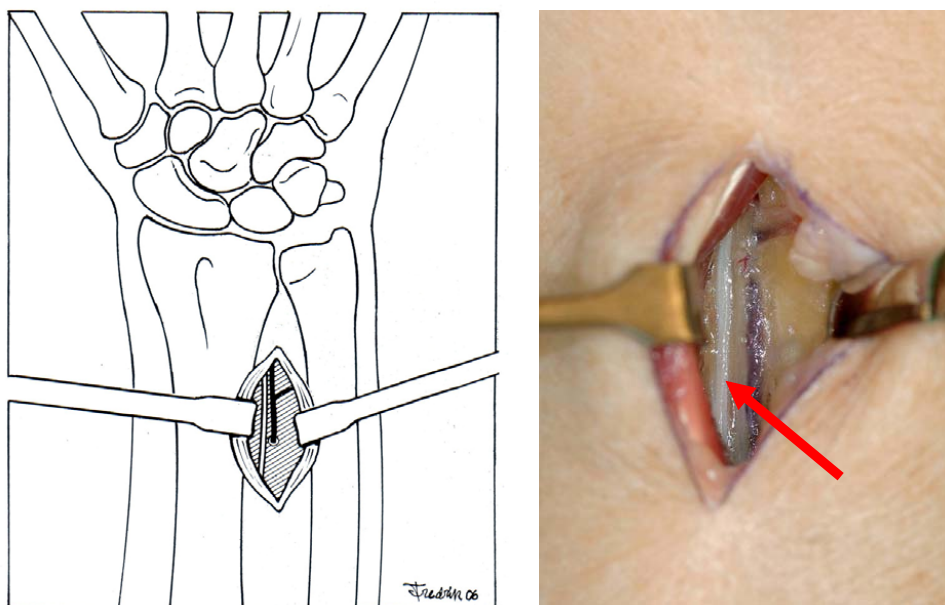
Figure 2. The posterious interosseous nerve (arrow) located on the interosseous membrane.

Statistics

Differences in continuous data between groups and within groups were tested using non-parametric Mann-Whitney U-test and Wilcoxon signed rank test, respectively. Fisher's exact test was used for categorical data. Correlations were performed using Spearman rank sum test and expressed as a coefficient (r_s) with a level of significance. Mixed model analysis focuses on the overall mean difference between patient groups and the overall time pattern of the improvement, thereby avoiding multiple testing at individual time points. Clinical differences of relevance between the patients under investigation can be adjusted for. Mixed model analyses were performed in paper I and II. Statistical analysis was performed using SPSS 14.0 for Windows (SPSS Inc., Chicago, IL, USA). $P < 0.05$ was considered statistically significant.

Results

This section gives a summary of the results with some comments. For further details, the reader is referred to the individual papers.

Paper I - no difference in clinical improvement after carpal tunnel release.

The aim of this study was to compare the clinical outcomes after surgical carpal tunnel release in diabetic and non-diabetic patients. The number of patients with normal sensory function increased significantly in both patient groups from the preoperative examination to the 1 year follow-up. For both patient groups, grip strength decreased temporarily at 6 weeks but recovered completely after 12 weeks. At one year follow-up grip strength had improved significantly in both diabetic and non-diabetic patients compared to the preoperative measures. Pillar pain, which was most pronounced in the hypothenar region, showed a significant inverse correlation with grip strength at the 6 weeks follow-up. The often described initial decline in grip strength might therefore be related to postoperative pillar pain. The number of patients reporting cold intolerance decreased over time, but significantly less for the diabetic patients. Level of patient satisfaction was high in both patient groups. No important difference in results between Type 1 and Type 2 diabetic patients were found.

Paper II - impaired health-related quality of life in diabetic patients with CTS.

The SF-36 physical component score, prior to surgical carpal tunnel release, was significantly reduced for diabetic compared to non-diabetic patients. Mixed model analysis demonstrated no differences in post-surgical improvement over time between the two patient groups. The largest clinical effect was found for bodily pain. However, population norms were not reached for the diabetic patients as opposed to the non-diabetic patients. Preoperatively, no difference was found in mental component score, which however, deteriorated over time for diabetic patients. Before surgery, BCTQ demonstrated that diabetic patients experienced more pronounced "numbness in the hand" than non-diabetic patients. Large clinical improvements were found in symptom severity as well as in functional status score, for both diabetic and non-diabetic patients, with no differences between the two patient groups.

Paper III - **marked neurophysiologic impairment and recovery in diabetic patients.**

Diabetic patients demonstrate significantly impaired nerve conduction parameters, prior to as well as after surgical carpal tunnel release, compared to non-diabetic patients. However, neurophysiologic recovery after carpal tunnel release was not different between the two patient groups or between diabetic patients with or without peripheral neuropathy. In general, the largest neurophysiologic recovery was demonstrated for parameters with the greatest impairment, but normal values were seldom reached. Ulnar nerve measurements pointed towards the existence of subclinical neuropathy in the diabetic patients. Diabetic patients with peripheral neuropathy had significantly impaired nerve conduction parameters compared to diabetic patients without neuropathy. However, post-surgical recovery was the same regardless the presence of peripheral neuropathy.

Paper IV - no difference in IENFD at wrist level in diabetic and non-diabetic patients.

In skin biopsies taken from hairy and glabrous skin at wrist level, no difference was found in IENFD between diabetic and non-diabetic patients (Fig.3). Furthermore, we could not demonstrate any difference between Type 1 and Type 2 diabetic patients, or between subgroups of diabetic patients with or without peripheral neuropathy. However, IENFD was significantly higher in hairy compared to glabrous skin and higher in females than in males.
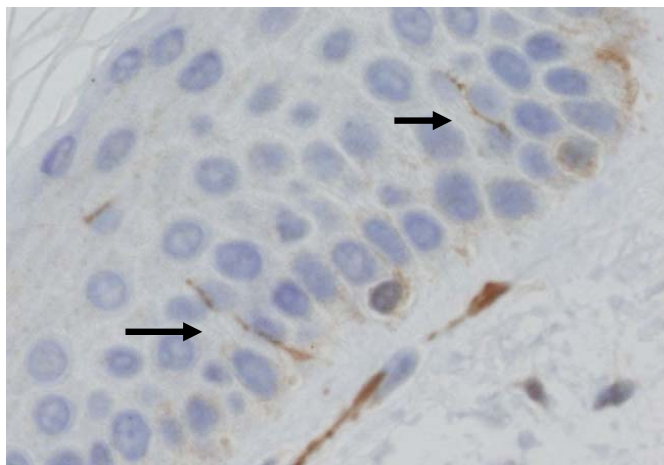

Figure 3. Intraepidermal nerve fibres (arrows).

Paper V - PIN biopsy allows for diagnosis of neuropathy.

The PIN biopsies demonstrated a reduced myelinated nerve fibre density in Type 2 diabetic patients compared to control samples with no history of neuropathy, CTS or trauma. A reduction in myelinated nerve fibre density has previously been proven a reliable criterion for diagnosis and staging of neuropathy in diabetes. The PIN biopsy procedure was found to fulfil the criteria for nerve biopsy which furthermore, was well tolerated by the patients.

Paper VI – nerve pathology may predispose patients to CTS.

PIN myelinated nerve fibre density was significantly reduced in diabetic and non-diabetic patients with CTS compared to control subjects (Fig.4). Furthermore, diabetic patients had a significantly lower nerve fibre density than non-diabetic patients. Endoneurial capillary density was also reduced in diabetic and non-diabetic patients compared to control subjects, but with no differences between diabetic and non-diabetic patients with CTS. A significant correlation was found between myelinated nerve fibre and endoneurial capillary densities. Although nerve pathology may be expected in diabetic patients, a comparable pathology in non-diabetic patients with no recognised metabolic disturbance or neurologic disease, other than CTS, is a novel and unexpected finding.
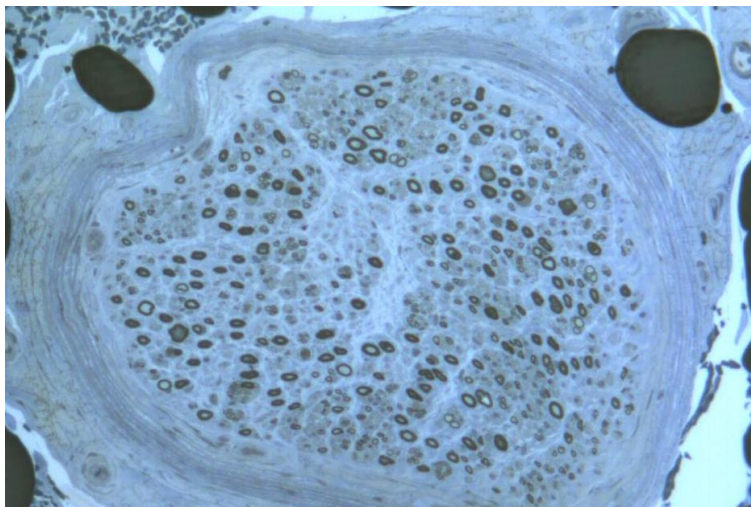

Figure 4. Light microscopy image from a posterior interosseous nerve (PIN) fascicle of a diabetic patient. A reduced number of myelinated nerve fibres are noted.

GENERAL DISCUSSION

CTS is the most common entrapment neuropathy encountered in diabetic patients. It occurs 4-5 times as frequent in the diabetic population compared with a normal healthy population. A Medline database search (Sept. 2009) on "carpal tunnel syndrome" revealed 6799 published articles on this subject. Thereby, it is the most commonly studied nerve entrapment. The majority of studies focus on CTS in general, why diabetic patients usually are excluded. Only two attempts have been made to perform studies on surgical carpal tunnel release in diabetic patients [118, 130]. Unfortunately, well designed studies are uncommon due to; inadequate diagnostic criteria, lack of standardised outcome measures, the observer not being blinded, statistically considering hands instead of patients, et cetera [21, 156].

Peripheral neuropathy is a common complication of diabetes. To my knowledge, no studies exist which provide results on decompression of the median nerve in diabetic patients with signs of peripheral neuropathy. Based on the double crush hypothesis [185], where diabetes is considered the first and entrapment the second crush, decompression of lower limb nerves has been performed for the treatment of diabetic neuropathy. However, a recent systematic review identified 142 publications, from which the authors have failed to identify a single randomized controlled trial, or any other well designed prospective study. They concluded that the role of decompression surgery for diabetic distal neuropathy remains totally unproven [34].

There are several strengths to the studies of this thesis. Diabetic patients with CTS were included consecutively, and subsequently age and gender matched with non-diabetic patients having idiopathic CTS. Strict eligibility criteria were used including oral glucose tolerance test of all non-diabetic patients. Operations were performed by the same surgeon, and standardised follow-up examinations were carried out independently by the same occupational therapist. Skin and nerve tissue samples were blinded as to whether they originated from a diabetic or a non-diabetic patient. Finally, there was a nearly 100% follow-up rate.

A limitation of the studies is the sample size, which may hamper the ability to detect important clinical differences, in other words a statistical type 2 error. The sample size generally restricts the statistical analyses to non-parametric methods. A possible limitation is that classification of peripheral neuropathy is based on nerve conduction studies only, and not confirmed by clinical examination. However, it is agreed that neurophysiologic studies are

sensitive, specific and validated measures of the presence of polyneuropathy [55]. A potential weakness is that the majority of the PIN biopsies representing control subjects originate from autopsy material. However, autolysis of peripheral nerves is a late phenomenon, and no morphological differences were to be found comparing PIN biopsies between autopsy samples and surgical control patients.

Clinical outcomes

The diabetic and non-diabetic patient groups in this study are representative of patients with CTS by means of; predominantly female representation, mid-aged patients, mainly having involvement of the dominant hand as well as bilateral symptoms. In a comparison between the two patients groups, the diabetic patients had CTS for a shorter period of time, but presented with more pronounced neurophysiologic abnormality. A possible explanation could be the resistance to ischemic conduction block found in diabetes, and their higher rate of hypertension, which increases perfusion pressure in the intraneural microvessels [101, 174]. Consequently, the presentation of CTS may be delayed, at which time the nerve pathology would be more prominent.

In the treatment of CTS, irrespective of surgical technique, results are generally considered to be rewarding with minimal complications and high satisfaction rates. With the exception of cold intolerance, results in this study have demonstrated that there are no differences in clinical outcome between diabetic and non-diabetic patients. However, there were indications towards a slower sensory recovery in Type 1 diabetic patients and diabetic patients with peripheral neuropathy. The resemblance of clinical outcome in diabetic and non-diabetic patients points toward a joint pathogenesis for CTS, despite the increased susceptibility to nerve compression in the former.

Cold intolerance (exaggerated reaction to cold exposure causing discomfort which can progress to pain) is a common problem following upper extremity trauma [37, 53]. While little is known about the mechanisms of cold intolerance, it is apparent that the clinical symptoms can be quite disabling. From a General Practice, symptoms of heat or cold intolerance were reported by more than one third of patients with diabetes, significantly more than in non-diabetic patients [95]. After sural nerve biopsy, 50% of diabetic patients complained of cold intolerance compared to only 5% of non-diabetic patients [40]. Surprisingly, in the present study, 60% of both patient groups reported cold intolerance prior to the operation. Although, diabetic as well as non-diabetic patients improved significantly

over time, it was to a much lesser extent for the diabetic patients. Using infrared thermography, postoperative relief of abnormal vasoregulation has been demonstrated for CTS patients [114]. After nerve injury correlation has been found to exist between sensory recovery and diminishment of cold intolerance [151]. No studies have previously reported on cold intolerance in diabetic patients with CTS. One can only speculate why cold intolerance was relieved to a lesser extent in diabetic patients. First of all, the endothelium produces a number of important vasodilatory mediators, including nitric oxide, which in diabetes is depleted due to hyperglycaemia and the activated polyol pathway. Such possible vasoregulatory imbalance might favour an earlier and prolonged vasoconstriction response to cold exposure. Secondly, thermal and pain sensation as well as autonomic functions are mediated by small nerve fibres, unmyelinated C-fibres and small myelinated Aδ fibres, which is reported to degenerate early in the course of diabetic neuropathy [102, 172]. However, in the present study no difference in IENFD between diabetic and non-diabetic patients could be demonstrated (Paper IV).

Health-related quality of life

Diabetes adversely affects quality of life due to burdens associated with strict maintenance of glycemic control [145], and the presence of diabetic co-morbidity and complications such as peripheral neuropathy, retinopathy and cardiac disease [39, 182, 187]. It was therefore not surprising to find the physical SF-36 baseline scores at a significantly lower level in the diabetic patient group. Even though SF-36 only includes a few issues related to the upper extremity the domains of bodily pain and role physical, have previously been proven sensitive to changes after carpal tunnel release in non-diabetic patients [7, 9, 87]. The involvement of the domain of bodily pain, is in accordance with the most important reason for patients to undergo carpal tunnel release, which is to achieve relief of pain and numbness [16]. The influence on role physical indicates that CTS, substantially, may affect the patient's ability to perform even fundamental activities of daily living and working tasks. In our patients, there were no differences in physical quality of life improvement between diabetic and non-diabetic patients, although diabetic patients did not reach that of the population norms.

It was even expected to find preoperative differences within the SF-36 mental domains comparing diabetic and non-diabetic patients [39]. Diabetes co-morbidity such as hypertension, which was frequent, are known to lower mental health perception [12]. At follow-up, the mental quality of life had decreased over time for diabetic patients, while it had

improved for non-diabetic patients. As the clinical outcomes described in Paper I did not differ between the two patient groups, the diverging mental health results might be ascribed to other factors than CTS, as for example the various diabetic co-morbidities or complications.

In studies of non-diabetic patients, the disease specific BCTQ has proven sensitive to detect and predict the outcome after carpal tunnel release [7, 88]. As in studies of non-diabetic patients with CTS, the clinical improvements were larger and faster for the symptom severity scale compared to the functional status scale. In fact, the symptom severity score continuously improved up to the one year follow-up, while the functional status score had reached a plateau at 12 weeks. The patients' self-reported CTS outcome assessment may be more responsive to clinical improvement than measures of sensory-motor impairment [7, 10, 86]. However, in this study a clear parallel exist among results from clinical outcomes (Paper I) and self-reported outcome questionnaires (Paper II), demonstrating significant improvement over time and no differences between diabetic and non-diabetic patients.

No obvious differences were found between diabetic patients with and without peripheral neuropathy. It might imply that the clinical symptoms of CTS are not masked by the symptoms of diabetic peripheral neuropathy. It is therefore advocated that tingling and/or numbness in the hand of diabetic patients, should not be attributed to diabetic neuropathy before CTS has confidentially been ruled out.

Neurophysiology

The primary pathology of CTS is thought to be focal demyelination and in advanced cases axonal loss. This leads to a more pronounced effect on nerve conduction velocity in the carpal tunnel segment, rather than a lowering of amplitude. The interaction of entrapment neuropathy and diabetic peripheral neuropathy represents a diagnostic challenge. Neurophysiologic evidence of asymptomatic CTS has been demonstrated in 20-30% of insulin and non-insulin dependent diabetic patients [4, 49]. Furthermore, paradoxical to increased susceptibility to focal nerve entrapment in diabetes, experimental and clinical nerve conduction studies have demonstrated increased resistance to ischemic block [101]. Whilst well documented for non-diabetic patients [68, 121, 180], neurophysiologic results after carpal tunnel release in diabetic patients have only been sparsely investigated, and conclusions have been conflicting [118, 130].

Several factors are involved in the impaired nerve conduction found in diabetes. Due to hyperglycaemia, metabolic and vascular factors cause axonal swelling, reduced nodal Na^+

current and disruption of the paranodal ion-channel barrier [80, 115, 161]. In experimental studies, increased levels of activating transcription factor 3 (ATF3), a marker of cellular injury, has been demonstrated with higher frequency in neurons and Schwann cells of diabetic rats during nerve compression [44]. Furthermore, nerve compression produces a more pronounced inhibition of axonal transport in diabetes [42]. Just as for the clinical results (Paper I) and the patients' self-reported outcome assessment (Paper II), there were no differences in neurophysiologic recovery after carpal tunnel release between diabetic and non-diabetic patients. This even applies for diabetic patients with peripheral neuropathy, where a more pronounced and homogeneous median nerve dysfunction was demonstrated, compared to diabetic patients without neuropathy. Together these results point towards a common pathogenesis of CTS in diabetic as well as non-diabetic patients, which is the subject of Paper VI. The important clinical implication concerns the fact that even though diabetic patients with CTS have significantly impaired nerve conduction parameters, compared to non-diabetic patients with CTS, they should be offered equal opportunity for surgical carpal tunnel release.

Small nerve fibre neuropathy

Skin biopsies have emerged as a valuable means of diagnosing and quantifying small nerve fibre pathology. This has become important as small nerve fibres are undetectable to routine nerve conduction study and the evaluation of sural nerve biopsies, which is an invasive procedure, carries a substantial morbidity for the patient. In the present study, skin biopsies were performed in order to provide insight into the pathological basis for symptoms related to diabetes as well as to CTS. Small nerve fibres are considered to degenerate early in the course of diabetic neuropathy [102, 172]. Several reports indicate that a reduction in IENFD among diabetic patients is mainly related to those suffering severe neuropathy symptoms or painful small fibre neuropathy [92, 143, 166]. On the other hand, complete denervation of the epidermis can be seen in patients with genetic insensitivity to pain, questioning whether loss of IENF is related to pain, or should be judged only as an indicator of neuropathy [125]. In CTS pain is known to accompany the characteristic paraesthesiae in nearly 40 % of the cases [167], and thermal deregulation, in terms of cold intolerance, was found in 60 % of our patients (Paper I).

The development of antibodies against a variety of neuronal marker proteins has allowed for immunohistochemical assessment of intraepidermal nerve fibres [45]. Contrary to recommendations by the European Federation of Neurological Societies (EFNS) [99], the

present study used light microscopy and manual nerve counting to evaluate 5 ụm thick sections from the skin biopsies. Confocal microscopy and image analysis systems are expensive and technically demanding equipment, which are not available at our institution. It was therefore necessary to apply a simpler but still reliable method. In routine histopathological investigation, thin 5-15 ụm sections are commonly used and have also been employed in previous studies on quantification of IENFD [91, 96]. The number of nerves counted is dependent on the thickness of the sections, which is why the present method has an inherent risk of underestimating the actual number of nerve fibres. Consequently, a direct comparison is not possible between our IENFD data, and the results from studies following the EFNS recommendations. Whilst one may be concerned about the low nerve count that the present technique provides, it is reassuring that normative data from the distal leg (unpublished data, by Thrainsdottir, Englund and Dahlin) is in the lower end of what was found in the forearm, and therefore comparable with results described by other authors [140].

No difference in IENFD at wrist level between diabetic or non-diabetic patients, or between diabetic patients with our without neuropathy, could be demonstrated. It might be due to the patients having mild neuropathy with no complaints of painful neuropathy (burning hands or feet). Furthermore, length dependent nerve pathology in the upper extremity is to some extent a reversible and rather late phenomenon, as shown in nerve conduction studies after institution of insulin treatment in diabetic patients [3]. To further explore the possibility of small nerve fibre neuropathy, an on-going study utilise electron microscopy to evaluate the PIN biopsies described in Paper VI.

No previous study has compared IENFD in glabrous and hairy skin at the same anatomical level. Both diabetic and non-diabetic patients demonstrated a significantly higher IENFD in hairy compared to glabrous skin. Furthermore, IENFD of females were higher than that of males. These results are in the context with the reportedly higher Aδ fibre nociceptor density in hairy compared to glabrous skin, and the difference in thermal pain thresholds described between males and females [72, 113]. From a philosophic point of view, it is through the sense of touch that our hand turns into such a specialized tool to explore and perceive the surrounding world. At the same time, detection of heat and pain are important warning signals for our survival. In order to functionally balance these important inputs to the exploring surface of glabrous skin, it seems reasonable that the densities of intraepidermal nociceptors are lower compared to hairy skin.

The PIN biopsy procedure

In hand surgery the PIN is regularly used as a nerve graft for bridging segmental digital nerve defects [191]. In addition, neurectomy of multiple nerve branches around the wrist, the PIN inclusive, is an accepted method for denervation of the wrist to achieve pain relief following post traumatic or degenerative arthropathy [62]. There are no risks of either sensory or functional deficits after the PIN biopsy procedure. Even after total denervation of the wrist, there has not been observed or reported changes consistent with Charcot joint disease [25].

Morphologic assessment of the PIN biopsies demonstrated a reduced myelinated nerve fibre density in Type 2 diabetic patients compared to autopsy control subjects. This is in accordance with results from sural nerve biopsies where myelinated nerve fibre density has shown to be a reliable indicator of neuropathy in diabetic patient [105, 109]. We argue that the PIN biopsy procedure fulfils the criteria for nerve biopsy [50] as it has a constant location, is easy accessible, leaves no sensory or motor deficit and it is not frequently subjected to local trauma or entrapment. Furthermore, if a corroborative functional assessment is desirable, nerve conduction studies can be performed on the superficial sensory branch of the same nerve and at the same distal level as the nerve biopsy. The procedure is not advocated for the diagnosis of diabetic neuropathy, but can be of value in detection of other conditions such as vasculitic neuropathy, amyloid neuropathy or sarcoidosis.

Large nerve fibre neuropathy

Characterisation of pathologic changes in human nerve compression has been difficult, due to ethical considerations and donor-site morbidity. In a post-mortem study of subclinical entrapment of the median and ulnar nerves a thickening of the perineurium and epineurium were observed. Furthermore, teased fibre analysis revealed thinning and retraction of the myelin as well as intercalated segments, suggestive of previous demyelination [122]. The limited amount of human nerve tissue available for analysis, make us reliant on experimental models in order to understand the pathological features of nerve compression. It is clear that animal models with application of compression clamps or silicon tubes around a nerve, however valuable, is not an authentic reflection of chronic nerve compression in humans. In addition, acute nerve compression differs from chronic nerve compression involving mechanisms such as inflammation, and stretching and tethering of the nerve during joint movements. Schwann cells are believed to be one of the primary mediators of demyelination seen in nerve compression, possibly initiated by mechanical stimulus [75].

Documentation of the PIN biopsy as a valid and low-morbidity procedure (Paper V) provides, for the first time, a method to quantify nerve pathology in the upper limb. The present results demonstrate a significant reduction in myelinated nerve fibre and endoneurial capillary densities in diabetic and non-diabetic patients with CTS compared to control subjects. The surprising finding suggests that distinct nerve pathology may exist even in non-diabetic patients with idiopathic CTS. A reduction in endoneurial capillary density will ultimately lead to reduced endoneurial oxygenation. Although not quantified, microangiopathy with reduplication of the basement membrane and thickening of the endothelium was observed in some of the diabetic patients. An ongoing electron microscopy study will clarify the microvascular pathology in detail.

As pathology in the PIN does not represent compression neuropathy, it is tempting to speculate that the reduction in myelinated nerve fibre and endoneurial capillary densities may indicate a predisposition for both diabetic as well as non-diabetic patients to the development of CTS. The further diminished myelinated nerve fibre density in diabetic patients, compared to non-diabetic patients with CTS, may partly explain the increased susceptibility to CTS in the former. Moreover, the shared pathology in patients with CTS, regardless the presence of diabetes, may explain the similarities in clinical and neurophysiologic outcomes after carpal tunnel release (Paper I-III).

The direct correlation between myelinated nerve fibre and endoneurial capillary densities provides the first mechanistic foundation for axonal nerve damage through a hypoxic endoneural environment. This implies some interesting speculations regarding vascular endothelial growth factor (VEGF), for which experimental studies have demonstrated its potential to activate Schwann cells and generate neovascularisation [157, 165].

The results from this thesis have direct clinical relevance, in terms of management of CTS, as an already severe reduction of myelinated nerve fibre and endoneurial capillary densities advocates early carpal tunnel release to avoid further axonal loss due to nerve compression.

Carpal tunnel syndrome and diabetes

Factors responsible for the development of compression neuropathies, relate either to the peripheral nerve, or the structures surrounding it at the point of compression. These factors are summarised in Fig. 5.

The characteristics of the *diabetic hand syndrome* symbolises structural changes of the connective tissue. Tenosynovial oedema [79] and accelerated glycosylation [24], with enhanced lysyl oxidase activity, results in collagen cross-link formation which lead to formation of less compliant connective tissue and fibrosis [35]. These features are suggested to endorse shear forces on the nerve as well as enhance compression by decreasing the volume of the carpal tunnel [149].

Experimental studies have provided the bulk of our knowledge with regard to metabolic alterations affecting the neuron. Hyperglycaemia, via oxidative stress and increased non-enzymatic glycation, leads to Schwann cell dedifferentiation, impaired mitochondrial function and apoptosis [75, 155]. During nerve compression, markers of injury in Schwann cells and nerve cell bodies are more pronounced in diabetes, together with an added impairment of axonal transport [41, 44]. Furthermore, nerve trauma in diabetic rats demonstrate impaired activation of extracellular-signal-regulated kinase 1/2 (Erk1/2), an important factor for proliferation of Schwann cells after injury [110]. Thereby, the diabetic nerve becomes more vulnerable to stress or injury and the repair capacity diminishes.

Sural nerve biopsies obtained from diabetic patients, have demonstrated basement membrane thickening and endothelial cell proliferation with luminal narrowing [57, 107]. Along with impaired rheologic properties of erythrocytes, it causes decreased nerve blood flow and induces endoneurial hypoxia [30, 124]. Disturbed microcirculation is believed to be a primary pathologic factor in CTS. A superimposed compression to an already hypoxic nerve is thought to increase susceptibility to nerve compression in diabetes.

Inherited genetic factors are well recognized in Type 1 and Type 2 diabetes [11, 97] while genetic predisposition to CTS, such as hereditary neuropathy with liability to pressure palsy (HNPP), is believed to be a rare feature [19, 169].

This thesis adds new information on the pathogenesis of CTS. 1) A key finding is the increased risk for endoneurial hypoxia due to a lower endoneurial capillary density 2) A reduced myelinated nerve fibre density in diabetic patients, compared to non-diabetic patients with CTS and healthy control subjects may partly explain the increased susceptibility to CTS in diabetic patients. 3) Although the above results may be expected in diabetic patients, comparable findings in non-diabetic patients with no other maladies than the CTS, point towards the existence of a personal predisposition to CTS.

VASCULAR TISSUE
- Basement membrane thickening
- Endothelial cell hyperplasia
- Impaired rheologic properties
- Hypoxia
- Endoneurial oedema
- **Reduced endoneurial capillary density**

NEURONE
- Abnormality in axonal transport
- Nerve cell body alterations (structure and metabolism)
- **Myelinated nerve fibre degeneration**

SCHWANN CELLS
- Dedifferentiation and apoptosis
- Demyelination with remyelination

PREDISPOSITION
- *Genetic factors?*

CONNECTIVE TISSUE
- Deposition of advanced glycation end products (AGEs)
- Glycation of collagen
- Decreased nerve gliding
- Narrowing of carpal tunnel space
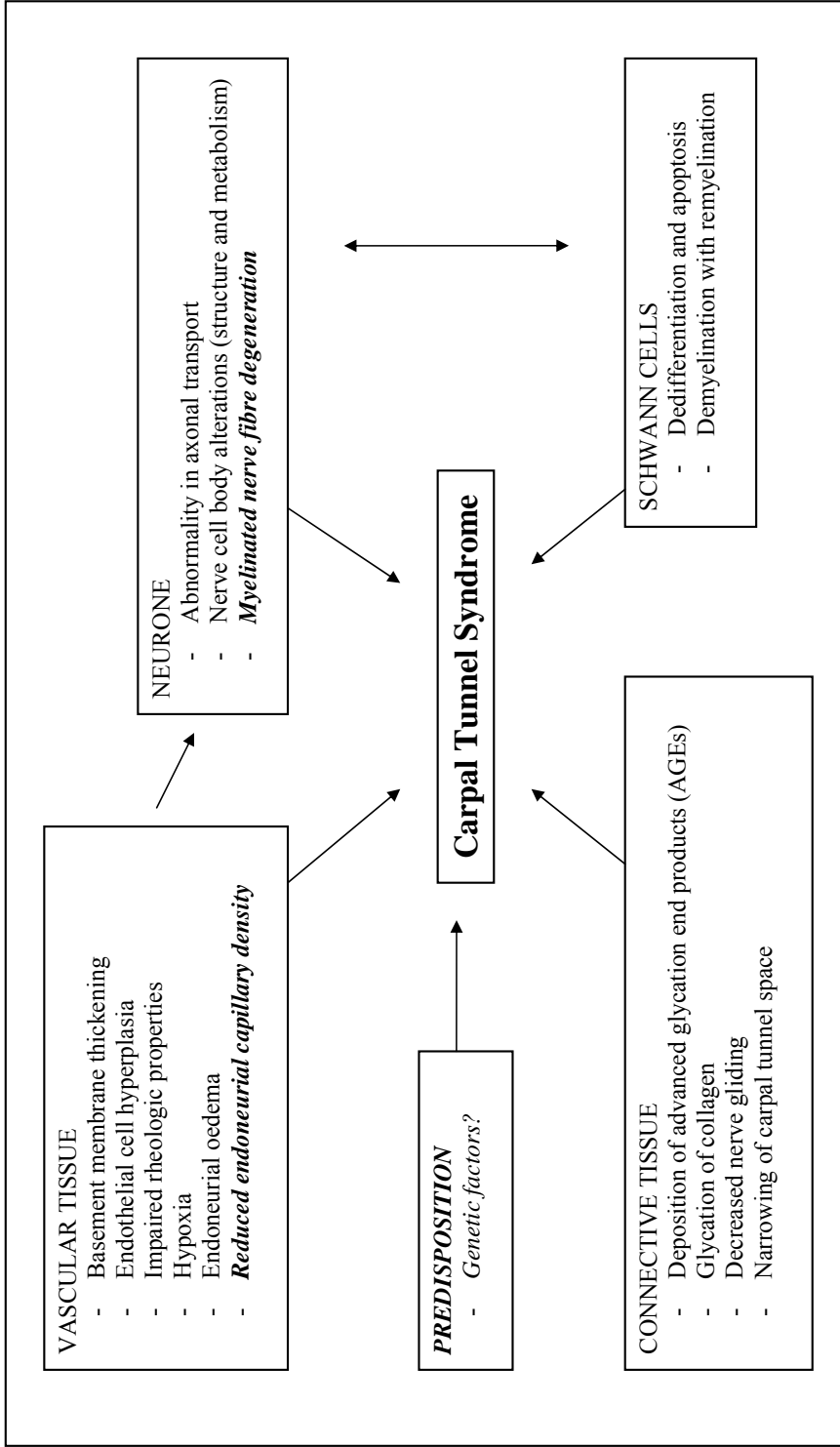
Carpal Tunnel Syndrome

Figure 5. Factors believed responsible for the increased susceptibility to carpal tunnel syndrome in diabetes. Aspects revealed by this thesis are marked in bold *italic.*

Perspectives

Management of diabetic patients requires a team effort involving; public health nurses, occupational- and physio-therapists, general practitioners and a wide range of specialised physicians such as endocrinologists, neurologists and neurological as well as hand surgeons. Therefore, it becomes a task in itself to pass on new knowledge to the various professions involved. In 2008, the American Academy of Orthopaedic Surgeons and the American Association of Neurological Surgeons concluded that sufficient evidence was not available to provide treatment recommendations for CTS associated with diabetes [90]. This thesis provides the first prospective, systematic evaluation of carpal tunnel release in diabetic patients. The present results will have an impact on evaluation of patients, indications for treatment, as well as provide information regarding postoperative outcome. Hopefully, these results will lead to an understanding and change of approach, towards offering diabetic patients with CTS the same opportunities for surgical carpal tunnel release as non-diabetic patients. Perhaps, wider indications for surgical carpal tunnel release are warranted in diabetic patients with CTS, due to the advanced nerve pathology. However, the present results do not advocate liberal indications concerning decompressive surgery of lower limb nerves for treatment of diabetic peripheral neuropathy.

An immense amount of studies are required, before we truly understand the complex pathology of CTS, in particular when it emerges together with diabetes. Although, we have provided answers to the questions raised in the planning of this thesis, a variety of new issues have revealed en route. A potential predisposition to CTS may change our current view on aetiology. The shared pathology of non-compressed nerves in patients with CTS requires further investigation. The hypoxic endoneurial milieu opens up for new treatment possibilities. Finally, the risk of recurrent CTS in diabetic patients may be considered in the future [43].

CONCLUSIONS

The results of this thesis support the following conclusions:

- Patients with diabetes and carpal tunnel syndrome (CTS) have the same beneficial outcome after surgical carpal tunnel release as non-diabetic patients.
- Cold intolerance, which is frequent in CTS, is relieved to a lesser extent in diabetic compared to non-diabetic patients after carpal tunnel release.
- Generic health-related quality of life is impaired in diabetic patients with CTS compared to non-diabetic patients with CTS and population norms.
- Diabetic patients experience similar disease-specific symptomatic and functional improvements after carpal tunnel release as non-diabetic patients.
- Marked neurophysiologic impairment or signs of peripheral neuropathy does not preclude significant recovery after carpal tunnel release in diabetic patients.
- At wrist level, intraepidermal nerve fibre density (IENFD) is not different between diabetic and non-diabetic patients.
- IENFD is higher in females and higher in hairy compared to glabrous skin.
- Biopsy of the posterior interosseous nerve is a low morbidity method for evaluation of peripheral nerve pathology.
- Reduction in myelinated nerve fibre and capillary densities may predispose patients to CTS and this is further accentuated in diabetes.

SUMMARY IN SWEDISH

Populärvetenskaplig sammanfattning

I medianusnerven, som löper i armen och handen, förmedlas elektriska impulser för att aktivera specifika muskler i underarmen och handen. I nerven skickas också impulser från känselkroppar i tummen, pek-, lång- och dela av ringfingret. Nerven kan utsättas för en inklämning i handledsnivå där den löper tillsammans med fingrarnas böjsenor under ett bindvävsband. Symptomen vid en kompression av nerven, s k karpaltunnelsyndrom, består av domningar i fingrarna, nedsatt finmotorik och känsel samt reducerad kraft i tummen. Man har uppskattat att ca 4% av befolkningen lider av ett karpaltunnelsyndrom. Hos personer med diabetes är karpaltunnelsyndrom vanligare och förekommer hos ca 15%. Om patienter med diabetes samtidigt har påverkan på sitt nervsystem, s k neuropati, har upp till 30% ett karpaltunnelsyndrom. Orsakerna till att det är vanligare hos diabetiker är ännu inte klarlagt, men man har diskuterat om inklämningen är relaterad till förändringar i karpaltunneln samt till sjukliga förändringar i nervstammens nervtrådar, i blodkärlen och i bindväven. Eftersom det saknas vetenskapliga studier om hur karpaltunnelsyndrom hos diabetiker bör behandlas föreligger det ett behov att skapa riktlinjer för detta.

I denna avhandling är patienter med diabetes och samtidigt karpaltunnelsyndrom samt en grupp med i för övrigt friska patienter med karpaltunnelsyndrom följda upp till ett år efter en kirurgisk behandling. Den kirurgiska behandlingen innebär att man delar bindvävsbandet som löper mellan handlovsbenen och formar karpaltunneln. I avhandlingen har patienternas symptom och funktion undersökts före och efter kirurgi. Vid den kirurgiska behandlingen har dessutom vävnadsprover tagits från huden över karpaltunneln och från underarmshud strax ovanför handryggen samt från en liten nerv strax ovanför handledsnivån (s k nervus interosseous posterior).

Resultaten visar att patienter med diabetes har samma effekt av den kirurgiska behandlingen av karpaltunnelsyndromet som patienter utan diabetes. Den enda skillnaden som kunde noteras var att upplevelsen av köldintolerans hos diabetikerna lindrades i mindre grad. Livskvaliteten förbättrades av den kirurgiska behandlingen hos både patientgrupperna, trots att patienterna med diabetes startade från en "lägre utgångspunkt". Patienterna med diabetes nådde efter kirurgin inte riktigt upp till den genomsnittliga befolkningens livskvalitet.

I överensstämmelse med det kliniska resultatet visade undersökning av nervfunktion med neurofysiologisk teknik (nervledningshastighet m.m.) att patienterna med diabetes, trots

en dålig nervfunktion innan operationen, uppnår samma typ av förbättring som patienterna utan diabetes. Denna förbättring var lika stor för diabetespatienterna med s k neuropati.

Vid undersökning av vävnadsprover från huden kunde man inte påvisa några tecken till påverkan av de små nervtrådar som bl a har betydelse för smärtkänseln och temperatursinnet. Däremot visade undersökningen av nervstammen från underarmen ett lägre antal nervtrådar samt ett lägre antal kapillärer (s k hårrörskärl; små blodkärl) inte bara hos patienterna med diabetes utan också hos de för övrigt friska patienterna med karpaltunnelsyndrom. Antalet nervtrådar var däremot ytterligare minskat hos patienter med diabetes. Detta kan vara en förklaring till att patienter med diabetes ofta får karpaltunnelsyndrom.

Sammanfattningsvis har avhandlingen visat att patienter med diabetes bör erbjudas samma möjlighet för operation av karpaltunnelsyndrom som patienter med karpaltunnelsyndrom men utan diabetes. Detta trots att patienterna med diabetes har en sämre "utgångsnivå" samt oavsett om det finns tecken till nervsjukdom (neuropati) orsakat av diabetes. Resultaten i avhandlingen pekar också på att det möjligtvis existerar en predisposition för karpaltunnelsyndrom oavsett om diabetes förekommer eller inte.

SUMMARY IN DANISH

Populærvidenskabligt resume.

Midternerven (nervus medianus) kan blive klemt ved håndledsniveau, når den sammen med fingrenes bøjesener passerer under et bindevævsbånd udspændt mellem håndrodens knogler. Symptomerne, ved dette såkaldte karpal tunnel syndrom, består af sovende fornemmelse i fingrene, nedsat finmotorik samt reduceret kraft i specielt tommelfingeren. Det er estimeret, at omkring 4% af den generelle befolkningen er besværet af denne lidelse. Hos diabetikere er hyppigheden af karpal tunnel syndrom imidlertid øget til omkring 15%, og stiger til op mod 30% hos diabetikere med samtidig nervebetændelse (neuropathi). Årsagerne til den øgede hyppighed er endnu ikke fuldt belyst, men menes at relatere sig til forandringer i stofskifte, blodkar samt bindevæv. Manglende studier om behandlingen af karpal tunnel syndrom hos diabetikere medfører, at der ikke foreligger anbefalinger eller retningslinier herfor.

I denne afhandling er patienter med diabetes og karpal tunnel syndrom, samt en gruppe af iøvrigt raske patienter med karpal tunnel syndrom, fulgt i op til et år efter operativ behandling. Der er foretaget registrering af patienternes klinske funktion og behandlings resultat, samt undersøgelse af vævsprøver fra hud og nerve (nervus interosseous posterior) på underarmen. Afhandlingen påviser, at diabetes patienter har den samme effekt af operativ behandling for karpal tunnel syndrom som patienter uden diabetes. Kun symptomer på kulde intolerance lindredes i mindre grad blandt diabetes patienter. Ligeledes fandtes forbedring af livskvalitet at være ens for de to patientgrupper, omend patienterne med diabetes startede fra et lavere udgangspunkt og efterfølgende ikke nåede op på niveau med gennemsnits befolkningen. I overensstemmelse med de kliniske resultater, viste nerveledningsundersøgelse at diabetes patienter på trods af dårligere nervefunktion inden operationen, ligeledes opnåede samme forbedring som patienter uden diabetes. Selv tilstedeværelse af neuropathi ændrede ikke på dette forhold. Ved undersøgelse af vævsprøver fra huden kunne der ikke påvises tegn på nervebetændelse i de såkaldte små nerve tråde, som bl.a. har betydning for smerte og temperatursans. Derimod påviste undersøgelse af nervevæv fra underarmen et reduceret antal nervetråde samt små blodkar (kapillærer), hos ikke bare patienter med diabetes, men også hos de iøvrigt raske patienter med karpal tunnel syndrom. Antallet af nervetråde og kapillære var yderligere reduceret hos patienterne med diabetes og kan være en del af forklaring på den øgede frekvens af karpal tunnel syndrom hos denne patient gruppe.

Det konkluderes, at patienter med diabetes bør tilbydes samme mulighed for operation for karpal tunnel syndrom som patienter uden diabetes, også selvom udgangspunktet er

ringere og uafhængigt af om der kan påvises tegn til neuropathi. Noget overraskende peger resultaterne fra undersøgelserne af nervevæv på, at der muligvis eksistere en fælles prædisposition til karpal tunnel syndrom uanset tilstedeværelsen af diabetes.

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