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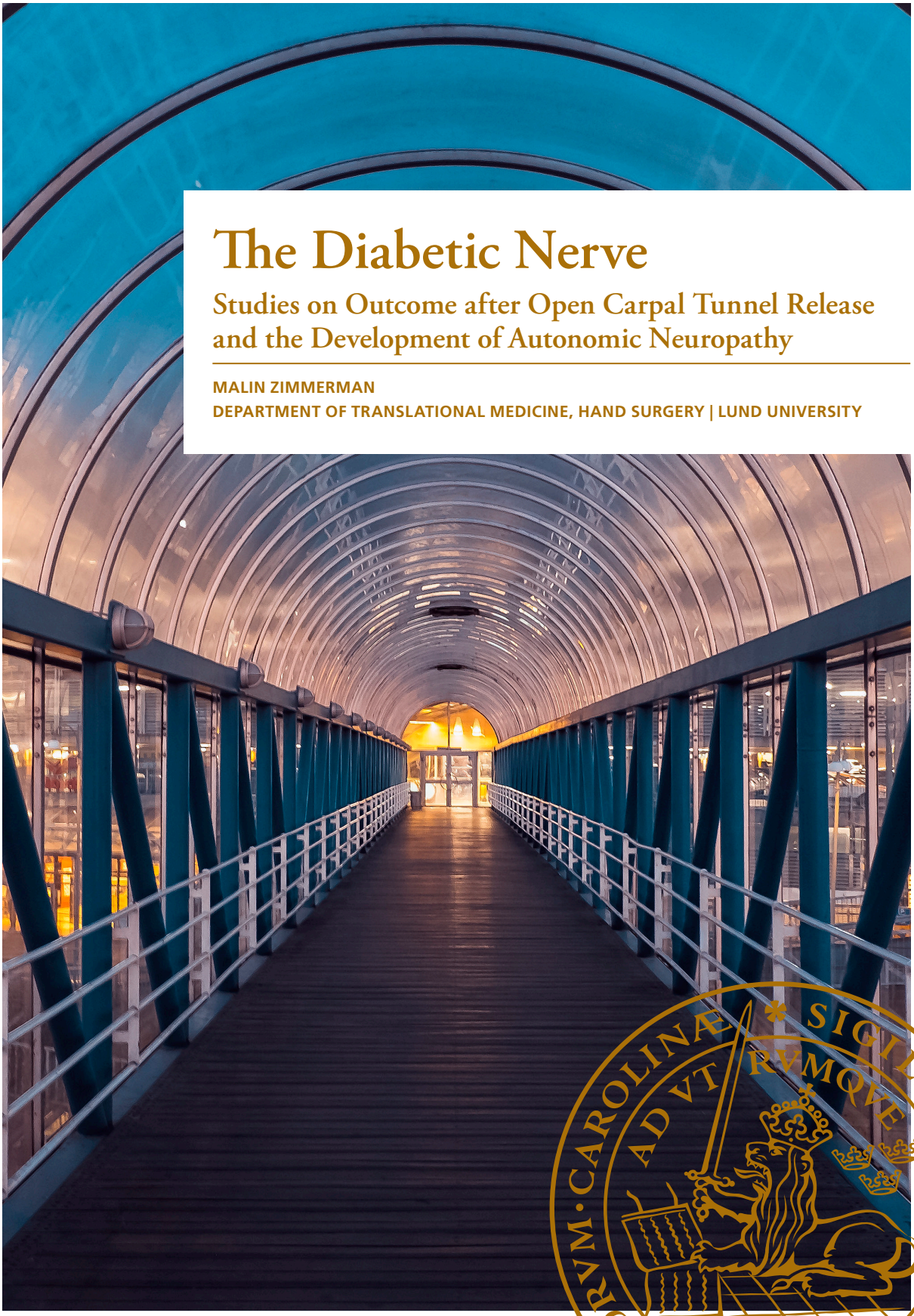

The Diabetic Nerve

Studies on Outcome after Open Carpal Tunnel Release and the Development of Autonomic Neuropathy

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The Diabetic Nerve

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Malin Zimmerman

LUND
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The Diabetic Nerve: Studies on Outcome after Open Carpal Tunnel Release and the Development of Autonomic Neuropathy

Abstract

Neuropathy, affecting both the peripheral and the autonomic nervous systems, is a common complication in patients with diabetes. Diabetic peripheral neuropathy includes the common compression neuropathy, carpal tunnel syndrome (CTS). This thesis focuses on the study of the diabetic nerve, using two different approaches.

The first part is directed to the role of potential risk factors, such as diabetes, metabolic syndrome and smoking, in unsatisfactory outcome after open carpal tunnel release (OCTR), the standard surgical treatment for CTS. The results are based on two different populations: a) a local registry including 493 patients (531 hands) operated on using OCTR due to primary CTS and b) pooled data from national registries, comprising 9049 patients (10770 hands) operated on for CTS using OCTR.

The second part concentrates on autonomic neuropathy, including inflammatory markers, in individuals with diabetes and impaired glucose tolerance (IGT). Two different populations were studied: a) 32 patients with type 1 diabetes recruited in 1985 at a University Hospital and b) 119 individuals recruited at primary care centres in 2004 [51 with type 2 diabetes, 29 with IGT and 39 with normal glucose tolerance (NGT)]. The groups were followed for 20 and 10 years, respectively.

In the first part, results were based on the patient-reported outcome measure (PROM) QuickDASH (scoring tool; Disabilities of the Arm, Shoulder and Hand). Patients with neuropathy had a 2.6 times higher chance of not having a clinically significant improvement after surgery than patients without neuropathy. Patients who smoked improved after surgery despite higher QuickDASH scores (indicating more severe symptoms) both before and after surgery. Patients with normal or mild electrophysiology results (indicating the degree of nerve injury induced by compression) showed limited improvement. The results from a national registry revealed that patients with or without diabetes benefitted similarly from OCTR, but diabetes was associated with an increased risk of incomplete symptom resolution. The results further show that pre-operative HbA1c levels were associated with post-operative outcome in patients with diabetes, and that patients with manifest retinopathy needed longer to recover after OCTR. Patients who developed diabetes after OCTR had more symptoms postoperatively than patients without diabetes.

In the second part, development of autonomic neuropathy was assessed over time. Autonomic symptoms increased over time in patients with type 2 diabetes, but did not correlate with expiration/inspiration (E/I) ratio. The E/I ratio did not correlate with HbA1c. In patients with type 1 diabetes, autonomic function, measured as the E/I ratio, deteriorated over time and was associated with HbA1c. Levels of the potential neuroprotective factors and inflammatory markers Heat Shock Protein 27 (HSP27), Macrophage Migration Inhibitory Factor (MIF) and Plasminogen Activator Inhibitor 1 (PAI-1), respectively, were not associated with autonomic function.

In summary, patients with diabetes without neuropathy benefitted from OCTR to the same extent as patients without diabetes. However, in patients with diabetic neuropathy symptom resolution after OCTR took longer and there was a risk of it being incomplete. Patient-reported symptoms of autonomic neuropathy did not correlate with objective measures and should therefore be actively sought for. In type 1 diabetes, glucose control acted as protection against the development of autonomic neuropathy.

Key words

Carpal tunnel syndrome, diabetic autonomic neuropathy, diabetic polyneuropathy

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”I may not have gone where I intended to go,
but I think I have ended up where I intended to be”

Douglas Adams

To my family

Table of Contents

Abstract

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In summary, patients with diabetes without neuropathy benefitted from OCTR to the same extent as patients without diabetes. However, in patients with diabetic neuropathy symptom resolution after OCTR took longer and there was a risk of it being incomplete. Patient-reported symptoms of autonomic neuropathy did not correlate with objective measures and should therefore be actively sought for. In type 1 diabetes, glucose control acted as protection against the development of autonomic neuropathy.

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Type 2 Diabetes
AGE	Advanced Glycation End Product
ANS	Autonomic Nervous System
CAN	Cardiovascular Autonomic Neuropathy
CNS	Central Nervous System
CTS	Carpal Tunnel Syndrome
DAG	Diacylglycerol
DCCT	Diabetes Control and Complications Trial
DSPN	Distal Symmetric Polyneuropathy
ECM	Extracellular Matrix
EDIC	Epidemiology of Diabetes Interventions and Complications
EDTA	Ethylenediamine Tetraacetic Acid
eGFR	Estimated Glomerular Filtration Rate
eNOS	Endothelial Nitric Oxide Synthase
ET-1	Endothelin-1
FFA	Free Fatty Acids
GADA	Glutamic Acid Decarboxylase Antibodies
GAPDH	Glyceraldehyde-3 Phosphate Dehydrogenase
HbA1c	Glycosylated Haemoglobin A
HSP27	Heat Shock Protein 27
IGT	Impaired Glucose Tolerance
kDa	kilo Dalton
LDL	Low Density Lipoprotein
MIF	Macrophage Migration Inhibitory Factor
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NGT	Normal Glucose Tolerance
NF-κβ	Nuclear Factor kappa-light-chain-enhancer of activated B-cells

OCTR	Open Carpal Tunnel Release
PAI-1	Plasminogen Activator Inhibitor 1
PARP	Poly (ADP-ribose) Polymerase
PKC	Protein Kinase C
PNS	Peripheral Nervous System
PROMs	Patient-Reported Outcome Measures
RAGE	AGE receptor
ROS	Reactive Oxygen Species
SCV	Sensory Conduction Velocity
sHSP	Small Heat Shock Proteins
SIDD	Severe Insulin-Deficient Diabetes
SNAP	Sensory Nerve Action Potential
TGF-β	Transforming Growth Factor β
T1D	Type 1 Diabetes Mellitus
T2D	Type 2 Diabetes Mellitus
UKPDS	United Kingdom Prospective Diabetes Study
VEGF	Vascular Endothelial Growth Factor
2PD	Two-point Discrimination

List of papers

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

Paper I: Outcome after open carpal tunnel release: impact of factors related to metabolic syndrome

Malin Zimmerman, Erik Dahlin, Niels O. B. Thomsen, Gert S. Andersson, Anders Björkman & Lars B. Dahlin.

Journal of Plastic Surgery and Hand Surgery, 2017, 51:3, 165-171.

Paper II: Impact of smoking and pre-operative electrophysiology on outcome after open carpal tunnel release

Erik Dahlin, Malin Zimmerman, Anders Björkman, Niels O.B. Thomsen, Gert S. Andersson & Lars B. Dahlin.

Journal of Plastic Surgery and Hand Surgery, 2017, 51:5, 329-335

Paper III: Open carpal tunnel release and diabetes – a retrospective study using PROMs and national quality registries

Malin Zimmerman, Katarina Eeg-Olofsson, Ann-Marie Svensson, Mikael Åström, Marianne Arner, Lars B. Dahlin.

2018, Submitted

Paper IV: Autonomic Neuropathy—a Prospective Cohort Study of Symptoms and E/I Ratio in Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes

Malin Zimmerman, Kaveh Pourhamidi, Olov Rolandsson and Lars B. Dahlin

Frontiers in Neurology, 2018, 9:154.

Paper V: Temporal trend of autonomic nerve function and HSP27, MIF and PAI-1 in type 1 diabetes

Malin Zimmerman, Sara Rolandsson Enes, Hanna Skärstrand, Kaveh Pourhamidi, Anders Gottsäter, Per Wollmer, Olov Rolandsson, Gunilla Westergren-Thorsson, Lars B. Dahlin

Journal of Clinical & Translational Endocrinology 2017, 8: 15–21

Thesis at a glance

Paper I: Outcome after open carpal tunnel release: impact of factors related to metabolic syndrome

Aim: To evaluate the influence of diabetes, obesity, hypertension and statin treatment on the outcome after open carpal tunnel release (OCTR).

Methods: QuickDASH questionnaires were completed before and one year after surgery by 493 patients (531 hands) operated on using OCTR, due to primary carpal tunnel syndrome (CTS). Data were taken from medical files and health declarations.

Results and conclusion: QuickDASH scores were higher in patients with diabetes (n=76) both before (median 56, interquartile range IQR [36-77]; compared to patients without diabetes: 48 [32-66]; $p<0.05$) and after surgery (31 [9-61] vs. 16 [5-43]; $p<0.001$). Patients with polyneuropathy (18 with diabetes, 7 without diabetes) had a 2.6 higher chance of having a less than the minimal clinically important change in QuickDASH than patients without polyneuropathy. Hypertension, obesity and statin treatment did not affect outcome. Patients with CTS and polyneuropathy should be informed about the risk of an unsatisfactory outcome after OCTR, whereas patients with diabetes without polyneuropathy can expect the same improvement as healthy patients.

Paper II: Impact of smoking and pre-operative electrophysiology on outcome after open carpal tunnel release

Aim: To evaluate outcome after OCTR in relation to smoking status and pre-operative electrophysiology values.

Methods: The same population and methods were used as in Paper I.

Results and conclusion: Patients who smoked (n=94) scored higher on the QuickDASH both before (61 [45-74] vs. patients who did not smoke: 48 [30-64]; $p<0.0001$) and after OCTR (34 [14-61] vs. 16 [5-41]; $p<0.0001$). In patients who smoked, the chances of having persistent symptoms (defined as a post-operative QuickDASH score >10) were 2.5 times higher than in patients who did not smoke. No clinically significant improvement (change in QuickDASH score >8) occurred in 124/493 patients. Patients with normal and extreme pre-operative electrophysiology values scored higher on the post-operative QuickDASH.

In conclusion, patients who smoke and patients with normal or extreme pre-operative electrophysiology values risk incomplete symptom resolution following OCTR. Patients who smoke should be advised to give up the habit before surgery in order to improve the results.

Paper III: Open carpal tunnel release and diabetes – a retrospective study using PROMs and national quality registries

Aim: To study outcome after OCTR in patients with and without diabetes using nationwide registries.

Methods: Data from the National Quality Register for Hand Surgery HAKIR were pooled with data from the Swedish National Diabetes Register NDR, resulting in 9049 patients (10770 hands) operated on for CTS during the study period. QuickDASH questionnaires and eight specific questions were used to assess outcome.

Results and conclusion: Patients with and without diabetes benefitted to the same extent from surgery, but the former risked incomplete symptom resolution. There were no differences in surgical outcome between type 1 and type 2 diabetes patients. Higher HbA1c levels were associated with more residual symptoms after OCTR. Manifest retinopathy (considered a proxy variable for neuropathy) in patients with diabetes was associated with longer recovery times after surgery. Older age and smoking were associated with less improvement after surgery. Patients who received their diabetes diagnosis after OCTR was performed had more postoperative symptoms than patients without diabetes.

To conclude, dysregulated diabetes may adversely affect the results of the surgery, and manifest retinopathy is associated with a longer recovery time after OCTR.

Paper IV: Autonomic Neuropathy—a Prospective Cohort Study of Symptoms and E/I Ratio in Normal Glucose Tolerance, Impaired Glucose Tolerance, and Type 2 Diabetes

Aim: To study prevalence and progression of autonomic neuropathy (based on the E/I ratio and symptom scores) over time in individuals with type 2 diabetes, IGT, and NGT.

Methods: In 2004, a total of 119 individuals were recruited to the study (51 with type 2 diabetes, 29 with IGT and 39 with NGT). The study population was followed for 10 years. Cardiac autonomic function was assessed using the E/I ratio and symptoms were evaluated using a symptom score (ASS). Blood samples were drawn at baseline and at follow-up.

Results and conclusion: ASS scores were higher at follow-up in the type 2 diabetes patients than in the group with NGT. The E/I ratio deteriorated over time, but no more than could be expected with ageing. The E/I ratio did not correlate with HbA1c, or with the symptom score.

Over time, the presence of autonomic symptoms increased in patients with type 2 diabetes. ASS can be useful for clinically evaluating the progression of autonomic dysfunction in patients with deranged glucose metabolism.

Paper V: Temporal trend of autonomic nerve function and HSP27, MIF and PAI-1 in type 1 diabetes

Aim: To investigate the temporal trend of cardiovascular autonomic neuropathy in patients with type 1 diabetes and to study the association between HSP27, MIF, PAI-1, and HbA1c levels and autonomic dysfunction.

Methods: In 1985, 32 patients with type 1 diabetes were recruited. The patients were subsequently assessed on four occasions during the following 20 years. Autonomic function was evaluated using the E/I ratio. Levels of serum proteins were compared to levels in a control group comprising healthy blood donors.

Results and conclusion: The E/I ratio deteriorated during the study period. Levels of HSP27, MIF and PAI-1 were not associated with autonomic neuropathy. At the final follow-up, levels of MIF and PAI-1 were lower in patients with type 1 diabetes than in controls. The deterioration of autonomic function was related to HbA1c levels. Strict glucose control in patients with type 1 diabetes might serve as a protection against autonomic neuropathy.

Populärvetenskaplig sammanfattning

Nervskador hos människor med diabetes

Föreliggande avhandling består av två delar och fokuserar på hur diabetes påverkar nerver samt två vanliga komplikationer till diabetes: karpaltunnelsyndrom och autonom neuropati. Huruvida resultatet efter kirurgisk behandling av karpaltunnelsyndrom påverkas av diabetes, rökning och metabolt syndrom utvärderades. Autonom neuropati hos människor med diabetes och med nedsatt glukostolerans undersöktes över tid.

Förekomsten av diabetes mellitus, nedsatt glukostolerans samt metabolt syndrom ökar i världens befolkning, och i takt med detta ökar också antalet människor som drabbas av komplikationer till diabetes. Nedsatt glukostolerans (IGT; impaired glucose tolerance) anses vara ett förstadium till diabetes typ 2. Det metabola syndromet består av en kombination av bukfetma, förhöjda blodfetter, nedsatt glukostolerans och förhöjt blodtryck.

Av alla patienter med diabetes lider 30-40% av diabetesrelaterade nervskador (neuropati) tio år efter insjuknandet. Neuropatin kan involvera det perifera och/eller det autonoma (icke-viljestyrda) nervsystemet. Det perifera nervsystemet är den del av nervsystemet som återfinns utanför hjärna och ryggmärg. Sjukdomar i det perifera nervsystemet, dvs. perifera neuropatier, kan yttra sig som känselnedsättning, domningar, ”sockerdrickskänsla” och muskelförtvining, framför allt i benen. De kan också drabba armarna, särskilt händerna, där också nervinklämningar som karpaltunnelsyndrom, med eller utan samtidig neuropati, förekommer oftare hos människor med diabetes. Karpaltunnelsyndrom är ett tillstånd där den s.k. medianusnerven kläms där den löper genom den trånga karpaltunneln i handleden. Karpaltunneln består av ett antal ben i botten och har ett tak bestående av ett tjockt ledband (ligament). Om det blir för trångt i tunneln, blir nerven klämd och orsakar stickningar, smärta och fumlighet i del av handen. Tillståndet förekommer hos ca 3% av befolkningen.

Behandlingen av karpaltunnelsyndrom är kirurgisk med friläggning av medianusnerven i handledsnivå (ett ingrepp som görs i lokalbedövning). Kunskapen om i vilken omfattning som nervfunktionen i händerna vid karpaltunnelsyndrom kan förbättras av kirurgi och om det finns ogynnsamma faktorer för funktionsåterkomst är otillräcklig. Tillståndet är vanligare hos människor med diabetes. Det finns därför anledning att ytterligare fördjupa sig inom området neuropati, relaterat till diabetes och metabolt syndrom. Den autonoma neuropatin som kan förekomma hos patienter med diabetes yttrar sig bl.a. i lågt blodtryck vid uppresning (ortostatism), inkontinensbesvär, magbesvär samt impotens. Den behandling som idag finns att tillgå syftar till symtomlindring.

Efter kirurgisk behandling av karpaltunnelsyndrom undersöktes patientrapporterade resultat, d.v.s. resultat av en enkät som patienten själv fyller i, i två grupper av patienter. Den ena gruppen bestod av 493 patienter som opererades på Handkirurgiska kliniken i Malmö. Patienterna skattade sina symtom före och 12 månader efter operationen i ett särskilt frågeformulär, s.k. QuickDASH, som visar funktionen i armen. Detta frågeformulär används ofta för att utröna funktionsnedsättningen vid sjukdomar i arm, axel och hand och frågorna rör bl.a. svårigheter att utföra vanliga dagliga sysslor, sömnkvalitet och hur besvärande symtomen är, inklusive stickningar. Självskattade symtom skiljde sig inte mellan patienter med och utan diabetes. Patienter med diabetesneuropati hade dock högre risk för kvarstående besvär efter operationen.

I samma grupp patienter undersöktes också hur rökning och nervledningshastighet i medianusnerven i den del som var påverkad i karpaltunneln påverkade operationsresultatet. Nervledningshastigheten undersöktes med s.k. neurofysiologisk teknik som ger ett mått på hur bra den inklämda nerven leder elektriska impulser. Det visade sig att patienter som rökte hade mer symtom både före och efter operationen jämfört med de som inte rökte. De patienter vilkas nerver hade en normal ledningshastighet före operationen, trots symptom på nervinklämning, förbättrades inte så mycket som förväntat (mätt med QuickDASH) av operationen.

Den andra studiegruppen baserades på data från det svenska handkirurgiska kvalitetsregistret (HAKIR), som samkördes med nationella diabetesregistret (NDR). Totalt 10770 operationer för karpaltunnelsyndrom utvärderades i studien. Det visade sig att patienter med diabetes hade mer kvarstående symtom ett år efter operationen. Ett högre långtidsblodsocker (HbA1c) före operationen var relaterat till mer kvarstående symtom efter operationen. Patienter som hade ögonbottenförändringar p.g.a. sin diabetessjukdom behövde längre tid för att symtomen skulle försvinna efter operationen än patienter utan sådana ögonförändringar.

För att undersöka hur autonom neuropati utvecklas över tid studerades patienter med nedsatt glukostolerans och diabetes typ 2 under tio år och jämfördes med friska personer med samma ålder. Studien visade att självskattade symtom på autonom neuropati ökade över tid hos patienter med typ 2 diabetes. För att objektivt värdera om patienterna hade autonom neuropati, mättes hur pulsen varierar med andningen. De objektiva mätningarna och vilka symtom patienterna upplevde hade inget samband. Den autonoma neuropatin hade inte heller något samband med långtidsblodsockret.

För att undersöka autonom neuropati hos patienter med diabetes typ 1 följdes även en grupp patienter med denna diabetestyp över en 20-årsperiod. Tre potentiellt nervskyddande eller inflammatoriska markörer i blod analyserades också, men

befanns inte ha något samband med den autonoma neuropatin. Den autonoma nervfunktionen försämrades över tid hos patienterna med diabetes typ 1.

De studier som ingår i avhandlingen ger möjlighet att dra följande generella slutsatser:

Patienter med diabetes har samma nytta av kirurgisk behandling av karpaltunnelsyndrom som patienter utan diabetes. Patienter med diabetesneuropati behöver längre tid för att symtomen ska ge vika och riskerar att symtomen inte försvinner helt efter operation. Patienter som röker bör sluta röka för att öka möjligheterna för ett gott operationsresultat.

Patientrapporterade symtom vid autonom neuropati skiljer sig från objektiva mätningar av autonom nervfunktion och bör aktivt efterfrågas hos patienter med diabetes. Strikt blodsockerkontroll verkar skydda mot utveckling av autonom neuropati hos patienter med diabetes typ 1.

Introduction

Diabetes is becoming one of today's biggest health challenges. Millions of people around the globe are affected by diabetes and its complications. Diabetes complications appear in the cardiovascular system, the kidneys (nephropathy), the eyes (retinopathy) and in the nervous systems (neuropathy), affecting the central, peripheral or autonomic nervous systems. The neuropathy, and its pathophysiology, associated with diabetes is not fully understood, and to date no curative treatment exists. Even though extensive resources are invested in understanding diabetes and improving its outcomes, knowledge regarding treatment and the prevention of complications remains deficient (1).

The early Egyptians described the first cases of diabetes, and noted polyuria in affected individuals. The Greek physician Aretaeus of Cappadocia defined the condition in detail. He called it diabetes mellitus; diabetes being the Greek word for "to pass through" and mellitus the Latin word for honey (2). The Persian physician Avicenna recognized diabetic complications as early as 1025 when he described diabetic gangrene in his pioneering work "The Canon of Medicine" (3).

One major turning point in the treatment of diabetes was the discovery of insulin which resulted in Frederick G. Banting and John Macleod being awarded the Nobel Prize in Physiology or Medicine in 1923 (4). They shared the award with their colleagues Charles Best and James Collip. Insulin revolutionized the treatment of diabetes, extending the life expectancy of people with type 1 diabetes from 30 years in the early 20th century to the current 70 years (5). During the last century, an array of diabetes medication was developed and treatment goals have come to include associated risk factors.

The Saint Vincent Declaration on diabetes care and research in Europe in 1989 recognized the growing burden of diabetes and urged European countries to take vigorous measures to reduce diabetes morbidity, mortality and complications (6). Some diabetes complications are more widely studied than others, for example the diabetic foot, leading to the development of protocols for multi-disciplinary care, whereas less is known about the diabetic hand (7). Retinopathy and nephropathy have received extensive attention in the literature, leading to the implementation of screening systems and risk-factor management. Another potentially devastating complication of diabetes that has been less extensively studied is diabetic neuropathy.

Both neuropathy and retinopathy are common microvascular complications in diabetes (8, 9). Retinopathy could be used as a proxy variable for neuropathy, since they often occur simultaneously (10, 11). The advantages of doing so are that retinopathy is easily and routinely assessed in standard diabetes care and is noted in the Swedish National Diabetes Register (NDR.se). The methods for assessing neuropathy include clinical examination, which is routinely performed, but may fail to detect early-stage small-fiber neuropathy (12), and electrophysiology, which may be painful for the patient and is not routinely performed.

Apart from causing neuropathy, diabetes increases the risk of peripheral nerve compression (i.e. compression neuropathy) (13). The most commonly occurring compression neuropathy is carpal tunnel syndrome (CTS), where the median nerve is compressed at wrist level inside the carpal tunnel. CTS is an excellent model of compression neuropathy to study, since it is frequently present in the general population (around 3%), can be defined in different stages and evaluated pre- and post-operatively using electrophysiology (14). The surgery is also standardized. Studying CTS can help us to further understand the pathology behind compression neuropathy, diabetic neuropathy and the mechanisms of recovery after nerve damage.

In Sweden, diabetes is treated with state-of-the-art medication and lifestyle modifications, supplemented by the use of technical devices (15). Patients go to regular follow-ups, their results are registered in a national quality registry and coexisting risk factors are treated appropriately. Despite this, and despite the developments in diabetes treatment, affected individuals suffer from a variety of complications for which our available treatment, aside from prevention, is, at best, symptom relief. Thus, studying neuropathy, which is the focus of the present thesis, is of great importance, leading to a better understanding of the condition and ultimately to making better treatment available to people with diabetes.

Background

The nervous system

The nervous system is traditionally divided into three parts – the central nervous system (CNS), consisting of the brain and the spinal cord; the peripheral nervous system (PNS), comprising the peripheral nerves (all the nerves outside the dura mater); and the autonomic nervous system (ANS) that controls all visceral functions (16). The PNS contains sensory nerves, carrying signals from the periphery to the CNS, and motor nerves transmitting signals from the CNS to the periphery. The ANS has both CNS and PNS parts and controls blood pressure, heart rate, digestion, temperature regulation and reproductive functions. The ANS is divided into the sympathetic, the parasympathetic and the enteric nervous systems (17). The sympathetic nervous system is activated in situations of distress, such as fear, in physical activity and excitement. The PNS is more active in sedentary activities and eating. The enteric nervous system comprises neuronal plexuses, i.e. submucosal and myenteric plexuses, in the bowel walls of the gastrointestinal tract (18). The nervous system is made up of neurons and neuroglial cells.

Anatomy of the peripheral nerve

The neuron

The nerve cell, i.e. the neuron, consists of a cell body (perikaryon), dendrites, one axon and presynaptic terminals. The perikaryon resides in the spinal cord (motor neurons) or in ganglia (sensory neurons) close to the CNS and is responsible for protein synthesis. Multiple processes, called dendrites, originate in the perikaryon. The axon originates from a special part of the perikaryon, the axon hillock. The axon's primary mission is to convey signals from the CNS to receptor organs, such as muscles, or vice versa; i.e. from a sensory receptor, such as a Paccini corpuscle, up to the CNS. The motor axon ends in a presynaptic terminal, where the electrical signal that has travelled along the axon is converted into chemical signals that act on the receptor organ (19).

Axons have a diameter of 0.2-15 μm and form the nerve fiber together with Schwann cells. Schwann cells are glial cells that produce myelin; an electrical insulation that enables faster conduction of electrical signals. Myelin is composed of lipoproteins in a lamellar structure. Some nerve fibers are myelinated; the axon is covered in a myelin sheath. Schwann cells and myelin sheaths join at the nodes of Ranvier along the axon. At the nodes of Ranvier, there is a complete interruption in the myelin, and the electrical signal is transmitted by jumping from one node of Ranvier to the next. This phenomenon is called saltatory conduction. This enables the myelinated axon to have conduction velocities of up to 60 m/s, compared to the unmyelinated axon that has a conduction velocity of around 1 m/s (20). Unmyelinated nerve fibers are thinner than myelinated nerve fibers, and the axons are invaginated in a Schwann cell.

Each axon and Schwann cell is surrounded by a basal lamina as well as collagen, fibroblasts, resident macrophages and mast cells in a tissue called endoneurium. A number of nerve fibers then group together to form bundles of fibers that, in conjunction with surrounding layers of fibroblasts and collagen, the perineurium, form fascicles. The perineurium, together with the barrier function of the intrafascicular capillaries, provides diffusion barriers (i.e. the blood-nerve barrier), and the nerve fibers within the fascicle can only be reached by active transportation through these barriers. The flattened perineurial cells are connected by a basal lamina. Outside the perineurium is the epineurium. The epineurium consists of loose connective tissue, and contains blood vessels that approach the nerve trunk segmentally. The epineurium, and the perineurium, act as a protective skeleton for the nerve by providing stability and cushioning against the surroundings. It allows stretching of the nerve without damaging it, since the amount of epineurium varies; in superficial nerves and when the nerve passes a joint there is more epineurial tissue. The epineurium contains blood vessels (i.e. vasa nervorum) that branch off into the perineurium, piercing the perineurium obliquely, and form intrafascicular capillaries, providing metabolic necessities (20).

Peripheral motor nerves end in motor end plates, where acetylcholine is released to trigger a motor response. The sensory nerve endings are either free or encapsulated. Encapsulated endings perceive pressure or movement, whereas the free nerve endings from unmyelinated axons distinguish heat, cold and pain and are located in the epidermis (21, 22).

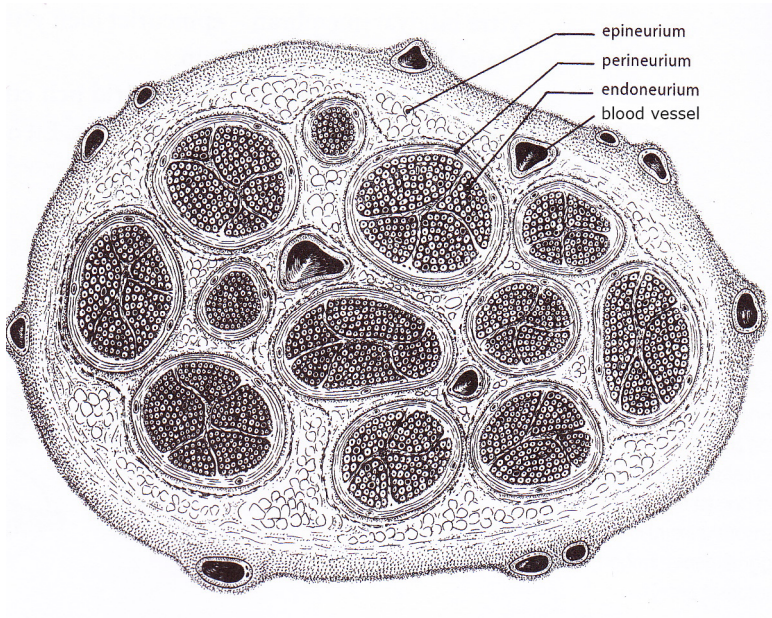

Figure 1.
Anatomy of the peripheral nerve. Adapted from Handkirurgi (23) with permission from Studentlitteratur.

Diabetes Mellitus

Approximately 442 million people worldwide suffer from Diabetes Mellitus (1). In Sweden, 4-6 % of the adult population suffer from diabetes (24). Traditionally, diabetes mellitus is divided into Diabetes Mellitus type 1 (T1D) and Diabetes Mellitus type 2 (T2D). Type 1 diabetes is an autoimmune disease, typically diagnosed in young age, and characterized by an inability to produce insulin. In contrast, type 2 diabetes is caused mainly by insulin resistance in muscle and liver cells, as well as failure of the insulin-producing β-cells in the pancreas (25), and is associated with overweight and lifestyle factors. New research, however, suggests that diabetes type 2 is made up rather of a number of subgroups with different disease characteristics (26). There is extensive research activity in this field and the future will hopefully reveal what implications these novel insights might have on the understanding and treatment of the complications, such as diabetic neuropathy. The current definitions of diabetes type 1 and 2 are used in the present thesis.

Diagnosis of diabetes, impaired glucose tolerance and metabolic syndrome

The World Health Organization (WHO) presents the following criteria for diabetes diagnosis:

Fasting plasma glucose ≥7.0 mmol/L *or* 2-h plasma glucose ≥11.1 mmol/L during an Oral Glucose Tolerance Test (OGTT) *or* HbA1c ≥57 mmol/mol (1)

The pre-stages of diabetes, i.e. impaired glucose tolerance (IGT), and the metabolic syndrome are increasingly common in the population (27).

The WHO defines IGT as fasting plasma glucose <7.0 mmol/L *and* 2-h plasma glucose during OGTT of 7.8-11.1 mmol/L (1). The International Diabetes Federation defines the metabolic syndrome as shown in Table 1 (28).

Table 1. Definition of metabolic syndrome:
Central obesity (BMI >30 kg/m^2 or measured as waist circumference with ethnicity specific values) *and* any two of the following four factors:

Raised triglycerides	≥1.7 mmol/L *or* specific treatment for this lipid abnormality
Reduced HDL cholesterol	<1.03 mmol/L in males <1.29 mmol/L in females *or* specific treatment for this lipid abnormality
Raised blood pressure	Systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg *or* treatment of previously diagnosed hypertension
Raised fasting plasma glucose	Fasting plasma glucose ≥ 5.6 mmol/L *or* previously diagnosed type 2 diabetes

Adapted from The International Diabetes Federation's worldwide consensus definition of the metabolic syndrome, 2006, with permission.

Diabetes complications

Both type 1 and type 2 diabetes may lead to numerous complications, such as chronic kidney disease (i.e. nephropathy), heart failure, retinopathy, neuropathy, diabetic foot, cardiovascular problems, pregnancy complications, gingivitis, and sleep apnea (29, 30). Complications in diabetes are frequently divided into macro- and micro-vascular complications.

Macrovascular complications

Diabetes Mellitus will be the 7th leading cause of death by 2030 (31) and among patients with type 2 diabetes at least 65% will die from cardiovascular disease (32). This is partly because risk factors for cardiovascular disease, such as hypertension, obesity and abnormal blood lipid levels, occur more frequently in patients with

diabetes than in a healthy population (33). Diabetes also aggravates atherosclerosis, and patients with diabetes are at high risk of contracting coronary, cerebral, and peripheral arterial disease. Patients with type 1 diabetes have an increased mortality from ischemic heart disease compared to the general population (34). Aggressive management of cardiovascular risk factors is thus advocated, and there is a need for sustained research to further improve cardiovascular outcomes in the presence of diabetes (35).

Microvascular complications

Microvascular complications in diabetes are caused by damage to small blood vessels, mainly by prolonged hyperglycemia (36). There are three major microvascular complications in diabetes: retinopathy, nephropathy and neuropathy.

In the retina, damage to small blood vessels leads to disruptions in retinal blood flow causing microaneurysms and retinopathy, ultimately resulting in blindness. The global prevalence of diabetic retinopathy in patients with diabetes is estimated to be around 35%, with the highest prevalence (86%) found in patients with type 1 diabetes and a diabetes duration of more than 20 years (37). To detect the disease, patients with diabetes are recommended to have their retina photographically screened every one or two years. If retinopathy is found to be present, laser treatment is recommended to prevent progression (38).

In the kidney, diabetes may lead to diabetic nephropathy with increased urine albumin excretion and a reduced glomerular filtration rate (GFR). This occurs in 20-40% of patients with diabetes (38). Screening patients with diabetes for albuminuria, in order to detect nephropathy, is recommended. Prevention of nephropathy includes early treatment of hypertension and adequate glucose control (38).

The diabetic foot, defined by Örneholm in her thesis as “infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease” (39), is another example of diabetes complications. The two main etiologies behind the diabetic foot are neuropathy and peripheral vascular disease. Diabetic foot problems may lead to foot ulcers and lower limb amputations.

Neuropathy

Many factors can cause neuropathy. One common way of classifying neuropathies is to divide them into hereditary neuropathies and acquired neuropathies. The most common hereditary neuropathy is Charcot-Marie-Tooth disease (40). Acquired neuropathies may be due to diabetes, alcohol, chemotherapy, vitamin deficiency,

autoimmune reactions (such as Guillan-Barré), vasculitis, radiation and infectious diseases (41).

The prevalence of neuropathy in patients with diabetes is 30-50% (42-44). Amongst the complications with diabetes, neuropathy is one of the less studied, particularly peripheral neuropathies other than distal symmetric polyneuropathy (DSPN) and autonomic neuropathy.

Definition of diabetic neuropathy

Peripheral diabetic neuropathy is defined as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (44). The most common presentation of peripheral neuropathy in diabetes is DSPN. DSPN is the leading cause of foot ulceration and lower extremity amputation (45) and a major contributor to falls in affected individuals (46). Patients often present with sensory disturbances, numbness and pain in a symmetric pattern, dependent on the duration of the disease, often starting distally in the foot. Other peripheral diabetic neuropathies include radiculoplexopathy, radiculopathy, mononeuritis multiplex, and mononeuropathy (12).

Pathophysiology

The precise mechanisms behind diabetic neuropathy are not fully understood. A schematic view of the proposed mechanisms lying behind diabetic microvascular complications and neuropathies is presented in Figure 1. Hyperglycemia is one of the main causal factors in neuropathy. Neurons and Schwann cells in peripheral neurons are sensitive to hyperglycemia since, when exposed to hyperglycemia, they are unable to effectively reduce the glucose levels inside the cells (47). Hyperglycemia induces oxidative stress, leading to increased production of free radicals (48). Four key mechanisms by which hyperglycemia leads to neuropathy in diabetes have been proposed: increased flow through the polyol pathway, production of AGE precursors, activation of PKC and increased activity of the hexosamine pathway (47) (Figure 1). Individual susceptibility to hyperglycemia is probably determined by both genetic factors and concomitant risk factors. In hyperglycemia, impaired trophic support and metabolic dysfunction lead to reduced axon caliber, segmental demyelination and loss of large myelinated nerve fibers. Eventually both large and small fibers degenerate, leading to sensory loss, ulcerations and amputations (49). Sensory nerve fibers are affected before motor fibers (49).

The mechanisms behind the development of neuropathy are probably partly different for type 1 and type 2 diabetes (50-52). In type 1 diabetes, there is robust

evidence that intensive glucose treatment reduces the risk of neuropathy. In the DCCT/EDIC trials, intensive treatment to normalize glucose levels in type 1 diabetes reduced the development of all micro- and macro-vascular complications, including neuropathy (53). Development of autonomic neuropathy was also significantly slower in the intensive treatment group (54). One possible mechanism behind neuropathy in type 1 diabetes is insulin deficiency, since the neurotrophic effects of insulin are weakened (12). There is also a loss of C-peptide in type 1 diabetes, contributing to neuropathy mainly by lowering eNOS, causing hypoxia (52).

In type 2 diabetes, metabolic factors other than hyperglycemia are believed to be important for the development of neuropathy (50). In a study of 3591 patients with type 2 diabetes, neuropathy prevalence was assessed both by questionnaire and by clinical examination (including inspection of the feet, ankle reflexes and vibration sensation) (42). The authors found that neuropathy in type 2 diabetes was present in 30% of patients and was associated with poor metabolic control, overweight and peripheral vascular disease. In contrast, in the DCCT trial, peripheral neuropathy was present in 39% of patients with type 1 diabetes (n=278) and was associated with diabetes duration, older age, C-peptide deficiency, retinopathy, HbA1c levels and male gender (43).

Dyslipidemia is believed to play a key role in development of neuropathy in type 2 diabetes, contributing to increased oxidative stress and damaging Schwann cells (12) (Figure 1). Insulin resistance in type 2 diabetes also contributes to neuropathy by disrupting the PI3-K/Akt-pathway, causing mitochondrial dysfunction (12).

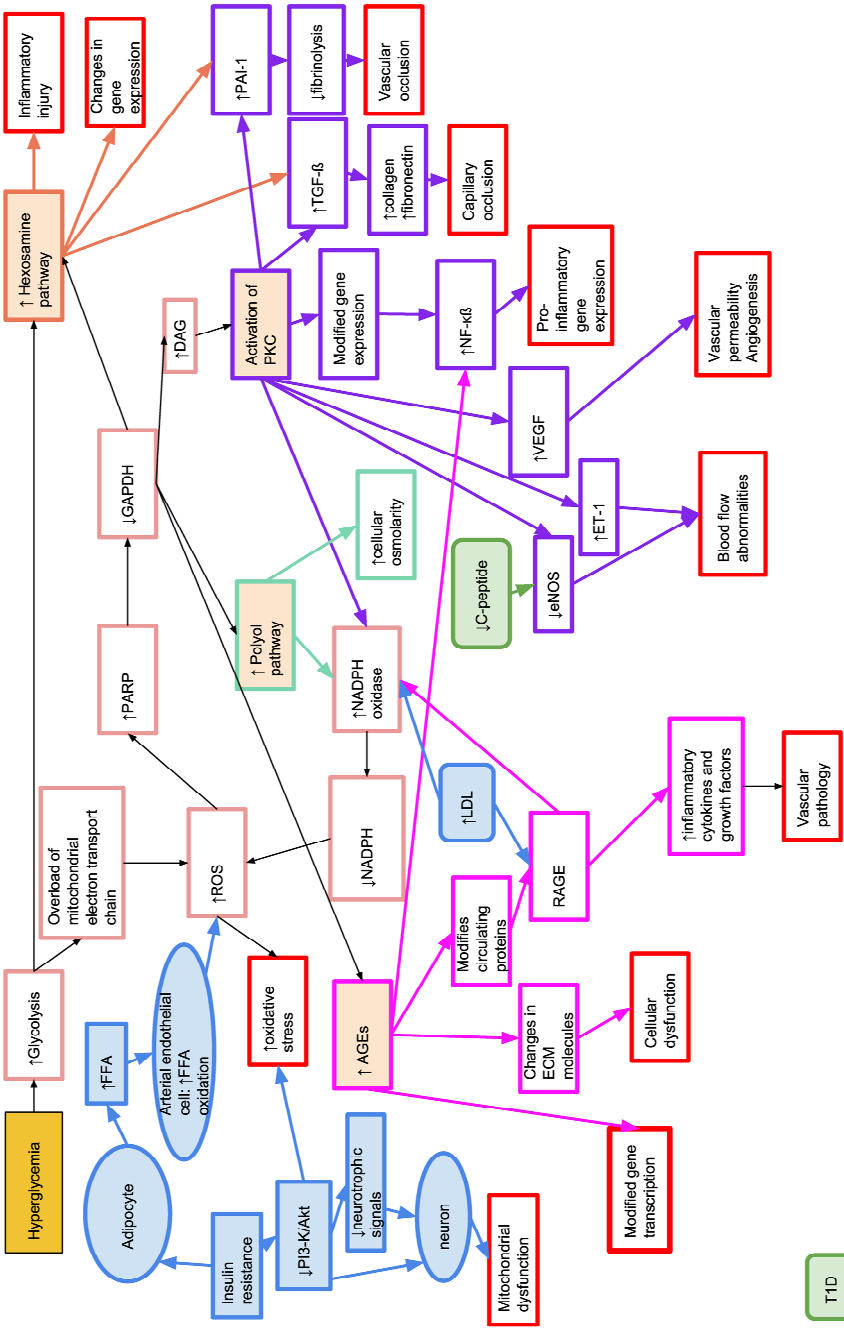

Figure 1.
Pathobiology in diabetic neuropathy (12, 47). These mechanisms leading to cell damage can happen in neurons, Schwann cells and vascular endothelial cells, causing nerve dysfunction and neuropathy.

The diabetic hand

The diabetic hand comprises various hand pathologies involving the hand in diabetic patients: limited joint mobility, Dupuytren's contracture, flexor tenosynovitis, hand infections, ulcerations due to peripheral neuropathy, carpal tunnel syndrome, ulnar neuropathy, skin and nail pathology, reduced hand strength and others, such as complex regional pain syndrome (CRPS) (7).

The diabetic hand is a common presentation. In a recent study of 376 patients with diabetes (318 with type 2 and 58 with type 1 diabetes), hand disorders were present in 14% of patients (55).

Mononeuropathies

Impaired circulation, due to vasculitis or infarction causing ischemia, can lead to mononeuropathies in peripheral nerves (56). These mononeuropathies are characterized by an acute onset and are self-resolving (49). In contrast, compression neuropathies have a gradual onset, are not self-resolving and are often progressive in nature. CTS is the most common compression neuropathy, followed by ulnar nerve entrapment.

Prevention of microvascular complications in diabetes

Metabolic control is related to development of diabetic complications, and the Japanese Kumamoto trial demonstrated that intensive glucose treatment slows the development of neuropathy and other microvascular complications in both type 1 and type 2 diabetes (57). As discussed above, other metabolic factors such as dyslipidemia are important contributors to the development of microvascular complications, particularly in type 2 diabetes, and glucose control does not seem to be sufficient to prevent all microvascular complications. It is also unclear whether strict glucose control can prevent the development of autonomic neuropathy. In the UK Prospective Diabetes Study (UKPDS), intensive glucose treatment reduced the risk of microvascular complications in type 2 diabetes, but there was no difference in heart-rate variability when deep breathing between the treatment groups at the 12-year follow-up (58). The heart rate at rest was, however, higher in the conventional treatment group, indicating the need for further studies in order to fully understand the development and possible treatment options for autonomic neuropathy in type 2 diabetes.

Pathophysiology – nerve compression lesion

Seddon divided peripheral nerve injury into three stages (59): neurapraxia, axonotmesis, and neurotmesis, and Sunderland (60) developed the classification to include five stages. In neurapraxia, the axon remains intact, but nerve function is disturbed. Electrophysiology measurements are abnormal across the lesion. It is considered a transient paralysis of the nerve fiber, and recovery is spontaneous. Neurapraxia is the same as Sunderland grade 1. In axonotmesis, the axon is damaged, but surrounding tissues remain intact. The axonal portion distal to the site of injury breaks down (Wallerian degeneration). Sunderland classified this as a grade 2 injury. In Sunderland grade 3, there is axonotmesis with endoneurium disruptions, and in Sunderland grade 4 there are also perineurium disruptions, and only the epineurium is preserved. In neurotmesis (Sunderland grade 5), the whole nerve fiber is transected. MacKinnon and Dellon added a sixth stage of nerve damage, describing variable injury to individual fascicles (61).

Pathological changes in the compressed peripheral nerve depend on the extent and duration of the compression. Initially, if there is only a slight compression trauma, disturbances in the intraneural microcirculation are noted with the formation of an epineurial edema, causing dynamic ischemia that provokes early-stage symptoms, such as paresthesia (62). In more extensive compression, there is a risk of increased vascular permeability leading to endoneurial edema and perineural thickening (63). This increases endoneurial pressure and impairs the intraneural microcirculation with a secondary non-dynamic ischemia. If the compression worsens, it will lead to localized demyelination, followed by a diffuse demyelination and thereafter a remyelination process, stimulated by the naked axon (64). Remyelination is carried out by Schwann cells, which are stimulated by mechanical forces – however, in the case of nerve compression the myelin laid down by the Schwann cells will be thin and weak and the remyelinated internodes will be shorter (65). If neurography is performed, it can be seen as a reduced conduction velocity, and the patient might complain of muscle weakness. In the early stages of nerve compression, the axon remains intact, and it is only in advanced stages that axonal integrity is compromised with axonal degeneration, leading to evident clinical signs, such as anesthesia and thenar atrophy in the case of CTS (66); observed as a low amplitude in electrophysiology testing.

A peripheral nerve that is compressed at one location is considered to be more susceptible to compression at another site, a phenomenon called “the double crush syndrome” (67). Symptoms from nerve compression in a peripheral nerve may thus be elicited from two simultaneously compressed sites. Nevertheless, it is often enough to decompress one of the sites, normally the most distal one. In the original description by Upton and McComas, it was suggested that if the peripheral nervous system had a disease, such as a neuropathy as in diabetes, the peripheral nerve was

more susceptible to nerve compression than in otherwise healthy subjects (67). This may be related to disturbances in axonal transport in the axons in diabetes (68), but other mechanisms have been suggested. In diabetes, the double crush may be viewed as diabetes constituting the first crush and the nerve entrapment (such as CTS) the second crush.

It is not fully understood why the diabetic nerve is more sensitive to compression, but it has been suggested that one underlying reason is nerve oedema. This nerve oedema might arise from increased vascular permeability and angiogenesis (Figure 1). This is potentially caused by upregulation of the vascular endothelial growth factor (VEGF), as Mojadiddi et al. described in their study of biopsies from the posterior interosseous nerve (PIN) in patients with CTS, where VEGF expression was higher in the nerve biopsies from patients with CTS and diabetes than in patients with CTS without diabetes (69). Thomsen et al., using the same PIN biopsies, demonstrated that myelinated nerve fibre and endocapillary densities were lower in nerves from patients with diabetes, leading to an increased susceptibility (70). In diabetes, the perineural basal lamina, consisting of collagen, laminin and glycosaminoglycans, can become thicker (71), as can the flexor retinaculum. This might also contribute to the compression pathology in diabetes.

Carpal tunnel syndrome

The most common nerve entrapment is carpal tunnel syndrome (CTS), estimated to affect 3% of the adult population, depending on diagnostic criteria (72). CTS was first described by Sir James Paget in 1854 (73).

There are multiple risk factors for the development of CTS, including female gender, obesity, diabetes mellitus, rheumatoid arthritis and hypothyroidism. Work-related factors are also associated with CTS, especially repetitive movements, high job strain (74), and vibration trauma.

The carpal tunnel consists of the carpal bones on the dorsal side of the wrist and the strong carpal ligament on the volar side. The median nerve passes through the tunnel together with the flexor tendons. When the nerve is compressed inside the tunnel, CTS symptoms occur. Symptoms include numbness and tingling in the thumb, index finger, middle finger and radial aspect of the ring finger, as well as pain, nocturnal awakening due to paresthesia in the hand, and clumsiness; i.e. impaired dexterity. More severe cases may present with thenar atrophy. Diagnosis is based on patient history and provocative tests; sometimes supported by electrophysiology. The most widely used tests are Phalen's test and Tinel's sign. Phalen's test is performed by holding the wrist in a flexed position to reduce space inside the carpal tunnel (75); the test is positive if paresthesia occurs within 30-60 seconds. Phalen's test has a sensitivity and specificity ranging from 40 to 80% (76). Tinel's sign,

described by Jules Tinel in 1917 (77) (also named the Tinel-Hoffman sign), is performed by gently tapping over the median nerve at wrist level. It is positive if paresthesia occurs. Tinel's sign has a specificity of 40-80%, and a sensitivity of 25-60% (76).

Another test described in the literature is the pressure provocation test (78), where pressure is put on the carpal tunnel for 30 seconds using the examiner's thumb. The test is positive if it elicits paresthesia in median-innervated areas. Sensitivity is reported to range from 4-80%, and specificity from 25-96% (79, 80).

Electrophysiology testing is recommended in patients where the diagnosis is uncertain, and is a prerequisite for the diagnosis of CTS in some countries. In Sweden, patients are customarily referred for electrophysiology testing if they have diabetes or if polyneuropathy is suspected for any reason.

CTS patients with milder symptoms, presenting with intermittent or only nocturnal symptoms of a minor character, can be treated with splinting, where the wrist is held in a neutral position, or with a local cortisone injection, that may provide limited relief from the symptoms (81). When conservative treatment fails, or in more severe CTS cases with constant symptoms, open carpal tunnel release (OCTR) is considered the gold standard of treatment. Under local anesthesia and using a forearm tourniquet, the carpal ligament is released under direct visualization (Figure 2). The patient should abstain from heavy lifting for up to six weeks after surgery to allow the surgically extended transverse carpal ligament to heal.

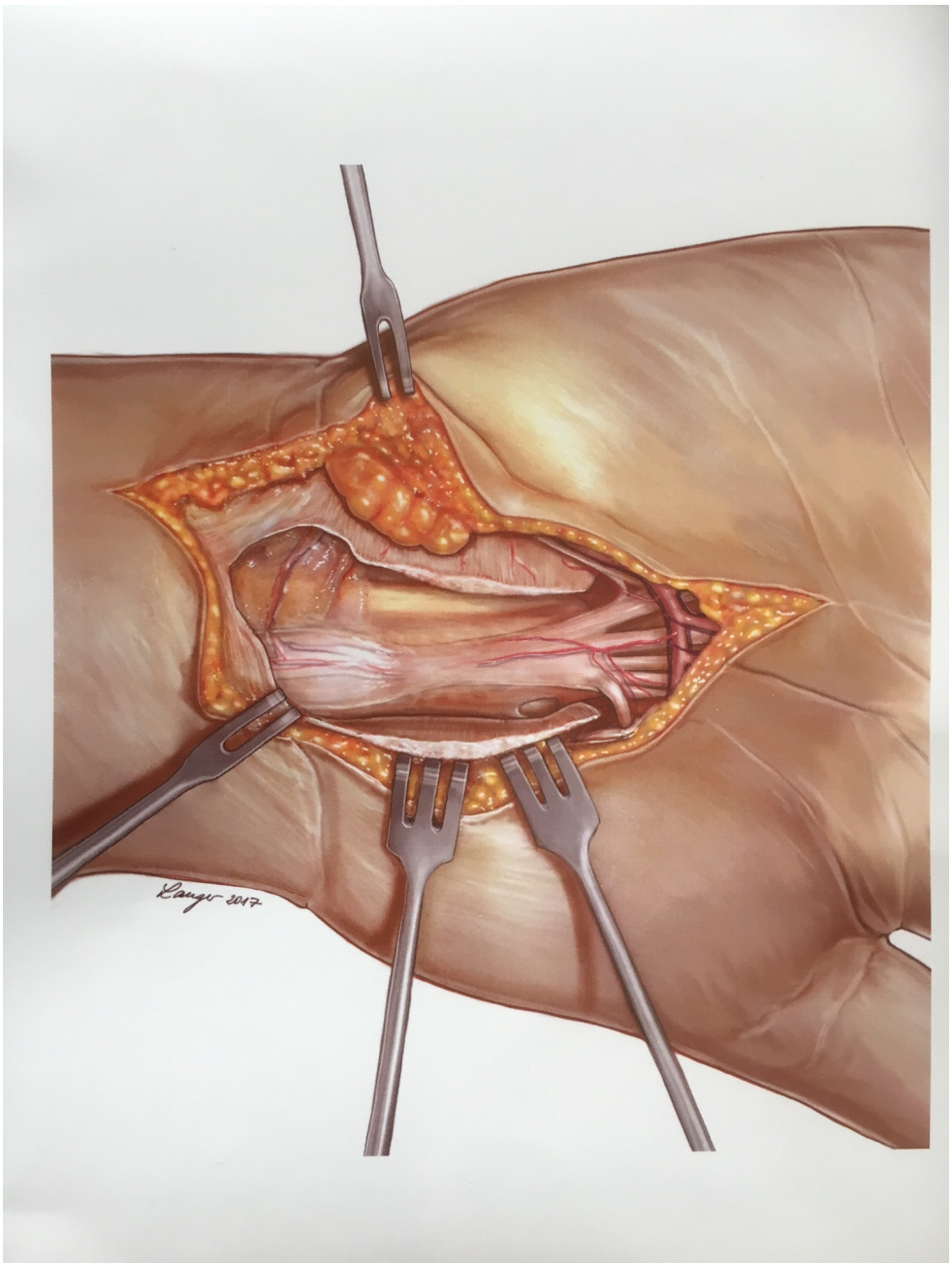

Figure 2.
Open Carpal Tunnel Release. Illustration by Martin Langer, with permission from the artist.

Table 2.
Overview of studies evaluating outcome after carpal tunnel release in patients with diabetes

Author/year	Study design	Number of patients	Number of hands	Diabetes	Type of diabetes	Neuropathy	Outcome measure	Follow-up time	Diabetes vs. no diabetes	Comments
Haupt et al 1993 **(88)**	Pro-spective	60	86	10	Not reported	Not reported	Motor function, sensory deficit, trophic changes, neurography and electromyography	Median 5.5 years (range 2-11 years) post-op	Marginally less pain relief in patients with diabetes	
al-Qattan et al 1994 **(83)**	Retro-spective	15	20	15/15	Not reported	15/15	Grading: excellent/good/ poor	18 months post-op	5 hands had poor improvement – all of these had normal/mild neurography pre-op	
Choi et al 1998 **(85)**	Retro-spective	154	294	19/154 (12%)	Not reported	3 (1.9%)	Symptom resolution (poor-excellent)	Pre-op, 1 week post-op, 3 months post-op, 12 months post-op	No difference	Good results for diabetes, double crush syndrome, severe neurography findings, long-standing symptoms
Ozkul et al 2002 **(82)**	Pro-spective	47	60	22	T2D	Excluded	PROM: global symptom score (GSS), neurography	Pre-op, 1 month post-op, 12 months post-op	Better PROMs and neurography recovery in patients without diabetes	Extensive exclusion criteria including insulin treatment
Mondelli et al 2004 **(86)**	Pro-spective case series	96	96	24/96 (25%)	T1D: 19 T2D: 5	6/24 (25%)	The Boston Questionnaire	Pre-op, 1 month post-op, 6 months post-op	No difference	
Thomsen et al 2009 **(84)**	Pro-spective	66		35/66 (53%)	T1D: 15 T2D: 20	14/35 (40%)	Monofilament, 2PD, APB strength, grip strength, key pinch, lateral pinch, pillar pain, post-operative questionnaire (VAS questions)	Pre-op, 6 weeks post-op, 12 weeks post-op, 52 weeks post-op	Patients with diabetes have the same beneficial outcome after carpal tunnel release as nondiabetic patients.	
Thomsen et al 2010 **(14)**	Pro-spective	66	66	35/66 (53%)	T1D: 15 T2D: 20	14/35 (40%)	Electrophysiology testing	Pre-op, 12 months post-op	Electrophysiology Improved as much in patients with as without diabetes	
Jenkins et al 2012 **(89)**	Pro-spective	1564	1564	176/1564 (11.3%)	Not reported	Not reported	QuickDASH	Pre-op, 12 months post-op	Diabetics: poorer functional scores after 12m but doubtful whether of clinical significance	
Isik et al 2013 **(90)**	Retro-spective case-control	74	99	36/74 (49%)	T2D	none	PROM questions on symptoms	Pre-op, 12 months post-op	Worse post-op symptoms in patients with diabetes	

Zyluk et al 2013 **(94)**	Retro-spective	386	386	41 (11%)	T1D: 11 T2D: 30	None	Levine questionnaire	Pre-op, 6 months post-op	Clinical benefit: no difference. DM patients had weaker grip strength and poorer perception of touch	
Ebrahimzadeh et al 2013 **(91)**	Retro-spective cohort	74	74	35/74 (47%)	T1D: 14 T2D: 21	Not reported	WHOQOL-BREEF; MHQ	Pre-op, 3 months post-op	Worse results in patients with diabetes	MHQ-scores better in DM2 than DM1
Cagle et al 2014 **(95)**	Pro-spective	826	950	90/950 (10%)	Not reported	20/950 (2%)	Boston Carpal Tunnel Outcomes questionnaire	Pre-op, 2 weeks post-op, 6 weeks post-op, 12 weeks post-op	Diabetics improve but take longer to do so	
Gulabi et al 2014 **(96)**	Pro-spective	69	69	27/69	T1D: 18 T2D: 9	Not reported	Boston Questionnaire	Pre-op, 6 months post-op, 10 years post-op	Diabetes patients worse at the 10y follow-up. No difference at 6m.	
Thomsen et al 2014 **(97)**	Pro-spective	66	66	35/66 (53%)	T1D: 15 T2D: 20	14/35 (40%)	Boston Carpal Tunnel Questionnaire, monofilament, 2PD, APB strength, grip strength, key pinch, lateral pinch, pillar pain, VAS questions	5 years post-op	Excellent long-term improvement in patients with diabetes	
Yucel 2015 **(92)**	Retro-spective	83	101	35/83 (42%)	Not reported	Not reported	VAS-questions, the Boston Carpal Tunnel Questionnaire, monofilament, grip and pinch strength	Not specified	Diabetes patients had more symptoms in BCTQ	
Thomsen et al 2017 **(98)**	Pro-spective	57	57	27/57 (47%)	T1D: 13 T2D: 14	10/27 (37%)	Electrophysiology parameters	5 years post-op	Long-term electrophysiology improvement was seen in both diabetes and non-diabetes patients	
Watchmaker et al 2017 **(87)**	Pro-spective	1031	1037	133 (13%)	Not reported	Not reported	Symptom survey	Pre-op, 6 months post-op	Diabetes had the same symptom resolution	Age related to worse outcome
Zimmerman et al 2017 **(99)**	Retro-spective	493	531	76 (15%)	T1D: 18 T2D: 58	18/76	QuickDASH	Pre-op, 12 months post-op	Diabetics with polyneuropathy had more persistent symptoms	
Zhang et al 2018 **(100)**	Retro-spective	904	1144	Not reported	Not reported	Not reported	Secondary surgery	1-60 months post-op	DM associated with greater risk of secondary surgery	

Outcome after open carpal tunnel release in patients with diabetes

Outcome after OCTR in patients with diabetes has long been debated by researchers and clinicians. Early studies on outcome often excluded patients with diabetes since there was a suspicion that they did not recover sufficiently after OCTR.

Table 2 presents an overview of studies on outcome after OCTR and diabetes that can be found in the PubMed database. A total of 801 diabetic hands have been investigated in 17 studies (Table 2). One of the studies excluded patients on insulin treatment due to its neurotrophic effects (82). One included only patients with diabetes (83) and reported poor improvement in 25%; all of these cases had normal or near-to-normal electrophysiology results pre-operatively, which the authors argue might explain the unsatisfactory results. Four studies reported no differences in outcome between patients with and without diabetes (84-87). Six of the studies reported less symptom relief in patients with diabetes (82, 88-92). One review from 2009 (not included in Table 2) concluded that diabetes is related to worse outcome, but that high-quality studies are lacking (93). Thus, there still remain conflicting results regarding outcome after OCTR in patients with diabetes. Many of the studies performed have small study samples and have not studied type 1 and type 2 diabetes separately. As discussed above, there are differences in the pathophysiology of diabetic neuropathy in the two types of diabetes, and there might also be differences in the compression neuropathies. The quality of the studies published earlier varies. As can be seen in Table 2, there is no gold standard when evaluating the effects of OCTR. The studies use a variety of PROM questionnaires and clinical tests and the lack of a gold standard makes comparisons difficult. There are thus good reasons to study outcome of OCTR in larger populations of patients with diabetes.

Complications

The infection rate when performing standard OCTR is low; reported to be around 0.3-1.1% (101, 102). The risk of infection is, however, higher in patients with diabetes (102). Other complications include iatrogenic nerve injury (most commonly to the median palmar cutaneous branch or the median recurrent motor branch), pillar pain, scar hypertrophy, CRPS and recurrent symptoms (103).

Autonomic neuropathy

Since diabetic neuropathy affects the longest nerve fibers first, and the longest autonomic nerve (the vagal nerve) is mainly parasympathetic, the first signs of diabetic autonomic neuropathy tend to be parasympathetic (104). However, most symptoms of autonomic neuropathy are a result of both parasympathetic and

sympathetic denervation (105). Common symptoms of autonomic neuropathy include those from the gastrointestinal tract, such as nocturnal diarrhea, fecal incontinence and gastroparesis (49); urinary tract symptoms, such as overflow incontinence and impaired emptying; sexual dysfunction; hypoglycemia unawareness; and anhidrosis (105). Troublesome as these symptoms may be, the biggest health risk is cardiovascular autonomic neuropathy (104).

Cardiovascular autonomic neuropathy

Cardiovascular autonomic neuropathy (CAN), defined as a deficiency of cardiovascular autonomic control in diabetes after exclusion of other causes (106), is commonly encountered in patients with diabetes (107). CAN leads to denervation of the heart and blood vessels, with a subsequent inability to compensate for changes in posture or activity level; as well as an increased risk of silent myocardial ischemia, diastolic dysfunction and sudden cardiac death. Hence, CAN is a risk factor for serious adverse cardiovascular events in diabetes (105, 107-109). In the ACCORD trial, CAN was associated with higher mortality in type 2 diabetes (110). It is important to assess CAN in the patient with diabetes in order to evaluate cardiovascular risks in situations that entail physiological stress, for example in pre-operative planning. Symptoms and signs of cardiovascular autonomic neuropathy are palpitations, reduced heart rate variability, increased number of ectopic beats, and silent myocardial infarction.

Risk factors for development of CAN include inadequate glucose control in both type 1 and type 2 diabetes. In type 2 diabetes, hypertension, dyslipidemia and obesity are additional risk factors (111). As described above, the natural course of diabetic autonomic neuropathy is believed to differ between type 1 and type 2 diabetes (50). In type 1 diabetes, glucose control strongly affects the prevention of neuropathy, whereas in type 2 diabetes it does not seem quite as important (50) and in type 1 diabetes, circulating autoantibodies are believed to play a part in the development of autonomic neuropathy (112). Furthermore, subclinical autonomic neuropathy is common, even among children and young adults with type 1 diabetes (113), but it is not clear whether such neuropathy progresses to overt neuropathy later in life. In summary, CAN is a serious diabetes complication that contributes to mortality, and much is still unknown about how it develops or how it may be prevented and treated. As Tesfaye et al. conclude in a report from 2010, longitudinal studies are needed to further clarify the natural course of CAN in diabetes and prediabetes (106).

Diagnosis of CAN

In a position statement from 2011, Spallone et al. conclude that there are a few autonomic tests that might be considered gold standard for diagnosing CAN; heart rate response to breathing and standing, heart rate response to Valsalva maneuver (should not be performed by patients with retinopathy), and blood pressure response to standing (111). Preferably, the results of two autonomic tests should be abnormal for a definitive diagnosis, but one test is sufficient to diagnose early CAN. Results should be interpreted within age-standardized normal values. The various tests for diagnosing CAN are presented in Table 3.

Table 3.
Tests for diagnosing CAN (adapted from Sundkvist et al (114, 115) and Boulton et al (116)

Deep-breathing test	Expiration/inspiration (E/I) ratio	With the patient in a supine position, six maximally paced breaths are drawn under continuous ECG registration. The E/I-ratio is then calculated by dividing the mean of the longest R-R intervals during expiration by the mean of the shortest R-R intervals during inspiration. Age-corrected normal values.
	Beat-to-beat heart rate variability	Same method as above. A difference of heart rate of >15 is normal, <10 abnormal.
Orthostatic tests	Acceleration index (AI)	Patient is secured to a tilt table and rapidly tilted to upright position during continuous ECG. AI = R-R interval at rest in supine position (A) minus the shortest R-R interval immediately after tilt (B) divided by A. The result is then multiplied by 100 to create the index. Signifies withdrawal of vagal tone and sympathetic activity.
	Brake index (BI)	Same method as above. BI = longest R-R interval during the first minute after tilting minus B divided by A. The result is then multiplied by 100 to create the index. Reflects reinstitution of vagal tone.
	Heart rate response to standing	After standing, R-R interval at beats 15 and 30 is measured on continous ECG. The normal response is tachycardia followed by reflex bradycardia. Often presented as 30:15 ratio.
	Systolic blood pressure response to standing	Systolic blood pressure is measured in the supine patient and then 2 minutes after standing up. Normal response is a fall of 10 mmHg and abnormal is a fall of 30 mmHg with symptoms.
Valsalva maneuver		The patient blows into the mouthpiece of a manometer, maintaining 40 mmHg for 15 seconds during ECG monitoring. Healthy subjects develop tachycardia and peripheral vasoconstriction during strain and an overshoot bradycardia and rise in blood pressure with release. The ratio of longest R-R to shortest R-R should be 1.2.
Resting heart rate		>100 beats per minute is abnormal
Diastolic blood pressure response to isometric exercise		The patient squeezes a handgrip dynamometer to establish a maximum. Grip is then squeezed at 30% maximum for 5 min. The normal response for diastolic blood pressure is a rise of 16 mmHg in the other arm.
ECG QT/QTc intervals		The QTc should be 440 ms.
Spectral analysis		Measured from 24-hour Holter ECG. Very-low-frequency peak (sympathetic dysfunction) Low-frequency peak (sympathetic dysfunction) High-frequency peak (parasympathetic dysfunction, reflects respiratory sinus arrhythmia) Low-frequency–to–high-frequency ratio (sympathetic imbalance)
Neurovascular flow		Using noninvasive laser Doppler measures of peripheral sympathetic responses to nociception.

Treatment

There is at present no cure for diabetic neuropathy, either peripheral or autonomic. Treatment is focused on prevention, using intensive glucose management, aggressive treatment of risk factors, such as hypertension and dyslipidemia as well as lifestyle modifications, which should be initiated early in the disease process before axonal degeneration becomes evident (117, 118).

Biomarkers related to presence and development of neuropathy

There are currently no known biomarkers for diagnosing or staging diabetic polyneuropathy. Finding such a biomarker would be of great value for the early detection of neuropathy, thus research into proteins and potential biomarkers possibly associated with diabetes should be a priority. In this thesis, I focused on three biomarkers: HSP27, MIF and PAI-1. HSP27 was chosen because of its neuroprotective potential (119, 120); MIF and PAI-1 were chosen as they are both inflammatory markers.

Heat shock proteins

Small heat shock proteins (sHSP) belong to a family of the molecular chaperones. Molecular chaperones are proteins that assist other proteins to achieve an active, functional state, without being part of the final product themselves (121). In general, sHSPs serve to protect the cell from outer stress, such as toxic chemicals, oxidative stress and heat shocks, and expression of the sHSPs is strongly associated with cell survival following exposure to these stressors (122). They play a crucial role in the development of cancer (123). Less is known about the role of sHSPs in neuronal cells. sHSPs are important for the protection of nerve cells in diabetic retina (124) and in a rat model of DM1, diabetic peripheral neuropathy was improved with a drug that modulates HSP90 and HSP70 (125).

HSP27

HSP27 plays a major role in inhibiting apoptosis and in cytoskeletal remodeling. Its role in cancer as a biomarker and possibly therapeutic agent is being intensively researched (126).

Following a nerve injury, a cascade of intracellular signaling causes the expression of transcription factors related to regeneration. HSP27 is one of the factors up-regulated by activating transcription factor 3 (ATF3), contributing to axonal regeneration (127, 128) and the survival of injured neurons (129). In medium- and large-sized sensory neurons, it is continuously expressed at low levels in the adult dorsal root ganglion. After damage to the peripheral axon, HSP27mRNA and

protein increase and contribute to neuron survival and regeneration of the axon (129). In the brain, HSP27 reduces ischemic damage following a stroke - its phosphorylation is a step towards preventing apoptosis (130, 131). Mutations in HSP27 are associated with peripheral neuropathies, such as Charcot-Marie-Tooth (132), indicating that the protein has an important role in normal nerve functioning. Based on this knowledge, one hypothesis is that HSP27 might also play a role in protecting neurons from the neuropathy seen in diabetes. In a recent report, HSP27 protected sensory neurons from diabetes (133), and higher levels of HSP27 are associated with fewer signs of peripheral neuropathy, as well as with better nerve functioning (119).

Macrophage Migration Inhibitory Factor (MIF)

MIF is an inflammatory marker that plays a key part in the development and pathogenesis of type 1 diabetes (134, 135). It is primarily produced by macrophages, but also in pancreatic beta cells, fat cells, liver cells and testicular and ovarian cells. In type 2 diabetes and impaired glucose tolerance, serum levels of MIF are higher than in people with a normal glucose status (136). High circulating levels of MIF are associated with an increased risk of cardiovascular events in patients with coronary artery disease and type 2 diabetes (137). Whether it has a role in diabetic neuropathy is not known, but it might be significant, considering the properties described above, and it is therefore interesting to study.

PAI-1

Plasminogen Activator Inhibitor 1 (PAI-1) is a significant component of the fibrinolytic system. It contributes to insulin resistance and is an inflammatory marker. In diabetic hyperglycemia, PAI-1 is upregulated both by increased activity in the hexosamine pathway and by Protein Kinase C (PKC) activation, leading to reduced fibrinolysis and a risk of vascular occlusion (47). PAI-1 forms complexes together with Tissue Plasminogen Activator (tPA). Maser et al (138) found higher circulating levels of tPA-PAI-1 complexes in men with diabetic neuropathy complications compared to male patients without diabetic neuropathy. This suggests that these tPA-PAI-1 complexes may predict diabetic complications in type 1 diabetes. It is interesting to continue investigating the role that PAI-1 might play in the development of diabetic neuropathy.

Aims

The overall aims of the present thesis were to evaluate different views of *the diabetic nerve*, and particularly to investigate:

1. The effects of nerve compression in the *peripheral nervous system*, focusing on treatment of CTS in diabetes and related risk factors
2. The effects of diabetes on the *autonomic nervous system.*

The specific aims of the two directions are:

1a. To evaluate outcome after OCTR, using the QuickDASH, and to investigate how surgical outcome is affected by diabetes as well as by obesity, hypertension and statin treatment,

1b. To evaluate how outcome after OCTR is affected by cigarette smoking and pre-operative electrophysiology values, as well as to assess characteristics of patients who did not improve following surgery,

2a. To investigate presence and temporal development of autonomic neuropathy in patients with type 2 diabetes,

2b. To investigate the temporal trend of autonomic neuropathy in patients with diabetes type 1 and to evaluate whether the progression of autonomic neuropathy in type 1 diabetes is associated with the neuroprotective marker HSP27, the inflammatory markers MIF and PAI-1 as well as with HbA1c

Methods

Study populations

Patients with CTS in Malmö-Lund, Sweden

The study population in Papers I and II comprises patients operated on with OCTR for CTS at the department of Hand Surgery, Skåne University Hospital, Malmö, between September 2009 and February 2011. Patients mainly came from the Malmö-Lund region in southern Sweden, where Malmö is the 3rd largest city in Sweden with a multi-cultural, ethnically mixed population. Patients are routinely asked to fill out QuickDASH questionnaires before surgery, and the questionnaire is sent to the patients by surface mail 12 months after surgery. A total of 962 patients (1044 hands) were operated on for CTS during the study period, and 514 patients completed the two QuickDASH questionnaires and were included in the study population. The 38 patients with bilateral CTS (i.e. they were operated on both sides) were included as only one hand with mean values from both hands. The 21 reoperations found in the original database were excluded. This resulted in a total of 493 patients.

The HAKIR population

The population in Paper III consists of all patients included in HAKIR (www.hakir.se) who had undergone OCTR between 2010 and 2016. A total of 10770 primary OCTRs on 9049 patients were registered in HAKIR during the study period. The database was matched to the Swedish National Diabetes Registry (NDR; www.ndr.se) and 1508 cases with diabetes were identified in the database.

Västerbotten Intervention Programme, Sweden

The study population of people with impaired glucose tolerance (IGT) and normal glucose tolerance (NGT) in Paper IV is drawn from the Västerbotten Intervention Programme, recruited in Skellefteå, Sweden, between 2003 and 2004 (119, 139). The patients with type 2 diabetes in Paper IV were recruited from primary care centers in Skellefteå during the same period. At baseline, 119 participants were included: 39 with NGT, 29 with IGT and 51 with type 2 diabetes. In 2014, 87 of the participants took part in the follow-up: 36 with NGT, 9 with IGT and 42 with T2D. Six participants had died during the study period and 31 chose to withdraw. The same examiner conducted all follow-ups.

Patients with type 1 diabetes in Malmö, Sweden

The study population in Paper V comprises patients with type 1 diabetes who were recruited at Skåne University Hospital (previously Malmö University Hospital), Sweden from 1984-1985. Originally, 110 patients were asked to participate and 58 agreed to do so. At the final follow-up in 2005, 32 patients participated. Twenty-four patients attended all follow-ups.

Medical records and declaration of health

The study population in Papers I and II had completed a pre-operative declaration of health, from which many variables were extracted. Some variables were also extracted from the medical files. These data can be viewed as "real world data", that is they are identical to the data that the treating clinician has access to. There are some obvious limitations to these data –they may, for example, be incomplete. The declaration of health has one major advantage – the patient writes down what medications he or she takes, which provides valuable and consistent information about their current medications.

Electrophysiology

Electrophysiology is a useful complement when investigating potential nerve injuries or conditions. It can help to diagnose the location of the lesion, whether there is axonal damage or demyelination, how severe the lesion is and whether there are any signs of recovery (Figure 3 and 4). However, with nerve conduction studies, patients with small fiber disease are missed, since electrophysiology primarily allows evaluation of the large diameter nerve fibers. Cooling-threshold tests are often advocated for detecting small-fiber neuropathy, but despite their frequent use in the clinic, this method is not reliable (49).

Figure 3.
The setup for electophysiology testing. Author's own picture.

Figure 4.
Performance of an electrophysiology test. Author's own picture.

Parameters

Sensory conduction velocity (SCV)

Sensory conduction velocity in the median nerve across the wrist (m/s) was used to compare nerve function between groups in Paper II. It is calculated by measuring the distance between the stimulation site and the recording site in millimeters and dividing the distance by the latency of the sensory nerve action potential (SNAP) in milliseconds. The first pathological finding from electrophysiology in CTS is slowing of the SCV in the median nerve across the carpal tunnel (65).

Sensory nerve action potential (SNAP)

SNAP measures the number of excitable sensory axons (140). SNAP is preserved in the first stages of compression neuropathy, since it is elicited distal to the compression and there is no axonal damage in the early stages (65). In Paper II, SNAP recorded from the median nerve in the middle finger was used. In very severe cases of CTS, SNAP may not be recordable at all.

Electrophysiology classification

In 1997, Padua et al. suggested a method of classifying electrophysiology findings in CTS (141). This classification uses six grades based on the electrophysiological results:

1. Negative = normal electrophysiological results
2. Minimal CTS = segmental tests are abnormal
3. Mild CTS = median distal motor latency is normal, but conduction velocity between wrist and finger is abnormal
4. Moderate CTS = both median distal motor latency and the conduction velocity between wrist and finger are abnormal
5. Severe CTS = sensory response is absent and median distal motor latency is abnormal
6. Extreme CTS = thenar motor responses are absent

A simplified version of Padua's classification was used in Paper II, and patients classified with minimal or negative CTS were presented as one group and classified as normal. Please note that this is a classification based solely on electrophysiological findings.

Definition of polyneuropathy

In this thesis, polyneuropathy was defined as either diagnosed earlier (diagnosis found in medical records) or as diagnosed by electrophysiology.

HAKIR

HAKIR is the National Quality Register for Hand Surgery in Sweden (www.hakir.se). It was launched 1, February 2010. All the major hand surgery departments in Sweden participate in HAKIR, as well as two smaller private units. In Sweden, many carpal tunnel releases are also performed in orthopaedic departments and smaller private units, but these are not yet connected to HAKIR. All patients are included, apart from those without a Swedish social security number, with protected identities or who refuse to participate. Initial registration in HAKIR is based on a PROM questionnaire that the patient fills in before surgery and at three and 12 months after surgery, as well as on registration of codes and complications by the nursing staff. An extended registration can be added for implants etc., which includes additional functional examination of the patient at baseline and at three and 12 months post-operatively, as well as extended surgery registration (142). The PROM questionnaire consists of the 11 items included in the QuickDASH, as well as eight Likert scale questions (Appendix 2). The eight Likert scale questions, called HQ-8 questions, are as follows: 1) pain on load, 2) pain on motion without load, 3) pain at rest, 4) stiffness, 5) weakness, 6) numbness/tingling in fingers, 7) cold sensitivity, 8) ability to perform daily activities. They are scored from 0–100, where 0 represents no problem and 100 represents worst problem imaginable. Between 2010 and 2013 the design of the questions was a visual analogue scale, but it was changed to a numeric 11-point box scale in 2013. The verbal anchors at the beginning and at the end of the scale remained unchanged. There are also two questions regarding patient satisfaction. These items were not included in Paper III, since the design of the questions was changed during the study period. The response rate for three months in 2016 was 43.1% and for twelve months 43.3% (143).

NDR

The Swedish National Diabetes Register (www.ndr.nu) was started in 1996 in response to the St. Vincent Declaration (6) and includes adult patients (>18 years) with diabetes in Sweden (excluding gestational diabetes), with data on diabetes complications, blood samples, risk factors and treatment. Approximately 90% of people with diabetes in Sweden are included in the NDR (144). Treating clinics and primary care units continuously report to the NDR (145). The NDR is planning to

include PROM data in the register, and a questionnaire with a total of 33 items is currently being evaluated.

QuickDASH

The use of PROMs is a well-established tradition in CTS, and there are a few to choose from. The most commonly used are the Disabilities of the Arm, Shoulder and Hand (DASH), the shortened version of the DASH (the QuickDASH), the Boston Carpal Tunnel Questionnaire (BCTQ, also known as the Levine questionnaire), and the Michigan Hand Outcomes Questionnaire. They all have advantages and disadvantages, but they also all have good validity, reliability, and responsiveness as well as comprehensive frameworks (146).

The BCTQ is a disease-specific questionnaire in two modules. One module assesses symptoms (Symptom Severity Scale) with 11 questions and the other assesses functional status (Functional Status Scale) with eight questions (147, 148). The Michigan Hand Outcomes Questionnaire (149) is not specific for CTS and comprises 37 items to assess hand function.

The DASH outcome measure is not disease-specific, but is commonly used to assess patient-reported outcomes in upper extremity pathology and has been extensively studied for this purpose. The DASH consists of 30 items (150) that assess symptoms as well as ability to perform various activities. The QuickDASH is the shortened version of DASH, with only 11 items (151). The patient is asked to answer the questions based on how he or she felt during the preceding week. Each item has five options, ranging from 1 = no difficulty, to 5 = impossible to perform, and all items consider the patient's symptoms and the difficulty of performing daily activities. A total score is then calculated, ranging from 0-100 (higher scores indicate more severe symptoms). The QuickDASH was used in this thesis, and can be found in Appendix 1.

Markers of neuroprotection and inflammation in serum

The analyses of HSP27 were performed at the same time (2010) at the same laboratory using an ELISA kit (Calbiochem, San Diego, CA) with a lowest detection limit of 312 pg/ml in Umeå, Sweden. The same method was used to analyse MIF and PAI-1 (analysis performed in 2016 in Lund, Sweden). The possibility that the storage affected the samples cannot be excluded, but they were stored at -80°C in a freezer, which is standard practice when storing biological samples and probably has only a minor influence on the contents. Performing the analysis at the same time and using the same method was probably more important.

The control group in Paper V consisted of 397 healthy blood donors (34% women; mean age 43 ± 8 years). The control group was age- and gender-matched to the participants in the study.

Autonomic testing

The E/I ratio is measured with the patient in a supine position, according to Sundkvist (114). The R-R intervals are recorded on a continuous ECG during six maximal breaths. The ratio is calculated from the mean of the R-R intervals during inspiration and expiration. The ratio is then adjusted to age-related normal values (116, 152).

Intra-subject reproducibility in autonomic testing is good in patients with diabetes (153, 154), as well as in healthy subjects, where the reproducibility for the E/I-ratio has been reported to be 0.89 (95% CI 0.71-0.96) (155).

An abnormal E/I ratio is a marker of autonomic dysfunction. Previously it has been considered to measure primarily parasympathetic vagal dysfunction (156). The Toronto Expert Group concluded that heart rate variation during deep breathing measures mainly parasympathetic function and that the test can be used when diagnosing cardiovascular autonomic neuropathy (111). Subsequently, newer research and more finely tuned measuring methods have shown that heart rate variability measures rather the fluctuations of autonomic input to the heart and that the heart rate is controlled by a delicate balance between the parasympathetic and the sympathetic nervous system (157).

Autonomic testing is subject to confounding, and the most relevant confounder is age (111), for which adjustments have to be made when testing the autonomic function. In Paper V, we attempted to control for this by using the group in our population with normal glucose tolerance as a reference group when defining abnormal E/I ratio, since age distribution was the same across our study groups.

Autonomic Symptom Score

A questionnaire with seven items regarding autonomic symptoms was used in Paper IV (Appendix 3). The items were: 1) postural hypotension, 2) urinary incontinence, 3) nocturnal diarrhea, 4) gustatory sweating, 5) gastric atony, 6) hypoglycemia unawareness and 7) erectile dysfunction. Participants were asked about how often they experienced the symptoms and the answers were scored as 0 = never, 1 = sometimes and 2 = often. The scores were then added up to a total score; the ASS score (158).

Impaired glucose tolerance (IGT)

In Paper IV, two standardized oral glucose tolerance tests were used to verify glycemic status in patients with IGT and NGT. The tests were performed after overnight fasting and interpreted according to the 1999 World Health Organization's recommendations (159). A person classified as NGT had to have a fasting plasma glucose level of <7.0 mmol/L and a 2-hour fasting plasma glucose level of <8.9 mmol/L. People classified as IGT have a fasting plasma glucose level of <7 mmol/L and a 2-hour fasting plasma glucose level of ≥8.9 mmol/L and <12.2 mmol/L.

Statistical methods

The hand patient presents with a special statistical challenge – i.e. one patient, two hands. In our studies on CTS, some included patients were operated on bilaterally. In the study group from Papers I and II, 38/493 (7.7%) patients were operated on bilaterally. This proportion is so small that the possible statistical dependence would be marginal. In Paper III, 1721/10770 (16%) were operated on bilaterally during the study period.

Multiple ways of analyzing the problem of two hands from one patient have been proposed (160). Including each hand as an individual case produces a statistical error since the common statistical methods assume statistical independence, and two hands from one person are more similar than two hands from two separate individuals. This method was used in Paper III, since we judged it would give the most clinically relevant result and the proportion of bilaterally operated patients was relatively small. Removing the bilaterally operated patients would skew the results. Randomly choosing one of the hands to be included in the study is another possible method, but is less clinically appealing. Some previous studies have included only the worst hand in patients with bilateral symptoms, but this approach may create a bias. It might be that symptoms affecting the dominant hand are perceived as more incapacitating for the patients than those affecting the non-dominant hand. Another option is to include a mean value from both hands, as was done in Papers I-II. The downside with this approach is that it levels out any discrepancies between the hands – when CTS affects the dominant hand it is normally perceived as more disturbing than when it affects the non-dominant hand. One cannot assume that the patient has similar symptoms in both hands.

Results and comments

The reader is referred to the individual papers for details. The findings in each paper are briefly summarized below.

Paper I

Diabetic neuropathy increases the risk of unsatisfactory outcome after OCTR

Paper I aimed to evaluate clinical outcome after OCTR in patients with diabetes, obesity, hypertension and statin treatment. Patients with diabetes had more comorbidities and lower sensory conduction velocities in the median nerve at wrist level compared to those without diabetes. QuickDASH scores were higher in patients with diabetes, both before and after surgery, but the differences could be fully explained by the presence of polyneuropathy. These results suggest that diabetes itself does not affect outcome after OCTR, but patients with concomitant polyneuropathy risk an unsatisfactory outcome and should receive information pre-operatively regarding this risk. Obesity, hypertension and statin treatment did not affect outcome after OCTR.

Additional results – type 1 and type 2 diabetes

Among the 76 patients in the population with diabetes, 18 (24%) had type 1 diabetes and 57 (75%) had type 2 diabetes (data missing in one patient). Patients with type 2 diabetes were, as expected, older, had a higher BMI and more often had hypertension, but no statistically significant differences in QuickDASH scores were seen (Table 4).

Table 4.
Comparison between type 1 and type 2 diabetes (Kruskal-Wallis and Chi-square)

	Type 1 diabetes (n=18)	Type 2 diabetes (n=57)	P-value
Age, years median [IQR]	48 [35-64]	62 [53-72]	**0.028**
Female gender, n (%)	8 (44)	37 (65)	0.122
BMI, kg/m^2 median [IQR]	25 [23-27]	31 [27-34]	**<0.0001**
Hypertension, n (%)	4 (22)	33 (58)	**0.011**
Smoking, n (%)	3 (17)	11 (19)	0.803
Statin treatment, n (%)	7 (39)	31 (54)	0.252
Polyneuropathy, n (%)	6 (33)	12 (21)	0.288
SCV (m/s) median [IQR]	29 [20-37]	26 [19-33]	0.298
Pre-operative QuickDASH score median [IQR]	47 [33-64]	57 [41-77]	0.241
Post-operative QuickDASH score median [IQR]	23 |7-60]	34 [11-66]	0.343
Change in total QuickDASH score median [IQR]	19 [3-31]	19 [4-38]	0.904

Paper II

Smoking and normal electrophysiology are predictors of unsatisfactory outcome after OCTR

Paper II aimed to evaluate clinical outcome after OCTR in relation to smoking status and pre-operative nerve function (measured using electrophysiology). Patients who smoked had better nerve function than patients who did not, but despite this the smokers had higher QuickDASH scores both before and after surgery, indicating that they had more symptoms. Normal electrophysiology results before surgery were associated with unsatisfactory outcome. Pre-operative electrophysiology results did not correlate with self-reported QuickDASH scores.

Additional results

One hundred and thirteen (21%) hands were operated by specialists in hand surgery, 224 (42%) by residents in hand surgery and 191 (36%) by residents in orthopaedic surgery (three cases were omitted due to missing data). There were no differences in pre-operative scores, post-operative scores or in change in total scores between these groups. The surgeon's experience did not affect the outcome of OCTR in contrast to other procedures, such as surgical treatment of distal radius fractures (161). All surgeons, however, had long experience of orthopaedic surgery. Similar results were recently reported in a study from the Netherlands (162).

Paper III

Patients with diabetes have more symptoms

This paper aimed to investigate outcome after OCTR on a national level in Sweden, and to investigate whether patient-reported outcomes differed between patients with and without diabetes. Patients with diabetes had more symptoms both before and after surgery than patients without diabetes, but the relative improvement did not differ. Higher pre-operative HbA1c levels were associated with higher post-operative QuickDASH scores. Results in patients with type 1 diabetes did not differ from those in patients with type 2. Patients with manifest retinopathy needed a longer recovery time after OCTR than patients without retinopathy. Smoking and older age were associated with unsatisfactory outcomes after OCTR. Patients who received their diabetes diagnosis after OCTR had more symptoms after surgery than patients without diabetes.

Paper IV

Patient-reported symptoms of autonomic neuropathy increase over time in type 2 diabetes

This study aimed to investigate the prevalence and development over time of autonomic neuropathy in patients with type 2 diabetes, as well as in those with impaired (IGT) and normal glucose tolerance (NGT). The E/I ratio deteriorated over time in type 2 diabetes and in people with NGT. The E/I ratio was not associated with HbA1c levels, duration of diabetes or patient-reported symptoms of autonomic neuropathy. The E/I ratio was associated with the level of Body Mass Index (BMI) in patients with type 2 diabetes. The number of patient-reported symptoms was higher in the patients with type 2 diabetes than in individuals with NGT at follow-up, but the symptom score did not correlate with E/I-ratio and HbA1c levels.

Paper V

Autonomic function deteriorates over time in type 1 diabetes

Paper V aimed to investigate the temporal trend of CAN in type 1 diabetes and whether progression of CAN is associated with the potentially neuroprotective protein HSP27, the inflammatory markers MIF and PAI-1 and with HbA1c.

Cardiovascular autonomic function deteriorated over time (20 years), but was not associated with any of the biomarkers apart from HbA1. Strict glucose control might help check the development and progression of autonomic neuropathy in type 1 diabetes.

Additional results

Renal disease could possibly affect the biomarkers used. We had data on s-creatinine and EDTA-clearance from 2005. There were no correlations between creatinine and MIF, PAI-1 and HSP27 (values from 2005). When correlating clearance and MIF, PAI-1 and HSP27, there was a positive correlation for MIF; however, R2 was only 0.16. My interpretation is that renal function did not affect biomarker levels. The correlation found for MIF is very weak and difficult to assess.

General discussion

The present studies contribute to the knowledge of two complications in diabetes that have not yet been extensively studied – mononeuropathy and autonomic neuropathy. In addition to the substantial literature concerning the treatment of CTS, the results from the present thesis can be used in developing more specific guidelines for treating CTS patients, particularly in the form of recommendations for patients with concurrent risk factors, such as diabetes and smoking, as well as for judging indications for surgery and outcome in relation to pre-operative electrophysiology. The results may even be applicable to other nerve compression lesions and mononeuropathies. The included studies also contribute to a deeper understanding of the natural course and pathophysiology of autonomic neuropathy in type 1 and type 2 diabetes. Autonomic neuropathy often receives less attention than other diabetic complications, and raising awareness of the condition might help affected individuals to get proper care and promote further research to improve treatment and prevention.

The peripheral nerve in diabetes

The present thesis concludes, based on two different populations, that patients with diabetes and CTS improve after OCTR as measured by patient-reported outcomes (PROMs), but risk incomplete symptom resolution. The presence of a peripheral neuropathy adversely affects the outcome of surgery. Many previously published studies on the subject have not stated whether the investigated patients had type 1 or type 2 diabetes, or whether or not neuropathy was present. The strength of the present thesis is that the results from the first studies in a smaller population (Papers I and II) could be confirmed in a larger, national study (Paper III). The results are consistent with the prospective studies carried out by Thomsen et al (14, 84, 97, 98), where patients with diabetes and neuropathy made a slower electrophysiological recovery. In addition, Ozkul et al conducted a prospective study on type 2 diabetes patients, and found that both electrophysiology and PROM results were worse in patients with diabetes (82). However, in a study by Isik et al, patients with type 2 diabetes had more pain at night, paresthesia, weakness and numbness at 12 months post-operatively than patients without diabetes (90). Again, comparisons between studies are difficult since there is no consensus about which outcome measure to use. In another study by Jenkins et al, QuickDASH was used to evaluate outcome

after OCTR, and they found that the difference between patients with and without diabetes was 5.9 at one year post-operative. Whether this difference has any clinical importance at all is open to question since they also used 8 as the minimal clinically important difference in the QuickDASH (89). This could also be applied to my studies; in Paper I the difference was 8 points, and in Paper III it was 4 points twelve months post-operatively. Even though patients with diabetes scored higher in the QuickDASH both before and after surgery, the relative improvement was equivalent to the improvement in patients without diabetes. Hence, there is no reason to abstain from surgical treatment of patients with diabetes who are affected by CTS. However, it is wise to perform electrophysiology testing on these patients before surgery, to evaluate the presence or absence of polyneuropathy, since it seems the presence of a polyneuropathy is associated with a less satisfactory outcome. This is supported by the novel finding that patients with diabetic polyneuropathy had poorer symptom resolution (Paper I), and that patients with manifest retinopathy needed a longer recovery period after OCTR (Paper III). As retinopathy can be considered a proxy variable for neuropathy (this is discussed more in detail in the following section), it seems that neuropathy adversely affects outcome after OCTR in CTS. Thus, the diabetic nerve might both be more susceptible to compression and need longer to recover after release from that compression (95). This might be attributable to the lower nerve fiber density found in diabetic nerves compared to the nerves of healthy people (70) and an impaired regeneration process.

The components of the metabolic syndrome, i.e. obesity, hypertension and statin treatment (as a proxy variable for dyslipidemia), which are all known risk factors for the development of diabetic neuropathy and CTS (163), were also investigated regarding their impact on the outcome after OCTR. As we did not have any data on lipid levels from included patients, statin treatment was used as a proxy variable. There has been some concern that statin treatment might cause neuropathy (164) and, potentially, a statin-induced neuropathy could mimic CTS. However, I found nothing to support this hypothesis. The above-mentioned variables were frequently present in the study population (Papers I and II; with obesity in 28% of patients, hypertension in 29% and statin treatment in 17%). The results, however, did not support the hypothesis, and no metabolic risk factor, excluding diabetes, affected patient-reported outcome after OCTR for CTS.

As discussed further below, there are multiple PROMs to choose from when evaluating CTS. QuickDASH was used in this thesis, and although not disease-specific for CTS, the QuickDASH is well suited for evaluation of CTS and postoperative outcomes (165).

Retinopathy and neuropathy

An emerging body of evidence suggests that retinopathy and neuropathy develop simultaneously (10, 11). Large nerve fiber neuropathy can be assessed by means of electrophysiology testing, but this diagnostic modality misses small nerve fiber neuropathy and may even require skin biopsies for a secure diagnosis. Corneal confocal microscopy is a possible new, non-invasive way of diagnosing small fiber neuropathy (166-168). New findings suggest that neurodegenerative retinal changes precede vascular retinopathy in asymptomatic children with type 1 diabetes; perhaps because retinal neurons are vulnerable to the metabolic changes that come with diabetes, and the loss of nerve fibers weakens the blood-retinal barrier, subsequently leading to microaneurysms and retinal thickening (169). In the present thesis, patients with retinopathy needed a longer recovery time after OCTR than patients without retinopathy. One possible explanation is that patients with retinopathy also had more pronounced neuropathy and, therefore, needed more time to recover. A clinical examination is currently the gold standard in screening for distal symmetric polyneuropathy. The American Diabetes Association (ADA) recommends the following clinical tests, graded as reduced or absent (51): for large myelinated nerve fibers - ankle reflexes, perception of vibration with a 128-Hz tuning fork, light touch perception with a 10-g monofilament and proprioception; and for small unmyelinated nerve fibers - cold/hot discrimination and pinprick sensation. Corneal confocal microscopy could possibly be a valuable addition to the clinical examination, as a tool for diagnosing diabetic autonomic neuropathy (170). One future clinical application might be the addition of corneal confocal microscopy in standard screening for patients with diabetes. The treating physician could use this information when treating diabetes patients with CTS, in order to gain an adequate perception of their neuropathy status.

In a study from 2018, Ahlqvist et al suggested a new classification of type 2 diabetes (26). In their work, severe insulin-deficient diabetes (SIDD) had a higher prevalence of retinopathy than the other clusters. This group of patients was characterized by poor metabolic control and insulin deficiency. Neuropathy was not discussed in the study, but if retinopathy might be considered a proxy variable for neuropathy, since these two complications often go hand in hand, one would expect the prevalence of neuropathy to be higher in the patients classified as SIDD. Being able to classify patients with type 2 diabetes more precisely offers new possibilities for tailored diabetes treatment and, in the context of neuropathy, for close monitoring of the patients at the greatest risk. Perhaps it may even lead to discoveries of new treatments aimed at neuropathy.

Patients with retinopathy had higher QuickDASH scores at three months post-operatively, but at 12 months no difference was seen in outcome measured by the PROM QuickDASH (Paper III). This suggests that these patients also had more

nerve damage, and that recovery took longer after OCTR. Mustafa et al. assessed the prevalence of hand disorders in 1000 patients with type 2 diabetes, and found that retinopathy was significantly associated with CTS, even if patients with symptoms suggestive of diabetic polyneuropathy were excluded from the analyses (171). In the DCCT/EDIC cohort of patients with type 1 diabetes, cheirorthropathy (defined as the presence of at least one of the following: adhesive capsulitis, CTS, trigger finger, Dupuytren's, and/or positive prayer sign; CTS present in 30% of patients) was associated with the presence of retinopathy (172). In 406 type 1 diabetes and 38 type 2 diabetes patients, who were followed for 17 years, overweight, hyperglycemia, and tobacco use were predictors of retinopathy (173).

To sum up, it seems that neuropathy and retinopathy are closely related complications in diabetes. The presence of retinopathy is related to that of CTS, and to slower recovery after OCTR, measured using the PROM QuickDASH.

Differences between type 1 diabetes and type 2 diabetes in outcome after OCTR and presence of autonomic neuropathy

In the present thesis, there were no differences between patients with type 1 and type 2 diabetes in patient-reported outcome after OCTR. In Paper III, QuickDASH scores were higher before surgery in patients with type 2 diabetes. In the study population from Papers I and II, both pre-operative and post-operative scores tended, although not statistically significantly, to be higher in type 2 diabetes patients (Table 4). However, patients with type 2 diabetes were older, and age was related to less satisfactory results (Paper III).

Autonomic neuropathy, measured as the E/I ratio, deteriorated over time in both type 1 and type 2 diabetes. In type 1 diabetes, the temporal trend was associated with HbA1c levels, however, there was no such association in type 2 diabetes. Mechanisms that affect the development and prognosis of neuropathy probably differ between type 1 and type 2 diabetes. In the ACCORD trial, intensive glucose treatment did not affect mortality in patients with type 2 diabetes and CAN (110), strengthening the hypothesis that in type 2 diabetes factors other than hyperglycemia affect the development of neuropathy. Other risk factors for diabetic neuropathy, such as obesity, dyslipidemia and hypertension, are also more prevalent in the population with type 2 diabetes. However, data from the EURODIAB study shows that cardiovascular risk factors were associated with the incidence of neuropathy in type 1 diabetes (174), and a natural conclusion is that treatment of these risk factors will reduce the risk of developing neuropathy in both type 1 and type 2 diabetes.

One other theory is that patients with type 1 diabetes are diagnosed much earlier in the course of the disease than patients with type 2 diabetes, who may have undiagnosed diabetes and pre-stages of diabetes for a longer period before being

diagnosed and treated. In a cohort from Toronto of 467 subjects with risk factors for diabetes, peripheral neuropathy was present in almost 50% of the participants with impaired glucose tolerance (175). However, these results could not be confirmed in one study conducted on the same population that I used in Paper IV, using electrophysiology, thermal thresholds and intraepidermal nerve fiber density; no differences in nerve fiber function were found between the IGT and NGT groups (176). In Paper IV, we aimed to investigate the evolution of autonomic neuropathy in both patients with diabetes type 2 and people with IGT. At baseline, 29 people had IGT, but at follow-up this was reduced to only nine. Of these, five had been classified as IGT at baseline and four had moved from the NGT group to the IGT group. It was therefore not possible to draw any conclusions from this small sample. In conclusion, it remains unclear whether autonomic neuropathy regularly appears in pre-diabetes stages.

A weak association was found between BMI and the E/I ratio in type 2 diabetes patients in Paper IV. In a review from 2014, Stuckey et al concluded that heart rate variability was impaired in women with metabolic syndrome, while the data was unconvincing in men (177). Regarding gender differences, diabetic neuropathy occurs earlier in the disease in men than in women, according to one study (178). Careful interpretation is needed, but the differences might arise from gender differences in willingness to seek medical advice or accessibility to medical care. When evaluating OCTR using QuickDASH, women score their symptoms higher than men, both before and after surgery (Zimmerman et al, unpublished results). This is, however, partly related to the fact that some items in the QuickDASH require a greater grip strength (such as opening a tight or new jar), and women score higher on these items. It is possible that the normal difference in grip strength between men and women gives rise to the observed differences in QuickDASH.

Pre-operative HbA1c levels were associated with outcome after OCTR, where higher levels were associated with more post-operative symptoms (Paper III). This novel finding suggests that glycemic control is an important factor for outcome after OCTR. Recently, Peterson et al demonstrated that HbA1c levels correlated with sural nerve amplitude in patients with type 2 diabetes and prediabetes (179). Longer myelinated nerve fibers are at greater risk of demyelination and degeneration in compression pathology (70, 180), suggesting that glycemic control is important in protecting and preserving nerve fibers in CTS and type 2 diabetes. The same seems to be true for type 1 diabetes. A recent study demonstrated that in children with type 1 diabetes, neuropathy was more prevalent in those with multiple daily insulin injections than in those with continuous subcutaneous insulin infusion (181). It seems that intensive glucose control (as provided by continuous insulin infusion) can protect peripheral nerves in type 1 diabetes, as well as in autonomic neuropathy, as suggested in Paper IV, and as seen in a number of large treatment trials (57, 182). Strict glucose control might preserve nerve fibers in the median nerve, whereas

inadequate glucose control might speed up demyelination and degeneration of axons. This will lead to greater susceptibility to compression and to a more severe compression pathology, with smaller margins for the compressed nerve as well as a subsequent impaired capacity to recover after surgery. In type 2 diabetes, dyslipidemia and insulin resistance probably have effects on cellular dysfunction equal to that of hyperglycemia (12).

There were no post-operative differences in outcome after OCTR between patients with type 1 and type 2 diabetes (Papers I and III). The results from our local population were thus confirmed in a larger, national cohort. Patients with type 1 diabetes more frequently had retinopathy and polyneuropathy, and one would therefore expect the patients with type 1 diabetes to have worse outcomes following OCTR, as neuropathy occurs more frequently in them than in type 2 diabetes patients. However, patients with type 2 diabetes were older than patients with type 1 diabetes in both populations (Paper I: median 62 vs. 48 years, Paper III: 68 vs. 49 years). It is possible that age differences contribute to the fact that there were no significant differences between type 1 and type 2 diabetes regarding outcome, since age was also associated with a poorer outcome (Paper III). In Paper V, type 1 diabetes patients had a median age of 31 years at baseline, and in Paper IV, type 2 diabetes patients had a median age of 61 years at baseline. One can take into consideration the slow loss of nerve fibers in peripheral nerves that occurs with ageing (183) as a contributing factor.

Electrophysiology, CTS and OCTR

Patients with normal nerve function, or signs of mild nerve dysfunction, on electrophysiology testing had unsatisfactory results following surgery (Paper II), a finding that is consistent with some previously published studies (83, 184). Other studies, however, have not found any correlation between pre-operative nerve function, as measured by electrophysiology, and post-operative results (185). In a study of 62 patients, Longstaff et al concluded that electrophysiology results did not correlate with surgical outcome; however, 22 patients had no or very mild abnormalities in the electrophysiology testing and only ten of them experienced complete symptom relief after surgery (186). In this thesis, no relation was found between pre-operative QuickDASH scores and pre-operative SCV of the median nerve, which is a novel finding and consistent with previous studies using other outcome measures (185, 187). In Sweden, electrophysiology is normally only performed when the clinical diagnosis is not entirely clear, if there are significant comorbidities, such as diabetes, or in order to differentiate between various nerve pathologies. Thus, an electrophysiology test is not seen as necessary when the clinical picture is typical. If the patient has a normal nerve function as measured on the electrophysiology test, it is plausible that CTS may not be the correct diagnosis,

or, perhaps, that the nerve compression is at a very early stage with no structural changes as yet. These results stress the importance of a correct diagnosis, and if CTS is suspected, but electrophysiology is normal, surgical improvement cannot be expected.

Patients who were classified as extreme CTS, based on electrophysiology findings, also had higher QuickDASH scores post-operatively (Paper II). This indicates that very severe CTS, where the compression has probably propagated into extensive axonal damage with degeneration, has a poorer prognosis than milder variants. In the study by Longstaff et al, four patients had extremely severe abnormalities in the electrophysiology testing, and none of them had complete symptom relief (186). With this in mind, it is reasonable to recommend that patients should be operated on before CTS has progressed to this severe stage. If a patient presents with signs of thenar atrophy or altered 2PD, prompt surgery is warranted. The patient should be informed preoperatively that residual symptoms may persist after surgery.

Patients who did not improve following OCTR

In this thesis, 25% of patients did not improve following OCTR; defined by having less than the minimal clinically important difference in QuickDASH, <8 (Paper II). The only variable that differed between these patients and the patients with a change >8 in the QuickDASH was the pre-operative electrophysiology findings, where patients with <8 had better conduction velocities and SNAP. There was also a higher proportion of patients with polyneuropathy in the group with a change < 8. Semple and Cargill had the same findings in 1969 – they saw failure in 25% of their 150 surgical procedures within a follow-up time of 2-7 years (188). Unfortunately, there was too much missing data in the population used in Paper III to allow analysis of the number of patients with a change <8 in this material. It is possible that the group that does not improve is heterogeneous in its nature. Part of the explanation might be, as discussed above, that some patients with no or very mild structural changes might be misdiagnosed and that patients with very severe structural damage might not fully recover after surgery. There might also be other factors influencing surgical outcome that we have yet to identify.

Smoking, CTS and OCTR

Patients who smoked had more symptoms than patients who did not, both before and after surgery (Paper II), despite having better nerve function. It is possible that smokers experience more symptoms early on in the course of CTS and are therefore diagnosed earlier, before the compression has led to more extensive nerve damage. Nevertheless, patients who smoked had higher QuickDASH scores after surgery than non-smokers. The question can be asked whether the impaired microcirculation

which comes with smoking generally in tissues and in particular in the peripheral nerve, entails a condition mimicking diabetic neuropathy. A recent review concluded that smoking might be associated with a greater risk of developing diabetic neuropathy (189). Possible causative mechanisms are damage to the vasa nervorum, leading to ischemic changes, toxic effects and oxidative stress.

As presented in this thesis, smoking leads to a poorer surgical outcome following OCTR, as measured using QuickDASH. In one earlier study, smoking was found to be associated with less symptom resolution (190). That study, however, did not use any validated PROM to evaluate symptoms. The study reported in Paper II is also, to my knowledge, the first to show that symptoms in patients who smoke are worse even before surgery, regardless of electrophysiological status. That smokers had higher nerve conduction velocities in the median nerve at wrist level implies that they had less nerve damage than non-smoking patients, despite having more symptoms. This finding suggests that other mechanisms than demyelination or axonal loss are primarily responsible for symptoms elicited in smoking combined with CTS, perhaps a toxic and ischemic effect, or at least disturbed microcirculation, on the median nerve. It is also possible that other upper extremity conditions affected the QuickDASH results in patients who smoked – for example, people who smoke more often have impaired peripheral circulation (191) and joint disease (192).

It is possible that symptoms in smokers may improve only if they stop smoking. At the very least, patients with CTS who are active smokers should be advised to stop prior to surgery, not only to improve the outcome of OCTR, but also to reduce the risk of post-operative complications. One limitation of HAKIR is that it does not include data on smoking status, and the effect of smoking on OCTR outcomes could not, therefore, be assessed in the larger population in Paper III. Thus, it would be advisable to include the factor ‘smoking’ in the HAKIR register.

Autonomic neuropathy

The E/I ratio is suitable for evaluating the presence of autonomic neuropathy in diabetes since it is easy to perform with simple equipment, is non-invasive and can be carried out in a primary care setting. These are the principal reasons for the choice of method in Papers IV and V. To further strengthen the diagnosis of CAN, one more test should be added (111), and blood pressure response to standing is a simple test that also can be used in a primary care setting. In earlier research, the E/I ratio was judged to measure parasympathetic nerve function, since respiratory sinus arrhythmia at normal respiratory frequencies is vagally modulated (111, 114). However, at lower respiratory frequencies, both the parasympathetic and the sympathetic nervous systems can mediate heart rate (157). I hypothesize that since autonomic neuropathy affects the parasympathetic nervous system first (105),

perhaps the E/I ratio does not reveal the neuropathy if the sympathetic nervous system can compensate and the E/I ratio might appear normal even if there is a parasympathetic denervation. The addition of other tests, such as the blood-pressure response to standing, that can be used to assess sympathetic function (105), or brake index that reflects reinstitution of vagal tone (193), might then be a way of strengthening the diagnosis, as described in Paper V.

The patient-reported symptoms of autonomic neuropathy did not correlate with the E/I ratio in type 2 diabetes, as reported in Paper IV. This finding is consistent with the results from the Rochester Diabetic Neuropathy Study (194). As hypothesized above, perhaps the E/I ratio is not sensitive enough to detect early autonomic neuropathy, or perhaps the patients experience symptoms before any abnormalities can be measured. Thus, it is recommended that a symptom assessment be added in the evaluation of autonomic neuropathy.

Biomarkers

Serum levels of HSP27 were not associated with autonomic neuropathy in Paper V, and I therefore found nothing to support the hypothesis that it might serve as protection from autonomic neuropathy in type 1 diabetes. Since the blood samples were obtained late in the course of the disease, it is possible that the results would have been different if blood samples had been obtained at the onset of diabetes.

In Paper V, MIF levels were lower in type 1 diabetes patients than in controls at the final follow-up. MIF concentrations also dropped over time in the type 1 diabetes patients; a phenomenon that was not seen in the control subjects. MIF can be linked to several phenomena in patients with diabetes; both to the pancreatic beta cells for the general disease, and to specific tissues affected by the disease, such as the peripheral nerve. Previous studies have linked serum concentrations of MIF to insulin resistance, impaired glucose tolerance and type 2 diabetes (136, 195, 196). The loss of insulin production in type 1 diabetes is due to the autoimmune destruction of the insulin-producing beta cells in the pancreas. In a study on diabetic mice, MIF depletion protected pancreatic beta cells and insulin levels (197). MIF probably promotes apoptosis of pancreatic beta cells (198). The patients with diabetes in Paper V had a long duration and their diabetes was well-controlled. It is possible that inflammation is higher in the early course of the disease, and that the level of inflammation is controlled by intensive treatment. One may even consider that if MIF is produced by pancreatic beta cells, circulating levels of MIF will be lower late in the disease when there are not many beta cells left.

MIF most probably also plays a role in neuroinflammatory pathways (199). In an animal model, local administration of MIF antibodies at the site of a transected sciatic nerve slowed the regeneration process and promoted Schwann cell apoptosis

(200). MIF is known to slow neuronal degeneration and promote axonal regeneration after nerve injuries in animal models (201, 202). The findings on MIF in spinal cord injury are summarized in a recent review (203), and the evidence shows that MIF levels are up-regulated in both acute and chronic spinal cord injury in both animal models and human subjects. However, the results are conflicting as to whether or not MIF plays a neuroprotective role in spinal cord injuries. In diabetic neuropathies, the role of MIF remains unclear. One previous study found no correlation between serum MIF levels and the clinical stages of neuropathy (196) – MIF serum levels were, however, higher in patients with diabetes than in healthy subjects. In Paper V, no correlation was found between MIF and the E/I ratio. One previous study showed that serum MIF levels were higher in type 2 diabetes than in individuals with normal glucose status (136). However, we could not confirm this in type 1 diabetes; in contrast MIF levels were lower in type 1 diabetes patients than in controls (Paper V). In conclusion, MIF is an interesting protein in the setting of both diabetes and neuropathy, and further research is needed to clarify its role in inflammation and neuroprotection. One suggestion is to continue by evaluating nervous tissue using biopsies.

The other inflammatory marker, PAI-1, was also lower in the patients examined in 2005 than in the same patients in 1998. One study on patients with type 2 diabetes reported that serum levels of PAI-1 were related to diabetic peripheral neuropathy (204). Another recent study linked PAI-1 levels to depression in patients with type 2 diabetes (205). PAI-1 is associated with obesity and insulin resistance (206), probably due to the low-grade inflammation that is characteristic of obesity and PAI-1 being produced in adipocytes. In patients with impaired glucose tolerance, PAI-1 is a strong predictor for the development of type 2 diabetes (207). Its role is more obscure in type 1 diabetes. One small study demonstrated an overexpression of PAI-1 in donated eyes from deceased patients (five donors with type 1 diabetes and five donors with type 2 diabetes) with diabetic retinopathy (208). As discussed above, retinopathy and neuropathy seem closely related in diabetes, but further research is needed to determine whether PAI-1 is overexpressed in diabetic nerves.

Recently, PAI-1 levels were shown to predict a reduced estimated glomerular filtration rate (eGFR) in patients with type 1 diabetes (209). Apart from being an important component in inflammation, PAI-1 is known to play a role in atherosclerosis in diabetes. This might be more important in type 1 diabetes, and perhaps also a relevant mechanism in diabetic neuropathy, as impaired circulation might affect the development of neuropathy in diabetes. Further studies are needed to determine the exact role PAI-1 has in the development of diabetic neuropathy and its relation to recovery of nerve function after surgery involving the peripheral nerve (210).

Patient-reported outcome measures – general comments

It seems reasonable to include PROMs when evaluating treatments for various conditions, as is indicated by the present findings that pre-operative QuickDASH scores did not correlate with pre-operative electrophysiology values (Paper II) and ASS did not correlate with the E/I ratio (Paper IV). The fact that the symptoms experienced by the patient do not correlate with our objective measures requires treating physicians to listen to what the patient is saying. Another important aspect is that PROMs may help physicians to effectively communicate to their patients what they can expect from treatment in comprehensible terms. When testing for autonomic neuropathy in the everyday clinic, a simple questionnaire, like that used at present, regarding symptoms of autonomic neuropathy might be useful in evaluating progression. It is possible that patient symptoms appear before the manifestation of any measurable abnormality. Another possibility is that other conditions which the patient might have are reflected in the PROMS, for example, the ASS has a question on erectile dysfunction that may have many etiologies.

The use of PROMs in CTS and OCTR

As PROMs gain in popularity, concerns have been raised that, as a proportion of the population is functionally illiterate, they will have great difficulty understanding the questionnaires. One study concluded that the DASH and QuickDASH are difficult to understand and require an education level equivalent to that of an undergraduate, whereas the Michigan Hand Outcomes Questionnaire only requires the educational level of a 13-15-year-old subject (211). Using an automated web-tool to calculate readability (https://www.webpagefx.com/tools/read-able/check.php) provides contradictory results - the English version of the QuickDASH scores 71.9 on the Flesch Kincaid Reading Ease score and 5.5 on the Flesch Kincaid Grade Level (212), meaning that the text should easily be understood by a 12-13-year-old subject. Essential as PROMs are for conducting research and developing clinical practice, we must ensure that they can be read and understood by a majority of the patients for whom they are designed, as well as being applicable in a global setting.

Some of the items in commonly used PROMs also risk becoming outdated. In the BCTQ one item asks about difficulties holding a book while reading and another about trouble gripping a telephone receiver. In DASH, there is one question regarding ability to write when today more and more writing is done on a computer or cell phone and not with a regular pen. The Michigan Hand Outcomes Questionnaire contains one item about picking up a coin – an activity that will soon probably be a thing of the past.

The QuickDASH, together with Likert-scale items on symptom severity, is used by the Swedish National Quality Register for Hand Surgery HAKIR, presumably

because the QuickDASH is widely used in Sweden and a short questionnaire has practical implications. The QuickDASH was also used in the studies on OCTR included in this thesis. The QuickDASH is specific for upper extremity pathology, but not specific for CTS. It is completed by the patient alone. Since it consists of only 11 items, it is not time-consuming and is suitable for a real-world study. The QuickDASH is easily available online, at no cost. The DASH has been compared to the Boston Carpal Tunnel Questionnaire and is sensitive to clinical change (responsiveness) and reliable for assessing CTS (213). When studying outcome, based on QuickDASH (Papers I, II and III), I used 8 as the minimal clinically important difference (214). Other more recent studies have reported a change in QuickDASH of 15.91 (215), 18.7 (216), and 20 (217) as the minimal clinically important difference. I used a cut-off at 10 for remaining disability, as measured by the QuickDASH (218).

To summarize, the QuickDASH is a simple, reliable and sensitive questionnaire, and it was well suited for the purpose of evaluating outcome after OCTR in the present thesis. The studies are based on real-world data, and in clinical work, a questionnaire that is quick and easy to use is probably invaluable in achieving higher response rates. The other PROMs that are commonly used to evaluate OCTR; DASH, BCTQ and the Michigan Hand Outcomes Questionnaire, are more extensive and provide more information, but at the cost of being more time-consuming for the patient. From this perspective, QuickDASH is the shortest and most convenient of the questionnaires described here while providing reliable data on the patients' symptoms. It is therefore the primary choice of PROM.

The use of PROMs in autonomic neuropathy

A number of PROM questionnaires exist for evaluating diabetic neuropathy, but few are properly validated or include questions on autonomic neuropathy (219). One PROM for diabetic neuropathy that is worth mentioning is the Norfolk Quality of Life – Diabetic Neuropathy (Norfolk QOL-DN) (220), comprising a total of 47 questions. The Norfolk QOL-DN includes six items asking about symptoms of autonomic dysfunction: vomiting after meals, diarrhea or loss of bowel control, head rush or dizziness upon standing, problems with erection (males), problems with vaginal dryness (females) and involuntary urinating when laughing or coughing. The patients score the extent to which these symptoms affect their activities of daily life (ADL) on a 5-point Likert scale.

A 7-item questionnaire was used to assess autonomic function (Paper IV). An item regarding female sexual dysfunction was missing. To assess autonomic symptoms in the everyday clinic easily, I would suggest, for convenience, the development of a questionnaire for future research that is as short as the one used in Paper IV, but with updated items.

Strengths and limitations

In Papers I and II, the major strengths are the relatively large population size together with the extensive amount of data available for each patient. The major limitation in Papers I and II is that 47% of the patients operated on during the study period could not be included because they had not completed both QuickDASH questionnaires. The same is true for Paper III, where the data is unique due to its size and to the fact that the population is studied on a national level, but follow-up data is missing in 57% of cases. This is in line with response rates found in other studies (221, 222). Some limitations, as discussed below, arise from the nature of the registries used. However, they consist of real-world data, which is relevant in this context.

In Papers IV and V, the main strengths are the well-defined cohorts and the long follow-up time. One limitation of Paper IV is that there might be a survival bias. It is possible that it was the participants with the poorest health who died or withdrew during the study period. The aim of the study in Paper IV was also to evaluate individuals with IGT. This turned out to be challenging as, for many participants in the IGT group, the glucose tolerance status changed during the study period, with some normalizing their glucose tolerance and others developing type 2 diabetes. In the end, the IGT group was so small that it was not possible to study this group reliably.

In the absence of data on lipid levels, we used statin treatment as a proxy variable. This might be misleading since many patients receive statin treatment for cardiovascular secondary prevention even though their lipid levels were within normal values.

The PROM in Paper IV was chosen in 1984 – the Norfolk QOL-DN would perhaps have been chosen today when designing a study on diabetic neuropathy. The main limitations of this questionnaire are that it has not been validated and that it lacks an item regarding female sexual dysfunction.

The E/I ratio was the only variable used to detect autonomic dysfunction in Paper V, and it is possible that using only one method is not sufficient to reliably detect autonomic neuropathy. The E/I ratio has multiple confounders (111). To control for these, testing was standardized by having the same examiner perform all tests at all follow-ups and patients refraining from exercise and bigger meals two hours before testing. Another possible confounder is treatment with beta blockers that may affect heart rate variability. In Paper V, I adjusted for beta blocker treatment in the regression analysis; in Paper IV, data on beta blocker treatment was only available for the last two follow-ups. Only 3/30 in 1998 and 2/31 in 2005 received treatment with beta blockers and such a small number is unlikely to affect the overall results.

Working with national quality registries

The study design of combining data from HAKIR and NDR is unique and provides new insights within a large population. The major concern with national registries is the quality of the data. In NDR, many connected units use automated data transfer from patient files into the register. The patients come for regular follow-ups as part of their diabetes treatment. Both these factors contribute to the fact that many variables in NDR contain complete, reliable data. In HAKIR, the major problem encountered was the follow-up rate. This was approximately 43%, which was lower than in Papers I and II (response rate 51%). In future when using substantial amounts of data ("big data") and artificial intelligence algorithms, such a response rate may be sufficient to predict the outcome of surgery in a specific patient (221, 222).

NDR contains no variable on autonomic neuropathy. There is only one variable regarding peripheral neuropathy concerning the foot, coded in four steps: healthy foot, neuropathy and/or angiopathy, previous foot ulcer/severe callus/previous amputation and ongoing severe diabetic foot complications (ulcer/critical ischemia/infection/osteoarthopathy/Charcot). This is thus a weak variable, and the possibilities of studying neuropathy on a national level in Sweden are therefore limited, making this a major limitation of NDR.

Main conclusions and future perspectives

Main conclusions

Surgically treated patients with diabetes and CTS can expect the same relative symptom relief as patients without diabetes, but risk residual symptoms. Patients with diabetic neuropathy risk unsatisfactory result after OCTR. Smokers have more symptoms than non-smokers and should be encouraged to stop smoking before surgery. Patients with normal nerve function experience limited improvement following OCTR.

Autonomic nerve function deteriorates over time in type 1 diabetes and is related to HbA1c. Improved glucose control might help protect against autonomic neuropathy in type 1 diabetes. No association was found between the neuroprotective and inflammatory proteins and the E/I ratio in type 1 diabetes. Autonomic symptoms increase over time in type 2 diabetes and a symptom scoring system might be useful in monitoring these patients.

Summary: key findings CTS

- Patients with diabetes and CTS improve after OCTR, but patients with diabetic neuropathy risk unsatisfactory results after OCTR.
- Obesity, hypertension and statin treatment do not affect outcome after OCTR.
- Smokers have more symptoms both before and after OCTR compared to non-smokers, but improve after surgery.
- Patients with normal electrophysiology results that are treated for CTS with OCTR have limited improvement following surgery
- 25% of treated patients show no improvement in QuickDASH

Summary: key findings autonomic neuropathy

- Autonomic symptoms increase over time in patients with type 2 diabetes
- Autonomic nerve function deteriorates over time in type 1 diabetes
- The deterioration is related to HbA1c, but not associated with HSP27, MIF and PAI-1 in type 1 diabetes
- Strict glucose control might protect against the development of autonomic neuropathy in type 1 diabetes

"One never notices what has been done;
one can only see what remains to be done."

- Marie Curie

Future perspectives

Carpal tunnel syndrome is, because of its high prevalence, an excellent model for the study of nerve compression and nerve pathology. Some aspects of CTS are not yet entirely clear. Why the diabetic nerve is more susceptible to compression and the complete molecular pathobiology behind diabetes neuropathy are not yet fully understood. A future line of research could be to study further subgroups of type 2 diabetes and investigate which patients are prone to developing neuropathy and nerve compression lesions. The second most common nerve compression lesion is ulnar nerve entrapment and less is known about how the ulnar nerve is affected by diabetes. Ulnar nerve entrapment is more difficult to treat than CTS, with variable results, and might be confused with an ischemic mononeuropathy. Other mononeuropathies in diabetes are ill-defined and the underlying pathology has not been clarified. A deeper understanding could possibly be achieved by using novel techniques, such as mass-spectrometry and synchrotron imaging on nerve and skin biopsies. Improved knowledge is a prerequisite for the development of new treatment strategies.

Secondly, in this thesis, a substantial number of patients did not experience any clinically significant improvement after surgery, measured by the PROM QuickDASH. If this is true, more research is needed to understand why and to further identify patients who are at risk. One possible future direction could be to study how socio-economic factors, such as education level and income, affect CTS presentation, diagnosis and outcome of treatment.

When working with national quality registries, it would be of great value to increase the post-operative responses. Perhaps one future possibility is to send the questionnaires electronically to the patient, to facilitate completion.

In autonomic neuropathy, further studies are recommended to include at least two autonomic tests. One interesting part of the autonomic nervous system not included in this thesis is the enteric nervous system. Neuropathy in the enteric nervous system leads to several disabling symptoms for the affected individual, and could be further studied using enteric biopsies. A simpler way of studying neuropathy could be to add corneal confocal microscopy to the routine screening of diabetes patients, in order to provide an earlier neuropathy diagnosis and staging.

One future improvement in detecting autonomic symptoms could be the development of a simple, validated questionnaire, suitable for use in the everyday clinic and to acquire real-world data that could be included in national quality registries, such as NDR. This would allow big-data collection and analysis in large populations. Better data could help us understand more of the underlying pathology and symptoms experienced by the patients in connection with the autonomic nervous system, and could also help in the development of more specific treatments.

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Appendix 1

The QuickDASH (Disability of Arm, Shoulder and Hand). Swedish version.

Hälsoenkät (arm/axel/hand)

Denna enkät berör Dina symtom och Din förmåga att utföra vissa aktiviteter.
Svara på **varje fråga**, baserat på hur Du har mått **den senaste veckan**, genom att kryssa för ett svarsalternativ för varje fråga.
Om det är någon aktivitet Du inte har utfört den senaste veckan får Du kryssa för det svar som Du bedömer **stämmer bäst** om Du hade utfört aktiviteten.
Det har ingen betydelse vilken arm eller hand Du använder för att utföra aktiviteten. Svara baserat på Din förmåga oavsett hur Du utför uppgiften.

	Ingen svårighet	**Viss svårighet**	**Måttlig svårighet**	**Stor svårighet**	**Omöjligt att göra**
1. Öppna en ny burk eller hårt sittande lock	☐	☐	☐	☐	☐
2. Utföra tunga hushållssysslor (t ex tvätta golv, putsa fönster, hänga tvätt)	☐	☐	☐	☐	☐
3. Bära matkassar eller portfölj	☐	☐	☐	☐	☐
4. Tvätta Din rygg	☐	☐	☐	☐	☐
5. Använda en kniv för att skära upp maten	☐	☐	☐	☐	☐
6. Fritidsaktiviteter som tar upp viss kraft eller stöt genom arm, axel eller hand (t ex spela golf, använda hammare, spela tennis, skytte, bowling)	☐	☐	☐	☐	☐

7. Under **den senaste veckan**, i vilken utsträckning har Dina arm-, axel- eller handproblem stört Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra?

☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

8. Under **den senaste veckan**, i vilken utsträckning har Dina arm-, axel- eller handproblem stört Ditt vanliga arbete eller andra dagliga aktiviteter?

☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Ange svårighetsgraden på Dina symtom **den senaste veckan**:

	Ingen	**Lätt**	**Måttlig**	**Svår**	**Mycket svår**
9. Värk/smärta i arm, axel eller hand	☐	☐	☐	☐	☐
10. Stickningar (sockerdrickskänsla) i arm, axel eller hand	☐	☐	☐	☐	☐

11. Har Du haft svårt att sova, under **den senaste veckan**, på grund av värk/smärta i arm, axel eller hand?

☐ Inte alls ☐ Viss svårighet ☐ Måttlig svårighet ☐ Stor svårighet ☐ Mycket stor svårighet

Appendix 2

The postoperative patient questionnaire from HAKIR.

Fylls i av personal

☐ **3 månader** ☐ **12 månader** ☐ **Annat** **(ange antal månader)** ☐☐

HAKIR
HANDKIRURGISKT KVALITETSREGISTER

PATIENTENKÄT (arm/hand)

Personnummer (ååååmmdd-nnnn):

Mobiltelefonnummer (070-111 22 33):

Mailadress:

Datum för ifyllande av enkät (ååää-mm-dd) ☐☐☐☐-☐☐-☐☐

Jag är (ange den hand du skriver med): ☐ Vänsterhänt ☐ Högerhänt ☐ Tvåhänt

Arm/hand som ska opereras: ☐ Vänster ☐ Höger

Enkäten gäller de besvär du har haft **den senaste veckan,** i den **arm/hand** som har opererats. Kryssa för det svarsalternativ som stämmer bäst överens med dina ev. besvär.

1. Smärta vid belastning

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

2. Smärta vid rörelser <u>utan</u> belastning

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

3. Vilovärk

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

4. Stelhet

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

5. Svaghet

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

6. Domningar/stickningar i fingrarna (”sockerdrickskänsla”)

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

7. Köldkänslighet (obehag/besvär när du utsätts för kyla)

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

8. Förmåga att utföra dagliga aktiviteter

	0	10	20	30	40	50	60	70	80	90	100	
Inga problem	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Värsta tänkbara problem

9. Hur upplever Du <u>resultatet</u> av operationen?

	0	10	20	30	40	50	60	70	80	90	100	
Helt nöjd	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Helt missnöjd

10. Hur upplever Du <u>bemötandet</u> på kliniken under behandlingstiden?

	0	10	20	30	40	50	60	70	80	90	100	
Helt nöjd	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	Helt missnöjd

Vänd! Version 9 (2015-01)

Fylls i av personal

HAKIR
HANDKIRURGISKT KVALITETSREGISTER

☐ **3 månader** ☐ **12 månader** ☐ **Annat** (ange antal månader) ☐☐

Hälsoenkät (arm/axel/hand)

Denna enkät berör Dina symtom och Din förmåga att utföra vissa aktiviteter. Svara på **varje fråga**, baserat på hur Du har mått **den senaste veckan**, genom att kryssa för ett svarsalternativ för varje fråga. Om det är någon aktivitet Du inte har utfört den senaste veckan får Du kryssa för det svar som Du bedömer **stämmer bäst** om Du hade utfört aktiviteten. Det har ingen betydelse vilken arm eller hand Du använder för att utföra aktiviteten. Svara baserat på Din förmåga oavsett hur Du utför uppgiften.

	Ingen svårighet	**Viss svårighet**	**Måttlig svårighet**	**Stor svårighet**	**Omöjligt att göra**
1. Öppna en ny burk eller hårt sittande lock	☐	☐	☐	☐	☐
2. Utföra tunga hushållssysslor (t ex tvätta golv, putsa fönster, hänga tvätt)	☐	☐	☐	☐	☐
3. Bära matkassar eller portfölj	☐	☐	☐	☐	☐
4. Tvätta Din rygg	☐	☐	☐	☐	☐
5. Använda en kniv för att skära upp maten	☐	☐	☐	☐	☐
6. Fritidsaktiviteter som tar upp viss kraft eller stöt genom arm, axel eller hand (t ex spela golf, använda hammare, spela tennis, skytte, bowling)	☐	☐	☐	☐	☐

7. Under **den senaste veckan**, i vilken utsträckning har Dina arm-, axel- eller handproblem stört Ditt vanliga umgänge med anhöriga, vänner, grannar eller andra?

☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

8. Under **den senaste veckan**, i vilken utsträckning har Dina arm-, axel- eller handproblem stört Ditt vanliga arbete eller andra dagliga aktiviteter?

☐ Inte alls ☐ Lite ☐ Måttligt ☐ Mycket ☐ Väldigt mycket

Ange svårighetsgraden på Dina symtom **den senaste veckan:**

	Ingen	**Lätt**	**Måttlig**	**Svår**	**Mycket svår**
9. Värk/smärta i arm, axel eller hand	☐	☐	☐	☐	☐
10. Stickningar (sockerdrickskänsla) i arm, axel eller hand	☐	☐	☐	☐	☐

11. Har Du haft svårt att sova, under **den senaste veckan**, på grund av värk/smärta i arm, axel eller hand?

☐ Inte alls ☐ Viss svårighet ☐ Måttlig svårighet ☐ Stor svårighet ☐ Mycket stor svårighet

Appendix 3

The Autonomic Symptom Score (ASS).

Anamnes autonom neuropati

0 = aldrig

1 = ibland

2 = ofta

Yrsel vid uppresning (postural hypotension)	
Svårt att kontrollera urinblåsan (sphincter loss)	
Nattlig diarré	
Svettningar efter måltid	
Magsymptom / illamående (gastric atony)	
Avsaknad av symptom vid hypoglykemi	
Impotens	

ASS-score	

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The Diabetic Nerve

The peripheral nervous system is adversely affected in diabetes, and many individuals with diabetes suffer from diabetic neuropathy. Nerve entrapment syndromes, such as carpal tunnel syndrome, are common in diabetes. This thesis aimed to investigate how results are following standard surgical treatment for carpal tunnel syndrome and if it differs between individuals with and without diabetes, as well as to investigate how autonomic neuropathy develops over time in individuals with diabetes.

The present thesis shows that patients with diabetes improve after open carpal tunnel release to the same extent as patients without diabetes, but risk residual symptoms. These results are useful for the clinician treating patients with carpal tunnel syndrome. Regarding autonomic neuropathy, in type 1 diabetes the results from the present thesis indicate that a strict glucose control is protective against the development of autonomic neuropathy. In type 2 diabetes, symptoms of autonomic neuropathy increase over time. I hope these results will prove useful to physicians treating patients with diabetes.

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