

Review

Carpal Tunnel Syndrome and Diabetes—A Comprehensive Review

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Abstract: Carpal tunnel syndrome (CTS) is the most common compression neuropathy in the general population and is frequently encountered among individuals with type 1 and 2 diabetes. The reason(s) why a peripheral nerve trunk in individuals with diabetes is more susceptible to nerve compression is still not completely clarified, but both biochemical and structural changes in the peripheral nerve are probably implicated. In particular, individuals with neuropathy, irrespective of aetiology, have a higher risk of peripheral nerve compression disorders, as reflected among individuals with diabetic neuropathy. Diagnosis of CTS in individuals with diabetes should be carefully evaluated; detailed case history, thorough clinical examination, and electrophysiological examination is recommended. Individuals with diabetes and CTS benefit from surgery to the same extent as otherwise healthy individuals with CTS. In the present review, we describe pathophysiological aspects of the nerve compression disorder CTS in relation to diabetes, current data contributing to the explanation of the increased risk for CTS in individuals with diabetes, as well as diagnostic methods, treatment options, and prognosis of CTS in diabetes.

Keywords: carpal tunnel syndrome; diabetic neuropathy; diabetes



Citation: Zimmerman, M.; Gottsäter, A.; Dahlin, L.B. Carpal Tunnel Syndrome and Diabetes—A Comprehensive Review. *J. Clin. Med.* **2022**, *11*, 1674. <https://doi.org/10.3390/jcm11061674>

Academic Editor: Hubertus Axer

Received: 28 January 2022

Accepted: 14 March 2022

Published: 17 March 2022

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1. Introduction

Nerve compression disorders are common among the general population, and the most frequently encountered lesions are carpal tunnel syndrome (CTS) and ulnar nerve entrapment at the elbow (UNE) [1]. Even if both conditions are considered as nerve compression disorders, they have substantially different characteristics, regarding the socioeconomic background of affected individuals as well as the individual nerve's susceptibility and reaction to trauma; factors that both impact outcome of surgical procedures [2,3]. The prevalence of CTS is 2.7% (depending on its definition) and the yearly incidences are 428 in women and 182 in men per 100,000 adults in Sweden [4,5], but figures may differ between both regions and countries [6–8]. In addition, the annual incidences of CTS surgery are higher in Sweden and the United States compared to, e.g., in the United Kingdom [1,5]. The aetiology behind CTS is multifactorial, and both intrinsic and extrinsic factors; i.e., factors related to both the peripheral nerve and the surroundings of the nerve trunk have to be considered. Frequent causes of CTS are endocrine disorders, like hypothyroidism, pregnancy, menopause, obesity, diabetes, Hand Arm Vibration Syndrome (HAVS), rheumatoid arthritis, traumatic injuries, such as fractures and dislocations of the distal radius and carpal bones, and repetitive motions of the wrist. However, in the majority of CTS cases, no specific cause can be identified, and the condition is considered as idiopathic. Recently, genome-wide association studies (GWAS) have reported 16 susceptibility loci for CTS [9], and as the variants in those genes are implicated

in both growth (i.e., anthropometric measurements) and enrichment of extracellular matrix architecture, the genetic risks are related to the environment of the carpal tunnel as well as to the vulnerability of the median nerve fibres to compression. CTS is also considered to be a part of the diabetic hand, which includes not only limited joint mobility, Dupuytren’s disease with contracture, and flexor tenosynovitis (i.e., trigger finger) [10,11], but also ulnar nerve compression at the elbow (UNE) [12]. Diabetes increases the risk of compression neuropathies [13,14], and a prominent feature may be inherent factors in the peripheral nerve trunk, comparable to HAVS [15–17]. This phenomenon is included in the double crush theory; a nerve already affected by some pathology is more susceptible to compression [15].

Here, we present an overview of the pathophysiology and vulnerability of the median nerve in CTS, with relevant diagnostic procedures, treatment options, and outcome of surgery in individuals with CTS and diabetes.

2. Neuropathy in Diabetes

The prevalence of diabetic neuropathy is estimated to be 30–50% in individuals with diabetes [18–20], and it increases with disease duration. Importantly, diabetic neuropathy may be present already at the time of diagnosis [21,22], where diabetic men are more prone than diabetic women to develop neuropathy [23]. The most common type of diabetic neuropathy is distal symmetric polyneuropathy, a major cause of diabetic foot complications [21]. Other neuropathy types in diabetes are autonomic neuropathy and mononeuropathies, including compression neuropathies [21].

There are several proposed mechanisms behind the development of neuropathy in diabetes. The main causal factor is considered to be hyperglycaemia [24], which leads to an increased oxidative stress and an increase in free radicals [25]. Pathophysiologically, there are four key elements behind the hyperglycaemic damage to peripheral nerves; increased activity in the polyol pathway, activation of protein kinase C (PKC), production of advanced glycation end products (AGE), and an increased activity of the hexosamine pathway [24]. For details, please see Figure 1.

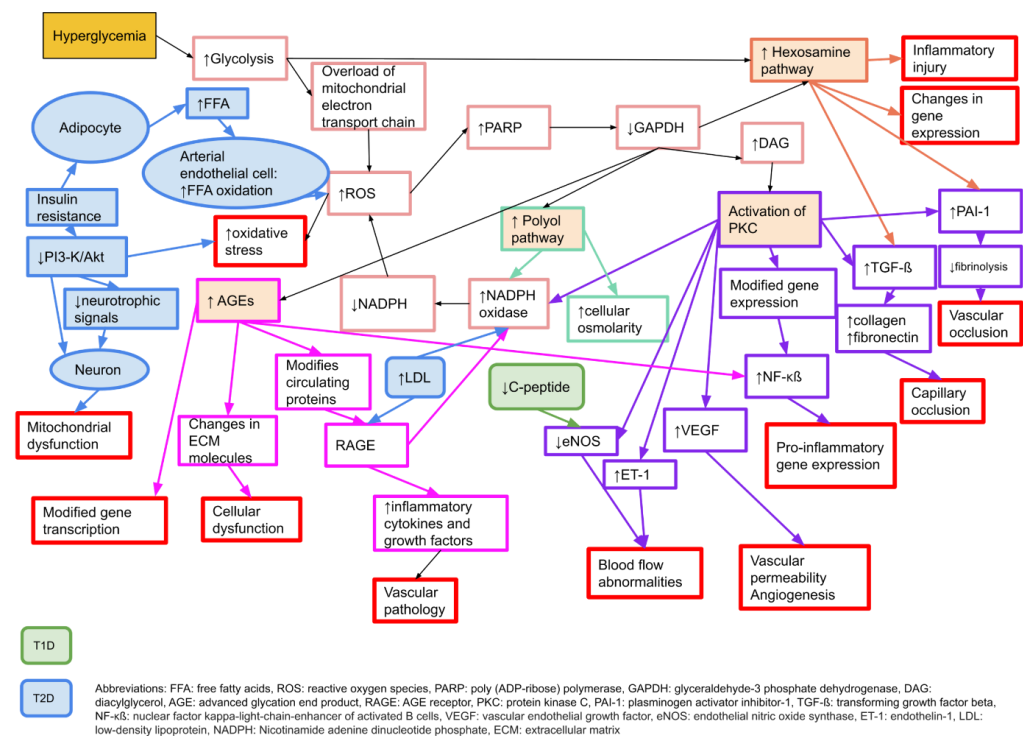


Figure 1. Molecular mechanisms behind microvascular complications in diabetes that may affect neurons, Schwann cells, and vascular endothelial cells, causing neuropathy or nerve dysfunction. Adapted from Zimmerman 2018 [26] with permission. T1D: type 1 diabetes, T2D: type 2 diabetes.

Alterations in axonal transport have also been described in experimental studies of diabetes [27,28]. These changes result in reduced axon calibre, segmental demyelination, and loss of myelinated nerve fibres [29] (Figure 2). Both micro- and macrovascular alterations in diabetes add additional stress on peripheral nerves. However, the mechanisms behind diabetic neuropathy differ between type 1 and type 2 diabetes [18,30,31]. In type 1 diabetes, intensive glucose control protects against neuropathy development [30,31], and insulin deficiency might contribute to neuropathy since insulin has a neurotrophic effect [32]. The loss of C-peptide in type 1 diabetes might also contribute to hypoxia by lowering eNOS [33]. In contrast, in type 2 diabetes, both hyperlipidaemia and insulin resistance may play a part in the development of neuropathy [32,34–36]. There is also evidence that glucose control may have a modest effect on lowering neuropathy complications in type 2 diabetes [37,38].

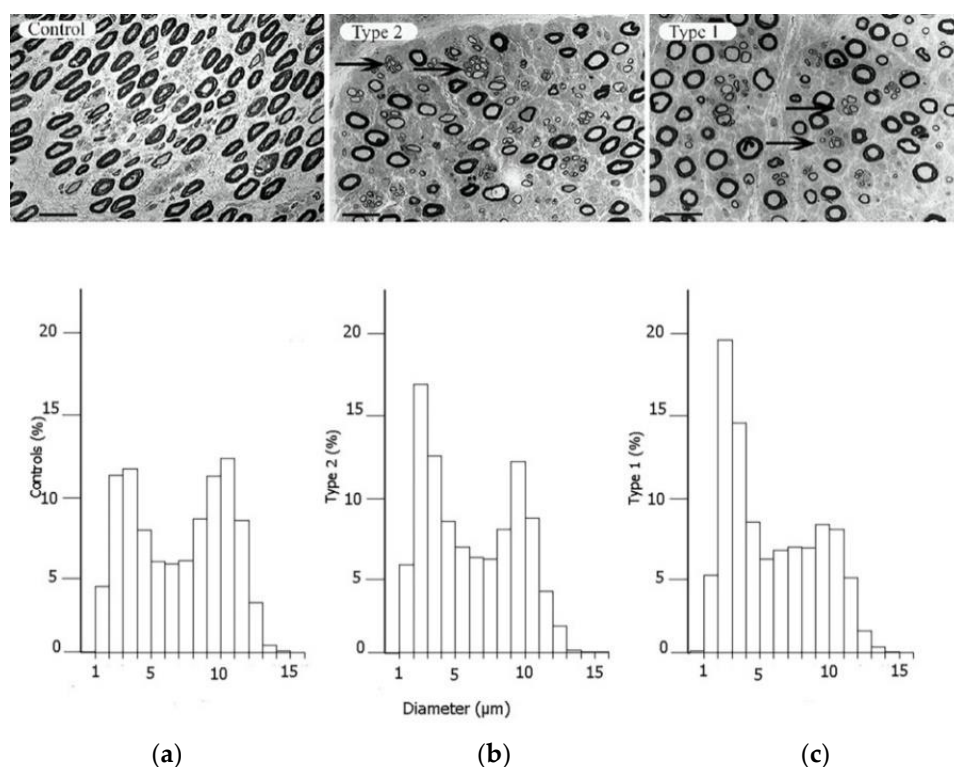


Figure 2. Electron micrographs of the posterior interosseous nerve, with diagram of size distribution of myelinated nerve fibres, from patients with CTS, where the individuals are healthy (a), have type 2 diabetes (b) or type 1 diabetes (c). The arrows in the upper panels indicate regenerative clusters. In the diagram on the lower panels, the size distribution of myelinated nerve fibres is based on the micrographs from the upper panels, indicating a redistribution of nerve fibres. Scale bar = 20 µm. Reproduced by kind permission by Osman et al., *Diabetologia* 2015 [39].

3. The Increased Susceptibility to Nerve Compression in Diabetes

A peripheral nerve trunk is a delicate structure, where the various components respond to an external trauma in different ways (for a classical review, see Sunderland 1978 [40]). The axons, with their associated Schwann cells, are enclosed by a basement membrane, and the myelinated and unmyelinated nerve fibres are assembled in bundles surrounded by a strong connective tissue layer with flattened cells (perineurium), providing both chemical and mechanical protection [40,41]. The connective tissue component inside the perineurial sheath is called the endoneurium. The bundles of nerve fibres with the perineurium (i.e., fascicles) are embedded in loose connective tissue components—epineurium. The nerve trunk is segmentally provided by small blood vessels that branch into the different connective tissue compartments, where the endoneurial blood vessels, mainly capillaries, are strongly resistant to trauma [42]. In contrast, the epineurial blood

vessels are sensitive to trauma with a risk of formation of epineurial oedema that may later form into fibrosis. The number of nerve fibres with a larger diameter, i.e., the myelinated fibres, are reduced, particularly in type 1 diabetes, with a resulting bimodal distribution of nerve fibres (Figure 2); i.e., a higher number of unmyelinated nerve fibres [39]. Myelinated nerve fibres are also more sensitive to nerve compression trauma than un-myelinated nerve fibres [43].

The intra-axonal communication system consists of a delicate system of anterograde and retrograde transport of various substances, such as structural, metabolic, and growth-related proteins, known as axonal transport, which is of utmost relevance in health and disease [44]. Axonal transport can not only be disturbed in diabetes with the development of neuropathy, but can be inhibited by applied nerve compression [27,45]. In experimental studies using diabetic rats, local compression of a nerve causes an increased inhibition of axonally transported proteins compared to in healthy rats [45]; the concept is conceivable that a nerve is more susceptible to compression when the peripheral nervous system is affected by a generalised disease, such as diabetes [15]. In this context, one has also to consider all related disturbances in diabetes, such as those occurring in the red blood corpuscles, the extra- and intraneural blood vessels, and in the connective tissue components whether in the nerve trunk or in the surroundings as in the carpal ligament, e.g., with glycosylation of collagen. The glycosylation of collagen leads to an increase in advanced glycation end products (AGE), causing cross-linking of collagen fibres in the transverse carpal ligament, resulting in increased stiffness and contributing to space limitation in the carpal tunnel [46]. Nerve oedema, originating from an increased vascular permeability and angiogenesis, due to upregulation of vascular endothelial growth factor (VEGF) in diabetes, may also contribute to the increased susceptibility to compression trauma [47]; a mechanism that has been related to increased endoneurial pressure with a risk of jeopardised blood supply to the nerve fibres in the fascicles [48]. Nerve oedema has been demonstrated in ultrasound studies, showing that the median nerve cross-sectional area is enlarged in diabetes [49]. Upregulation of VEGF and its receptors, but not of the hypoxia-inducible factor 1 α (HIF1 α), has been demonstrated in biopsies of the posterior interosseus nerve (PIN) from patients with CTS and diabetes [50]. The number of myelinated nerve fibres has been analysed in such biopsies of the posterior interosseous nerve, indicating that otherwise healthy subjects with CTS have a lower density of myelinated nerve fibres than those without CTS [16]. Interestingly, patients with diabetes and CTS have an even lower density of such myelinated nerve fibres, which may explain the increased susceptibility [16]. In accordance, subjects with HAVS also have structural changes in upper extremity nerves [51], resulting in a higher risk for additional CTS [17]. To conclude, diabetes may confer an increased susceptibility to the peripheral nerve, where the pathophysiological mechanisms are complex and involve both biochemical and structural alterations in the nerve.

4. Symptoms and Clinical Signs of CTS

In CTS, symptoms, clinical findings, and electrophysiology results depend on the magnitude, nature, and duration of the compression trauma. In individuals with diabetes, early signs of CTS may be mistaken for diabetic neuropathy [52]. Basically, one may relate the pathophysiological events in the nerve to the experienced symptomatology, irrespective of whether the affected individual has diabetes or not. Initially, due to the disturbances in intraneural microcirculation and possible dynamic ischemia by a slight compression trauma, paraesthesia, and numbness are induced in the median nerve innervated sensory area of the affected hand with worse symptoms during the night [53]. This might be detected as a metabolic conduction block on electrophysiology testing. As the compression worsens, endoneurial oedema may form, causing increased endoneurial pressure with further microcirculatory disturbances [54] and more constant symptoms. Eventually, the compression trauma at this stage leads to demyelination [55,56] and at a later stage, even axonal degeneration [57] with end-stage symptoms, such as anaesthesia and thenar atrophy [56]. The focal demyelination can be detected on the electrophysiology examination

as an increased latency with a decrease in nerve conduction velocity [58], while axonal degeneration is reflected in a reduced amplitude [59,60]. Patients with diabetes and CTS are twice as likely to present with advanced disease as measured by electrophysiology than those with CTS without concomitant diabetes [61]. After surgery, with the release of the carpal ligament, recovery of patient symptoms also depends on preoperative severity. The microcirculatory disturbances recover quickly, while the structural changes may disappear slowly or incompletely. Remyelination follows the demyelination process, but remyelinated segments have thinner myelin [62] with shorter internodal distances, observed as a permanently reduced conduction velocity. Recovery, requiring axonal regeneration in the nerve, may take longer and may be incomplete, with a reduced amplitude on the electrophysiological examination.

5. CTS and Type 1 and Type 2 Diabetes

In a recent study from the UK of 401,656 individuals, including 24,558 with diabetes, the odds ratio (OR) for CTS in diabetes was 2.31 (95% CI 2.17–2.46) [63]. Similar results were presented in a Swedish cohort study of 30,466 individuals showing a hazard ratio (HR) of 2.10 (95% CI 1.65–2.70) [14], and the pooled OR was 1.69 (1.45–1.96) in one large review controlling for confounders [64]. A meta-analysis indicated that associations with CTS were the same in type 1 and 2 diabetes [64], but more current research has confirmed that CTS is more common in type 1 patients (9). Incidence rates for CTS are reported to be 95.5/10,000 person-years for women and 58.1/10,000 person-years for men with type 1 diabetes, and 52.1/10,000 person-years for women and 31.6/10,000 person-years for men with type 2 diabetes [12] (Table 1). The higher incidence rates in type 1 diabetes may be attributed to the presence of neuropathy, which can be detected as alterations in the distribution of nerve fibres of different sizes in the posterior interosseous nerve (PIN) with more autophagy-related ultrastructures [39].

Table 1. Risk for CTS in diabetes related to sex.

OR (95% CI)	Men with Diabetes		Women with Diabetes	
	1.99 (1.81–2.19)		2.63 (2.42–2.86)	
	T1D	T2D	T1D	T2D
Prevalence	6.8%	5.0%	13.5%	10.1%
Incidence rate/ 10,000 person-years	58.1	31.6	95.5	52.1

References: [9,12]. CI: confidence interval, OR: odds ratio, T1D: type 1 diabetes, T2D: type 2 diabetes.

6. Sex Differences in CTS and Diabetes

Diabetic neuropathy might affect CTS presentation differently in men and women. Men generally present with worse electrophysiology results [65,66], which might be attributable to the higher prevalence of diabetes among men with CTS. Diabetic neuropathy also develops earlier and to a greater extent in men than in women [23,67]. In skin biopsies at wrist level, men have lower intraepidermal nerve fibre density (IENFD) than women, indicating that there might be less spare capacity in men, making male nerves more susceptible to compression trauma, such as CTS [68]. This does not, however, seem to translate to symptom presentation, as women with CTS and diabetic neuropathy experience more symptoms than men [69].

7. Value of Electrophysiology in CTS and Diabetes

Routines for preoperative electrophysiology testing to diagnose nerve compression disorders differ between countries. In Sweden, electrophysiology is not mandatory, but is often used to strengthen the diagnosis of CTS. In previous studies, 70% of all patients with CTS had undergone electrophysiology testing before surgery [70]. A general agreement seems to be that electrophysiology is not necessary in uncomplicated cases, but can aid

in differential diagnosis and in prognosticating surgical outcomes [71], which might be crucial in individuals with diabetes.

In individuals with both diabetic polyneuropathy and CTS, the use of electrophysiology has been debated [72], as diabetic polyneuropathy might obscure the electrophysiological findings of CTS [72,73], and electrophysiology does not always reveal a predominantly small-fibre neuropathy [32]. It may, however, be of value to generously admit individuals with diabetes and CTS for electrophysiology testing to diagnose potential polyneuropathy, enabling a better prognostication regarding surgical outcomes. In this setting, it might also be relevant to perform electrodiagnostic testing also on the lower extremities to evaluate the degree of diabetic neuropathy, as a potential differential diagnosis to CTS. However, if the individual has evident CTS, electrophysiology testing should not delay surgical treatment.

8. Treatment Options

There is strong evidence that the surgical release of the carpal ligament provides better symptom relief in CTS than conservative treatment options, including splinting, corticosteroid injection, and oral NSAIDs during follow-up, up to 18 months [74–76]. About two-thirds of individuals with CTS are treated surgically [77]. Historically, among some physicians, there has been a cautious approach to carpal tunnel release in CTS in individuals with diabetes, based on the notion that they may not benefit from surgery to the same extent as individuals without diabetes [78,79]. As a result of this, current research indicates that persons with long-term diabetes and CTS might still be undertreated [80].

9. Outcome of Surgery

The surgical outcome for CTS is difficult to compare between studies, since there is a lack of consensus on how to measure and evaluate nerve function and patient-related outcomes. In one prospective series, with extensive outcome measurements using monofilament, 2-point discrimination (2PD), the strength of the abductor pollicis brevis muscle, grip and pinch strength, pillar pain, and a VAS-questionnaire up to five years postoperatively, individuals with diabetes improved to the same extent as those without diabetes; the only observed difference at one year being remaining cold sensitivity in diabetes [81,82]. In the same cohort, electrophysiological measurements improved over five years in both individuals with and without diabetes and were not influenced by the presence of neuropathy [59,60]. Another prospective study, using QuickDASH, found that individuals with CTS and diabetes had poorer functional scores at 12 months postoperatively than those without diabetes (mean difference 7.5 points in the QuickDASH), but it is doubtful whether this difference was of clinical significance [83]. One retrospective study, comparing individuals with type 2 diabetes to those without diabetes, reported higher frequencies of night time pain, weakness, and paraesthesia in those with type 2 diabetes both pre- and postoperatively, and a higher frequency of postoperative numbness among individuals with diabetes following open carpal tunnel release (OCTR) [84]. Another retrospective study, using the Boston Carpal Tunnel Questionnaire, found no differences in surgical outcome at six months postoperatively between individuals with and without diabetes [85]. Two other prospective studies using the Boston Carpal Tunnel Questionnaire reported similar results; however, individuals with diabetes took longer times to improve [86] and had more symptoms at a 10-year follow-up [87]. In one prospective study on the resolution of daytime numbness, however, diabetes did not affect surgical results [88]. Another study, using a symptom score, reported substantial improvement in individuals with non-insulin-dependent diabetes, but this group still had more residual symptoms compared to individuals without diabetes [79].

Concomitant diabetic polyneuropathy has been associated with more residual symptoms, measured by QuickDASH at 12 months, following OCTR (i.e., median postoperative QuickDASH score of 61 compared to 20 in diabetic individuals without polyneuropathy) [89]. Worse diabetic control, reflected by higher preoperative HbA1c levels, has also been associated with higher QuickDASH scores at 12 months after OCTR. In the same study, those with diabetic retinopathy recovered slower than individuals with diabetes without retinopathy [90]. One recent meta-analysis concluded that there were no differences in improvement of patient-reported outcomes following carpal tunnel release between individuals with and without diabetes. Among the electrophysiology results, the only variable that showed less improvement in individuals with diabetes was the sensory conduction velocity [91], possibly due to pre-existing diabetic neuropathy. There is also data indicating that individuals with prediabetes have a worse surgery outcome than individuals without diabetes [90]. In theory, CTS could be the first symptom of diabetes, but screening individuals with CTS for diabetes has not been proven to be cost-effective [92]. Please see Table 2 for an overview of studies evaluating outcomes after OCTR in diabetes.

Individuals with diabetes also have a higher risk of surgical wound infection following OCTR [93], although infection rates are generally low [94]. Although higher preoperative HbA1c levels are associated with a higher frequency of surgical site infections [95], routine screening with HbA1c for the purpose of lowering surgical complications is not clinically valuable [96]. In all, there is substantial evidence that individuals with diabetes and CTS benefit from surgery.

Table 2. Overview of studies evaluating outcome after open carpal tunnel release in individuals’ CTS and with and without diabetes.

Author, Year	Study Design	N of Individuals (Hands)	Diabetes	Type of Diabetes	Neuropathy	Outcome Measure	Follow-Up Time	Results, Diabetes vs. No Diabetes
Haupt 1993 [78]	Prospective	60 (86)	10/60 (17%)	Not reported	Not reported	Motor function, sensory deficit, trophic changes, neurography and electro-myography	5.5 years	Marginally less pain relief in individuals with diabetes
al-Qattan 1994 [97]	Retrospective	15 (20)	15/15 (100%)	Not reported	15/15	Grading: excellent/good/poor	18 months	5 hands had poor improvement—all of these had normal/mild neurography pre-op
Choi 1998 [98]	Retrospective	154 (294)	19/154 (12%)	Not reported	3 (1.9%)	Symptom resolution (poor-excellent)	12 months	No difference
Ozkul 2002 [79]	Prospective	47 (60)	22/47 (47%)	T2D	Excluded	PROM: global symptom score, neurography	12 months	Better PROMs and neurography recovery in individuals without diabetes
Mondelli 2004 [99]	Prospective case series	96 (96)	24/96 (25%)	T1D: 19 T2D: 5	6/24 (25%)	BCTQ	6 months	No difference
Thomsen 2009 [81]	Prospective	66 (66)	35/66 (53%)	T1D: 15 T2D: 20	14/35 (40%)	Monofilament, 2PD, APB strength, grip strength, key pinch, lateral pinch, pillar pain, postoperative questionnaire (VAS questions)	52 weeks	Individuals with diabetes had the same beneficial outcome after carpal tunnel release as non-diabetes individuals
Thomsen 2010 [59]	Prospective	66 (66)	35/66 (53%)	T1D: 15 T2D: 20	14/35 (40%)	Electrophysiology testing	12 months	Electrophysiology improved as much in individuals with as without diabetes

Table 2. Cont.

Author, Year	Study Design	N of Individuals (Hands)	Diabetes	Type of Diabetes	Neuropathy	Outcome Measure	Follow-Up Time	Results, Diabetes vs. No Diabetes
Jenkins 2012 [83]	Prospective	1564 (1564)	176/1564 (11.3%)	Not reported	Not reported	QuickDASH	12 months	Poorer functional scores after 12 months in individuals with diabetes, but doubtful whether of clinical significance
Isik 2013 [84]	Retrospective case-control	74 (99)	36/74 (49%)	T2D	none	PROM questions on symptoms	12 months	Worse post-op symptoms in individuals with diabetes
Zyluk 2013 [85]	Retrospective	386 (386)	41/386 (11%)	T1D: 11 T2D: 30	None	BCTQ	6 months	Clinical benefit: no difference. DM individuals had weaker grip strength and poorer perception of touch
Ebrahimzadeh 2013 [100]	Retrospective	74 (74)	35/74 (47%)	T1D: 14 T2D: 21	Not reported	WHOQOL-BREEF; MHQ	3 months	Worse results in individuals with diabetes, MHQ-scores better in T2D than T1D
Cagle 2014 [86]	Prospective	826 (950)	90/950 (10%)	Not reported	20/950 (2%)	BCTQ	12 weeks	Individuals with diabetes improved but took longer
Gulabi 2014 [87]	Prospective	69 (69)	27/69 (39%)	T1D: 18 T2D: 9	Not reported	BCTQ	10 years	Individuals with diabetes worse at the 10 years follow-up. No difference at 6 m.
Thomsen 2014 [82]	Prospective	66 (66)	35/66 (53%)	T1D: 15 T2D: 20	14/35 (40%)	BCTQ, monofilament, 2PD, APB strength, grip strength, key pinch, lateral pinch, pillar pain, VAS questions	5 years	Excellent long-term improvement in individuals with diabetes

Table 2. Cont.

Author, Year	Study Design	N of Individuals (Hands)	Diabetes	Type of Diabetes	Neuropathy	Outcome Measure	Follow-Up Time	Results, Diabetes vs. No Diabetes
Yucel 2015 [101]	Retrospective	83 (101)	35/83 (42%)	Not reported	Not reported	VAS-questions, BCTQ, monofilament, grip and pinch strength	Not specified	Individuals with diabetes had more symptoms in BCTQ
Zimmerman 2016 [89]	Retrospective	493 (531)	76/531 (14%)	T1D: 18 T2D: 58	18/76	QuickDASH	12 months	Same improvement, but more persistent symptoms in individuals with diabetes and polyneuropathy
Thomsen 2017 [60]	Prospective	57 (57)	27/57 (47%)	T1D: 13 T2D: 14	10/27 (37%)	Electrophysiology parameters	5 years	Long-term electrophysiology improvement was seen in both diabetes and non-diabetes individuals
Watchmaker 2017 [88]	Prospective	1031 (1037)	133/1031 (13%)	Not reported	Not reported	Symptom survey	6 months	Individuals with diabetes had the same symptom resolution
Zhang 2018 [102]	Retrospective	904 (1144)	Not reported	Not reported	Not reported	Secondary surgery	60 months	DM associated with greater risk of secondary surgery
Zimmerman 2019 [90]	Retrospective	9049 (10,770)	1508/9049 (17%)	T1D: 335 T2D: 1150	Not reported	QuickDASH	12 months	Individuals with diabetes benefitted from surgery, but not to same extent as patients without diabetes

APB: adductor pollicis brevis muscle, BCTQ: Boston Carpal Tunnel Questionnaire, DM: diabetes mellitus, PROM: Patient-reported outcome measure, QuickDASH: short version of disabilities of arm, shoulder and hand, T1D: type 1 diabetes, T2D: type 2 diabetes, 2PD: two-point discrimination, VAS: visual analogue scale.

10. Controversies in Nerve Compression and Diabetes

Current data clearly states that individuals with CTS and diabetes benefit from surgery when the diagnosis of CTS is obvious [59,60,78,79,81–90,97–99,101]. This conclusion should not be confused with the discussions about the surgical release of nerves in the lower extremity. It has been suggested that nerves in the lower extremity of individuals with diabetes and sensorimotor polyneuropathy should be decompressed as a preventive procedure against “superimposed nerve entrapment”, with the intention to prevent diabetic foot ulcers [103–105]. The indications for such procedures have been questioned [106], but recent opinions have been raised that the scepticism concerning such a procedure should be reassessed [107]. To solve the question, standard definitions and outcome measures are used in prospective randomised controlled trials to determine the usefulness of such interventions [108,109]. However, there are no data to support that peripheral nerves in the upper extremity, such as the median nerve at carpal tunnel or the ulnar nerve at the elbow, should be surgically released on broader indications than presently performed.

11. Future Perspectives—The Diabetic Nerve

In order to improve the care of the diabetic hand, physicians and health care staff should ask simple questions and perform modest clinical tests for screening of diabetic hand-related diseases, such as CTS and UNE at the elbow. This could potentially lead to faster diagnosis and treatment. Hopefully, future studies will also shed more light on the pathophysiology of diabetic neuropathy, enabling the use of novel techniques. Recently, X-ray phase-contrast holographic nanotomography has been used to reveal the three-dimensional architecture of the nerve fibres in a human nerve (Figure 3). Interestingly, details of normal as well as degenerating and regenerating nerve fibres have been visualised, particularly the architecture of regenerative clusters in nerve biopsies from diabetic subjects [110] (Figure 3). This novel technique can be combined with mass spectrometry to analyse the proteomics in the nerve biopsies [111]. Identification of individuals at risk for the development of neuropathy, as well as CTS or UNE at the elbow, is crucial, with the intention of appropriately timed diagnosis and treatment [9]. Finally, national registers, in which diagnosis and outcomes of surgery of thousands of patients are assembled [90], constitute an additional step towards further refined treatment strategies in neuropathy and CTS.

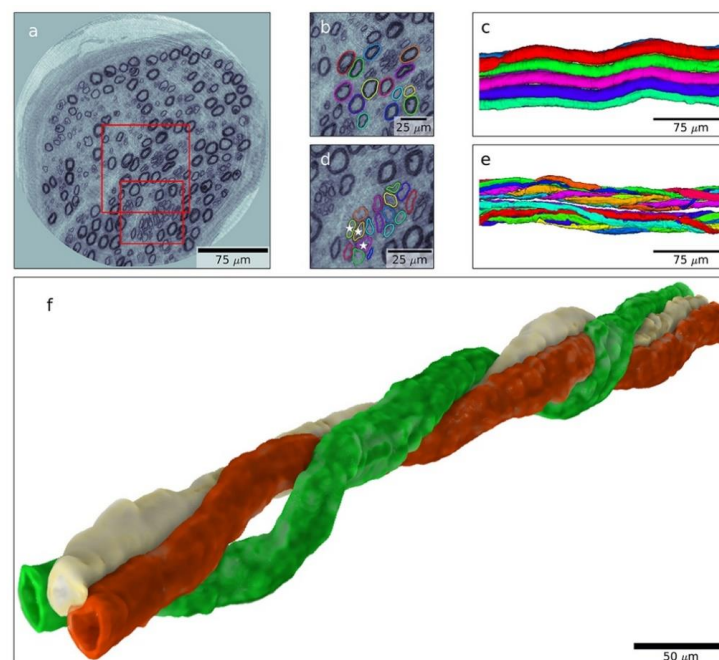


Figure 3. Nanotomogram with 3D images of a posterior interosseous nerve biopsy from an individual with type 1 diabetes. A tomographic slice (a) with an enlarged area (b) from which a 3D image is

created with normal myelinated nerve fibres (c). Enlarged area (d) with a regenerative cluster, i.e., regenerating nerve fibres (e), and with details of such a regenerative cluster (f), showing spiral-shaped nerve fibres that have regenerated. Length of bar indicated in the figure. Reproduced by kind permission from Dahlin et al., Scientific Reports 2020 [110].

12. Conclusions

Multiple mechanisms, including both biochemical and structural factors, contribute to the susceptibility of peripheral nerves to compression in diabetes, where CTS is more common among individuals with diabetes. CTS is more common in type 1 diabetes than in type 2 diabetes. A meticulous case history as well as a thorough clinical and electrophysiological examination are recommended to support the diagnosis and reveal neuro-pathy in individuals with diabetes and suspected CTS. Individuals with diabetes with CTS benefit from surgical treatment to the same extent as individuals with CTS but without diabetes. Symptom resolution may, however, be slower in those with diabetes, and pre-existing diabetic neuropathy may negatively influence surgical outcomes.

Author Contributions: Conceptualization, M.Z. and L.B.D.; writing—original draft preparation, L.B.D., M.Z. and A.G.; writing—review and editing, M.Z., L.B.D. and A.G.; supervision, L.B.D.; funding acquisition, M.Z. and L.B.D. All authors have read and agreed to the published version of the manuscript.

Funding: The research performed by the authors related to the present subject was supported by Swedish Diabetes Foundation, the Swedish Research Council (2021-01942), the Regional Agreement on Medical Training and Clinical Research (ALF) between Region Skåne and Lund University, Elly Olsson´s Foundation for scientific research, the Stig and Ragna Gorthon foundation, the Almroth Foundation, Kockska foundation, the Magnus Bergvall foundation (2020-03612), funds from Skåne University Hospital and local funds at Lund University.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Acknowledgments: The authors would like to thank Tina Folker for her administrative support.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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