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Focal Upper Limb Mononeuropathies in Patients with Diabetes Mellitus

Tayir Alon and Vera Bril

Abstract

In this chapter, we describe the prevalence, diagnostic methods, and treatment efficacy of compressive neuropathies of the median and the ulnar nerves in patients with diabetes mellitus (DM). Median neuropathy at the wrist is found in up to one-third of patients with DM, when demonstrated electrophysiologically, but is symptomatic as carpal tunnel syndrome (CTS) in a smaller proportion of these patients. It is clear that diabetes increases the risk of having clinical CTS. Diagnosis of CTS using nerve conduction studies is difficult in patients with DM and diabetic sensorimotor polyneuropathy (DSP) as median nerve conduction studies are affected predominantly by the diabetes state. We will discuss different electrodiagnostic and ultrasonography techniques for diagnosis and the outcomes of carpal tunnel release decompressive surgery in this special patient population. It is controversial whether DM is a risk factor for cubital tunnel syndrome or ulnar neuropathy at the elbow (UNE) or at the wrist (UNW). In this chapter, we will review the ultrasonographic and electrophysiological diagnostic techniques used in UNE and UNW and the efficacy of cubital tunnel release in DM patients.

Keywords: mononeuropathy, diabetes mellitus, carpal tunnel syndrome, nerve compression, diabetic sensorimotor polyneuropathy, median nerve, ulnar nerve, carpal tunnel syndrome, cubital tunnel syndrome

1. What causes the increased vulnerability to entrapment neuropathies in patients with DM

Entrapment neuropathies are more prevalent among patients with DM, and carpal tunnel syndrome (CTS) can guide a better understanding of the pathophysiology of entrapment neuropathies in this patient population. CTS is the most commonly studied entrapment syndrome and changes in the small arteries, such as vascular hypertrophy and intimal thickening, and noninflammatory fibroses of connective tissue are key pathologic features as discussed earlier in this book. In patients with DM, the reasons for the higher susceptibility to entrapment neuropathies are likely the combination of increased vulnerability of the nerves to compression arising from underlying diffuse DM-related nerve fiber injury and the presence of altered connective tissue structures within the carpal tunnel causing additional compression [1]. These two mechanisms are most likely relevant to all entrapment neuropathies in DM. Axonal, metabolic, and structural changes in DM that can

lead to higher susceptibility to external injury are well-known. Less information on altered connective tissue structure in areas of nerve compression is available in this patient population. Deger et al. found a statistically significant increase in neoangiogenesis in subsynovial connective tissue in DM CTS cases, correlating with greater expression of vascular endothelial growth factor (VEGF), in subsynovial connective tissue in DM than what is present in CTS in patients without DM [2, 3]. These findings are consistent with the findings of Tekin et al., showing DM CTS patients, when compared with non-DM CTS patients, have higher rates of synovial edema and vascular proliferation and increased vascular wall thickness [4]. Thus the increased neovascularization, arising from a proposed ischemia-reperfusion mechanism, and more apparent in patients with DM, impinges the tissue compartment space within the carpal tunnel. In their recently published review, Sharma and Jaggi summarize the current knowledge regarding the role of transforming growth factor (TGF- β), VEGF, and interleukins in the subsynovial connective tissue in CTS patients, with and without diabetes [5].

2. Median compressive neuropathy at the wrist in patients with diabetes mellitus (DM)

The high prevalence of DM among patients with clinical CTS was first noted in 1962 by Blodgett et al. who reported DM in 59/915 or 6.4% of consecutive patients diagnosed with CTS [6]. A higher prevalence of DM among patients with CTS was described in 1972 by Phalen, who reported DM in 14.6% or in 56/384 consecutive patients diagnosed with CTS [7]. Subsequent studies demonstrated a similar prevalence with the calculated odds ratio (OR) of 3.02 for CTS in DM [8, 9]. The risk of CTS is further increased in DM patients with neuropathic symptoms, as shown by Perkins et al., who found a similar frequency of clinical CTS in 14% of nonneuropathic DM subjects, increasing to 30% in those with diabetic sensorimotor polyneuropathy (DSP) of varying severity [10]. This prospective cohort study evaluated clinical CTS, defined rigorously, across a broad spectrum of DSP patients (Table 1). Pourmemari and Shiri performed a meta-analysis including over 90,000 subjects and examined DM as a risk factor for CTS. They found the association to be more modest with an unadjusted OR estimate of about 2 and less when controlling for potential confounding factors with a pooled estimate OR was 1.59 [11, 12]. This outcome may be related to varying definitions of CTS within different studies included in the meta-analysis. Comi et al. examined the prevalence of median neuropathy in patients with DM using electrophysiological studies, but not symptoms and signs of CTS.

Paresthesiae in hands or marked preponderance of sensory symptoms in the hands
Nocturnal hand symptoms awakening the patient
Symptoms precipitated by activities such as holding a newspaper or driving a car and relieved by hand shaking
Predilection for radial digits
Weak thenar muscles
Upper limb sensory loss solely within the distribution of the median nerve
4/6 criteria required to diagnose CTS in those with DM with or without DSP [10]
Electrodiagnostic criteria for CTS unreliable in the presence of DM [10]

Table 1.
Clinical criteria for the diagnosis of carpal tunnel syndrome in diabetes patients.

11.2% showed electrophysiology indicating focal median neuropathy. The prevalence was higher (16.1%) among patients with DSP [13]. Other studies have shown even higher rates, up to 23%, of asymptomatic median compressive neuropathy at the wrist in patients with DM [14]. The issue with this approach is that CTS is a clinical diagnosis, and the Perkins study showed that electrophysiological changes at the carpal tunnel are related to DSP and not indicative of the presence of CTS [10]. All of these studies indicate that although median neuropathy at the wrist is relatively common in patients with DM when tested by nerve conduction studies, clinical CTS is not found in a similar proportion. Symptomatic CTS was described in 9% of DM subjects in an early study [15], and the lifetime risk of symptomatic CTS in type 1 diabetes was calculated more recently to be as high as 85% by Singh et al. [16].

2.1 Electrophysiologic and ultrasonographic diagnostic techniques used in median compressive neuropathy at the wrist in patients with DM

DSP symptoms might mimic those of CTS in clinical practice. Nonetheless, clear symptoms for a diagnosis of CTS can be established even in those with advanced DSP [10]. Establishing the diagnosis of CTS based solely on electrophysiological diagnostic criteria is unreliable in DM patients, since the changes in electrophysiological parameters are due to DSP rather than CTS [10]. Various electrophysiological parameters are thought to distinguish CTS from DSP in subjects with DM, but none were found to be different in those with and without CTS in a population of subjects with DM [10]. Parameters such as median nerve distal motor or sensory latency, comparison of ratios of median (ulnar latencies or amplitudes or sensory conduction velocities), and others failed to differentiate those patients who had clinical CTS from those who did not in subjects with DM [10]. Consequently, in subjects with DM, it is prudent to be cautious in attributing changes in electrophysiological parameters to CTS rather than DM with or without DSP.

There have been attempts to establish electrodiagnostic methods that might distinguish CTS from DSP but doubt about the results which arise from the Perkins study [10]. For example, the median nerve distal motor latency or the median nerve sensory distal onset latency when stimulating at the palm or at the wrist crease has been reported to show differences between DM patients with CTS and idiopathic CTS in a small study [17], but those same parameters were not reliable in larger studies [10, 18]. Additional studies have reported other parameters that may be useful in diagnosis such as the median-radial sensory latency difference from the thumb, which showed 94% sensitivity in one study [19], and for a cutoff of 0.55, 82% sensitivity and 80% specificity in another study [18]. As the ulnar nerve is also susceptible to entrapment, a comparison of median nerve parameters to radial nerve parameters was thought to be preferable. Other studies have suggested using the median-ulnar sensory latency difference measured from the ring finger with 86% sensitivity in one study [19], and for a cutoff of 0.35, 90% sensitivity and 85% specificity in another study [18], although this sensory latency difference could not identify those with CTS in a larger study [10]. The lumbrical-interosseous latency difference was significantly different between CTS patients with and without DM, with sensitivity of up to 88.4% in two studies [17, 20], and for a cutoff of 1 ms had 78% sensitivity in another study [21].

Small studies have examined the feasibility of using ultrasonography to distinguish CTS with DM cases from DSP alone. Kim et al. found that all the cross-sectional areas (CSA) of the median nerve were larger in DSP patients compared with healthy controls, and the CSA of the median nerve at the wrist revealed no significant differences among DSP patients with and without CTS; however,

patients with CTS (with and without DM) had larger CSAs at the wrist and a higher wrist/forearm ratio compared with DSP patients. The cutoff value for the CSA at the wrist that yielded the highest sensitivity and specificity was 11.6 mm [22]. A smaller study found no ultrasound measurement (distal median CSA, wrist-forearm ratio, wrist-forearm difference) reached significance to detect CTS in patients with DSP [17].

2.2 Treatment efficacy for CTS in patients with DM

The outcome of open decompression of the median nerve by sectioning the carpal transverse ligament in DM patients has been evaluated in many studies. Several studies, with a post-procedure follow-up of up to 2 years, showed similar beneficial outcomes, in nerve conduction studies and symptoms, for patients with and without DM [23–29]. Some studies found that electrodiagnostic findings and assessment of symptoms and clinical signs improved significantly in both DM patients and in non-DM patients but that the improvement was less in the diabetic group [30–33]. Zhang et al. demonstrated an association of DM with an increased risk for secondary surgery following carpal tunnel decompression. They tested a total of 904 patients with and without DM, for a median follow-up length of less than a year [34]. Gulabi et al. compared the symptomatic outcome at 6 months and 10 years after decompression of 27 patients with DM and 42 patients with idiopathic CTS. They found that at 6 months, the outcomes were similar for the DM and non-DM groups, but at 10 years the DM group had poor outcomes possibly due to progression of DSP in the DM group [35]. Recently published results of a randomized controlled prospective study comparing the outcome of endoscopic carpal tunnel release versus open carpal tunnel release in DM patients suggest that the endoscopic approach is more beneficial for patients with diabetes. In this study, the patients who underwent endoscopic carpal tunnel release had better relief of symptoms and better function scores, less pillar pain and tenderness at 12 weeks after surgery, faster regain of grip and pinching functions, significantly faster return to work and significant improvement in wound healing, as well as reduction in wound infection and complications [36].

The evidence to date indicates that surgery in DM patients with CTS leads to an improvement in symptoms and signs of CTS that is very similar to non-DM patients with CTS. Given this background, it is reasonable to offer surgical therapy to DM patients with CTS when conservative treatments have failed, as is the case for idiopathic CTS, i.e., in those without DM.

3. Compressive ulnar neuropathy at the elbow in patients with DM

There is controversy over whether or not cubital tunnel syndrome is more common in those with DM. Stamboulis et al. found 12.2% of patients with cubital tunnel syndrome had DM [37]. In other studies, the prevalence of DM was the same in patients with cubital tunnel syndrome as in the general population, i.e., 6% in both groups, when the diagnosis of cubital tunnel syndrome was established on the combination of symptoms, objective clinical findings, and electrodiagnostic tests [38], and the severity of symptoms was also similar between those with and without DM [39]. In a case-control study, including only patients who had undergone ulnar nerve decompression, DM was not found to be a risk factor for ulnar neuropathy at the elbow [40]. The question of whether DM is a risk factor for cubital tunnel syndrome remains uncertain.

3.1 Electrophysiologic and ultrasonographic diagnostic techniques used in compressive ulnar neuropathy at the elbow in patients with DM

Rota et al. tested DM patients for ulnar neuropathy at the elbow irrespective of clinical symptoms and found that 34% had electrodiagnostic features of ulnar dysfunction due to chronic compression at the elbow. Most of the patients with neurophysiological abnormalities were asymptomatic, and only 6% had sensory symptoms and showed clinical signs of cubital tunnel syndrome [41].

It has been demonstrated in large cohorts that sensory nerve conduction velocity and amplitudes of sensory nerve action potentials are markedly lower in DM patients than in healthy controls, even more so in DM patients with known DSP [38, 42–45]. As asymptomatic ulnar nerve entrapment at the elbow (UNE) is relatively common among patients with DM, possibly due to the underlying DSP similar to CTS, when the diagnosis of cubital tunnel syndrome in patients with DM with or without DSP is in question, we rely mainly on changes in the motor conduction electrophysiologic parameters. Schady et al. studied 20 DM patients with cubital tunnel syndrome, demonstrated by hand wasting and weakness. All patients also had signs of DSP in the lower limbs. The nerve conduction studies in this cohort showed markedly reduced ulnar nerve compound muscle action potential (CMAP) amplitudes with a mean value of 1.2 versus 7.4 mV in controls and also reduced ulnar/median CMAP amplitude ratios. Less sensitive than the CMAP amplitudes was the ulnar nerve motor conduction velocity. This was disproportionately slowed across the elbow segment in only 8 of 34 affected ulnar nerves [43].

Only two studies have used ultrasonography for the diagnosis of ulnar compressive neuropathy at the elbow in patients with DM. Kang et al. had demonstrated that the cross-sectional area (CSA) of the ulnar nerve at the cubital tunnel outlet was significantly greater in patients with DSP than in healthy controls, with no correlation to nerve conduction study results [46]. It is possible that the larger CSA is a marker of DM and not specific for DSP or of ulnar compressive neuropathy at the elbow in patients with DM, as might be inferred from the second study. Chen et al. tested DM patients with and without confirmed DSP. They found that CSA of the ulnar nerve at the cubital tunnel outlet was greater in DM patients than that in the healthy control group, yet no difference was detected in the CSA of the ulnar nerve between DM patient with and without DSP [47]. These studies found no correlation between the cubital tunnel syndrome and the CSA or even between asymptomatic UNE and the CSA.

3.2 Treatment efficacy for ulnar compressive neuropathy at the elbow in patients with DM

A recent US national database review of more than 15,000 patients who underwent ulnar nerve decompression at the cubital tunnel found a low incidence of failure of cubital tunnel release requiring ipsilateral revision, but the presence of DM was an independent risk factor for revision with an adjusted odds ratio of 1.27 [48]. The presence of DM did not increase the risk for infection following cubital tunnel release [49]. Other smaller studies have found that DM is not associated with a poor surgical result, either clinically or electrophysiologically [50], or with a greater likelihood of revision surgery [51–53]. When satisfaction with treatment was assessed, having DM was not associated with a higher likelihood of dissatisfaction with treatment [54].

4. Ulnar compressive neuropathy at the wrist in patients with diabetes mellitus (DM)

Ulnar entrapment at the wrist is far less common, and thus less studied, than ulnar nerve entrapment at the elbow. The prevalence of DM among patients with ulnar tunnel syndrome at the wrist is yet to be determined, as no large-scale study has assessed the presence of this potential entrapment. In fact, the only relevant data comes from a single retrospective study of 31 patients who had an ulnar nerve palsy treated by ulnar tunnel (Guyon's canal) release, and 6 patients or 19% had DM [55].

4.1 Electrophysiologic and ultrasonographic diagnostic techniques used in ulnar compressive neuropathy at the wrist in patients with DM

The diagnosis of ulnar tunnel syndrome at the wrist is routinely based on the motor nerve conduction study parameters. Rota et al. tested DM patients for ulnar neuropathy at the wrist, and their electrodiagnostic study demonstrated relevant neurophysiological abnormalities in 11% of the patients, all of whom had DSP as well. The paper does not state how many of the patients presenting with these electrophysiological abnormalities were symptomatic [41].

There is a single paper regarding the use of ultrasonography for the diagnosis of ulnar compressive neuropathy at the wrist in patients with DM. Chen et al., who tested DM patients with and without confirmed DSP, showed that the CSA of the ulnar nerve at Guyon's canal was greater in DM patients than in the healthy control group, yet no difference was detected in the CSA of ulnar nerves between DM patients with and without DSP. No potential relationship to clinical signs or symptoms of ulnar tunnel syndrome was examined in this study [47].

5. Summary

Upper limb mononeuropathies are common in patients with DM with the most common being CTS. The diagnosis of CTS in DM is a clinical diagnosis as the electrophysiologic and ultrasonographic parameters do not reliably distinguish between CTS and DSP. Treatment can be highly effective in CTS patients with DM whether or not DSP is present. Asymptomatic ulnar nerve electrophysiological abnormalities are common in DM, but it is unclear if clinical entrapment syndromes at the elbow are more common or not. The success of surgical decompression of the ulnar nerve at the elbow in those with DM is similar to that in non-DM patients. Ulnar nerve entrapment at the wrist is infrequent, and data on diagnosis and treatment is limited or unavailable.

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Conflict of interest

All authors declare that they have no conflict of interest pertinent to this work.

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