



Research article

Prevalence of carpal tunnel syndrome in patients with long-term type 2 diabetes mellitus

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ARTICLE INFO

Keywords:

Carpal tunnel syndrome
 Type 2 diabetes mellitus
 Diabetic polyneuropathy
 Sensory nerve conduction velocity
 Motor nerve conduction Velocity
 Nerve conduction velocity

ABSTRACT

Generally, Carpal tunnel syndrome (CTS) is more common in diabetes mellitus (DM), especially in subjects with coexisting diabetic polyneuropathy (DPN) and/or long-term DM. Based on the analysis of nerve conduction velocity (NCV), the prevalence of CTS and the features of nerve injury were retrospectively explored in type 2 diabetes mellitus (T2DM) patients. In this cohort, there were 353 T2DM patients who were hospitalized in Taiyuan Central Hospital between January 2018 and January 2019. The pathological rates of NCVs between the left and right median nerves were compared, including the gender effect. The examinations were mainly directed to analyze the median nerve injury features. Among 353 patients, 139 patients (39.3%) presented with CTS. These 139 T2DM patients with CTS were then divided into groups based on the nerve injury location and injured nerve type. The prevalence of sensory nerve injury (SNI) was higher than that of motor nerve injury (MNI). The CTS patients had a significantly higher occurrence rate of SNI than MNI ($P < 0.05$). The abnormal rate of sensory nerve conduction velocity (SCV, $P = 0.01$) and motor nerve conduction velocity (MCV, $P < 0.05$) were higher in the right median nerve. No significant differences were detected for other nerves on either side. Significant differences in abnormal rates of SCV of the left ($P = 0.04$) and the right ($P = 0.03$) median nerves between the two genders were found. There were no significant abnormalities for other nerves on either side and either gender. Early screening of NCV is needed for T2DM patients to detect CTS with a high prevalence rate. This study suggests that early detection of NCV can identify CTS in the absence of clinical conditions and SNI may occur earlier in long-term T2DM patients with CTS.

1. Introduction

Carpal tunnel syndrome (CTS), characterized by the compression neuropathy of the median nerve of the palm, is the commonest among compression neuropathies in the upper extremity [1]. Anatomically, the carpal groove is a narrow U-shaped palmar concavity on the anterior part of the carpus attached to the transverse carpal ligament and surrounded by carpal bones that provides a narrow passageway for the median nerve, which makes the nerve highly susceptible to compression-related impairments, leading to the numbness, burning sensations and/or pain in affected fingers and hand. Above the limit of physical activities of the hand, tendon damage and inflammation, edema, and hormonal disturbances are among the commonest etiological factors contributing to nerve compression syndromes [1]. The CTS first manifests as intermittent dysesthesia and paresthesia symptoms in hand and fingers at night, which may last through the morning with associated muscle stiffness [2].

Although CTS starts to appear in the fingers, however, under severe conditions, the symptoms may spread to other parts of the arm and even to the shoulder regions. Consequently, weaknesses and atrophy of the thenar eminence muscles occur in the advanced stage of the disease and may respond poorly to surgical decompression [2]. Notably, manual workers often suffer from or are at high risk of developing CTS-related occupational health hazards due to their extensive hand movements and weight-lifting activities. Other pathophysiological risk factors include obesity, pregnancy, DM, arthritis, and hypothyroidism [2].

Importantly, DPN patients exhibit higher susceptibilities toward developing CTS, compared with their non-DPN DM counterparts [3]. In 2020, a nationwide health risk assessment survey indicated almost 30% of the DM individuals comorbid with DPN were diagnosed with CTS, in comparison to 14% of non-DPN DM cases [4]. Despite distinct pathological features between DPN and CTS, certain overlapping symptomatic presentations often lead to misinterpretation or misdiagnosis in DM

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patients. With the development of electrophysiological techniques, it's been feasible to segregate the symptoms of DPN from CTS, especially in DM patients. Given that an early diagnostic characterization of CTS is critical for a better treatment outcome and improved quality of life, electrophysiological examinations can be performed during the initial diagnosis to fully evaluate the degree of nerve impairment and disease stage instead of relying on the symptomatic observations alone. Here, we retrospectively analyzed in patients diagnosed with chronic and long-term T2DM, who were admitted to the Taiyuan Central Hospital between January 2018 and January 2019, and explored the prevalence of CTS and the characteristics of nerve injuries based on the NCV test scores.

2. Materials and methods

2.1. Patients

After receiving the study approval from the institutional review board, a medical database of 377 T2DM patients treated between January 2018 and January 2019, was analyzed for CTS pathology. All participants were inpatients, admitted to the department of Endocrinology and Neurology at Taiyuan Central Hospital, and met the diagnostic criteria for DM outlined by the World Health Organization in 1999 [5]. The requirement for informed consent from patients was waived since it is a retrospective investigation. Patient selection criteria for CTS included: 1) history of T2DM, 2) signs and/or symptoms of numbness, 3) pain in the radial side fingers, 4) thumb weakness, 5) thenar atrophy, and 6) abnormal median nerve conduction on electrophysiological examinations. While patients were excluded if they had: 1) spinal disease, 2) genetic metabolic disease, 3) kidney dysfunctions, 4) malnutrition, 5) liver disease, 6) connective-tissue disorder, 7) neuromuscular diseases, 8) trauma, 9) history of substance abuse, and 10) history of medication-induced peripheral neuropathy [6].

2.2. Case assessments

Several relevant baseline characteristics were retrieved for each case, including diagnosis for T2DM, duration of T2DM, age, gender, diagnosis of DNP and its duration if confirmed, diagnosis of CTS and its duration if confirmed, and records of T2DM-associated retinopathy (DR), foot (DF) and/or nephropathy (DN).

The onset and progression of DPN are relatively insidious when the patients first experience small fiber dysfunction-related symptoms like itching, pain, tingling, burning sensation, numbness, and hyperalgesia, but in the later stage, the muscle strength and sensorimotor functions are largely affected. Distal symmetric/sensory polyneuropathy is the commonly recognized form of DPN [7]. Two trained investigators evaluated the subjective symptoms of DPN using the Neuropathy Symptom Scoring (NSS) and the Neuropathy Disability Scoring (NDS) systems [8]. NSS assessed the sensory symptoms in the legs, such as fatigue, numbness, burning sensation, cramping, and tingling, symptom location, timing, and responses to treatments. While NDS evaluated lower body joint (ankle) reflexes, perception threshold of vibration in the tuning fork test, temperature sensitivity, and pain sensitivity by pin-pricking. The final diagnosis of DPN was concluded based on the scores of NSS and NDS tests [9].

For the NCV measurement an Oxford Medelec Synergy 5-channel electromyograph/evoked potential equipment was used. The instrument was located in a quiet, independent room with an indoor temperature slightly above 25 °C. Patient body temperatures were kept in the range of 32–36 °C. Subjects were set in a supine position, with their limbs relaxed, cleaned, and uncovered. The stimulus was delivered at 20–100mA with a frequency of 1Hz, a sensitivity of 5000 uV/div, a wave width of 0.2ms, and a scanning speed of 3ms/div.

The motor and sensory conduction velocities (MCV and SCV, respectively) were measured for the bilateral median, ulnar, common peroneal, and sural nerves by electromyographical analysis, which

revealed the injury site (unilateral, bilateral, or dominant hands) and the injury type (single motor nerve, single sensory nerve, or a combined motor and sensory nerve injury) in T2DM patients with CTS. The T2DM patients' left and right median nerve functions were compared for both genders. The normal values of NCVs of the Chinese version of the simple electromyogram manual (SEM) were compiled by an expert team of neurologists from the Beijing Xiehe Medical Hospital [10].

The examiner was blinded to the CTS diagnoses in the cohort of T2DM patients. The CTS diagnosis largely relies on the NCV scores of the median nerve across the carpal tunnel (CT) to date, indicating a normal flow of electrical signals in the other parts of the hands remains [1]. Extensive clinical investigations led by three major US scientific societies have recommended the diagnostic importance of electromyographical tests for CTS diagnosis [11]. The diagnostic criteria for DM-related CTS included: 1) history of T2DM; 2) application of the Boston CTS Questionnaire (BCTSQ) to correlate the clinical findings with NCV scores; 3) signs and/or symptoms of CTS on the radial side of the hand; 4) electrophysiological examinations to identify any abnormal median nerve conduction across the wrist, which might be accompanied by a prolonged distal latent period of median nerve motor and/or sensory functions, or by a reduced motor and/or sensation wave amplitude. Single wave amplitude reduction is normally not recommended as an indicator because it can also be observed in distal or proximal median neuropathy of the carpal tunnel [12] and 5) nerve impairments caused by other diseases (e.g., degenerative cervical radiculopathy, multiple peripheral neuropathy, thoracic outlet syndrome, motor neuron disease, and pronator teres syndrome) and proximal median nerve impairment. The diagnosis was determined if all, or a set of (1), (2), (4), and (5) conditions were present.

2.3. Statistical analysis

The gender, prevalence of DPN, prevalence of CTS, DR, DN and DF were described by cases number (percentage). The age, course of T2DM, duration of DPN and duration of CTS were described by mean \pm standard deviation. Detailed description. Chi-square test was used to compare the abnormality rates of SNI and MNI in patients of T2DM with CTS. Chi-square test was used to compare the abnormality rates of the patient's left and right median nerve, ulnar nerve, common peroneal nerve, tibial nerve and sural nerve in T2DM patients, and to compare the abnormality rates of SCV and MCV between male and female during T2DM patients. The p-value <0.05 indicates a statistical difference and the statistical software is SPSS 25.0.

3. Results

Initially, a total of three-hundred seventy-seven T2DM patients' cases were enrolled in the study. After excluding 3 severe spinal diseases, 4 severe liver and/or kidney diseases, 1 genetic metabolic disease, 2 malnutrition, 2 connective tissue disease, 3 trauma, 1 neuromuscular disease, 1 isoniazid medication, 5 chronic drinking habit, 2 exposure to some toxic substances (such as pesticides, heavy metals, etc.)-related cases, finally, 353 cases of T2DM patients were selected for the analysis. There were 192 males and 161 females, with a mean age of 60.33 \pm 8.53 years. In this cohort, there were 45 reported cases of DN and/or DR, 19 DF, 235 DPN [7], and 139 CTS (39.3%) cases. Moreover, 152 patients received oral antidiabetic drugs as well as subcutaneous insulin injection at the same time, 31 patients used subcutaneous insulin injection alone, 143 patients only used oral antidiabetic drugs, and 27 patients attempted to control their diabetic conditions through diet control and physical exercises (Table 1).

Next, we distributed 139 T2DM cases with CTS into three groups based on their injury locations: the unilateral, bilateral, and dominant side nerve injury groups, with their cases being 48(34.5%), 91(65.5%), and 101 (72.7%), respectively. Further, these cases were distributed into three groups according to the nerve injury types: single motor nerve

Table 1. Baseline patient characteristics.

Item	(N = 353)
Gender (M/F)	192/161
Age (year), mean ± SD	60.33 ± 8.53
T2DM duration (year), mean ± SD	12.72 ± 7.31
DPN presence, n (%)	235 (66.6)
CTS presence, n (%)	139 (39.4)
DPN duration, (months), mean ± SD	26.20 ± 17.47
CTS duration, (months), mean ± SD	19.85 ± 15.70
DR and/or DN, n (%)	45 (12.7)
DF n (%)	19 (5.4)

T2DM, type 2 diabetes mellitus; CTS, carpal tunnel syndrome; DPN, diabetic polyneuropathy; DR, diabetic retinopathy; DF, diabetic foot; DN, diabetic nephropathy.

injury (sMNI), single sensory nerve injury (sSNI), and combined motor and sensory nerve injury groups, with 19(13.7%), 72(51.8%), and 48 (34.5%) cases, respectively. Among these patients, 67 (48.2%) cases reported MNI, and 120 (86.3%) cases had SNI, indicating that the rate of occurrence of SNI was much higher than that of MNI in this study group ($P < 0.05$).

The abnormal NCV rates were compared between the left and right median nerves in T2DM cases. Moreover, there were significant differences in the SCV ($P = 0.01$), and MCV ($P < 0.05$) values between the median nerves of the two hands, where values for the right hand were higher than those of the left hand. Notably, we couldn't detect abnormalities in any other nerves between the two hands of these patients (Table 2).

Furthermore, we found abnormal SCV and MCV rates of the sural, median, tibial, common peroneal, and ulnar nerves between the two sides of each subject. Interestingly, significant gender-specific differences were observed in abnormal SCV rates of the left ($P = 0.04$), and the right ($P = 0.03$) median nerves. There were no statistically significant differences for other nerves between males and females (Table 3 and Table 4).

4. Discussion

CTS develops due to the abnormal compression of the median nerve in the carpal tunnel of the hand and is frequently observed in individuals engaged in excessive manual activities. CTS pathology features tendon injury, swelling, pain, and inflammation in the palm and wrist areas [13]. In DM patients, the risk of developing CTS increases proportionally with the length of DM pathology, indicating gradual degeneration of the carpal tunnel surrounding bones and ligaments during the course of the disease [14]. Furthermore, DM patients with DPN exhibit an accelerated risk of developing CTS compared to their non-DPN counterparts [3]. Generally, CTS is more common in chronic T2DM patients with co-existing DPN pathology [1]. According to a statistical report, the rate of prevalence of CTS is only 2% among the general population, while that rises to 14% in T2DM patients without DPN and 30% in case of T2DM combined with DPN [4].

Table 2. Comparison of abnormal rate between left and right nerves for the same name in diabetic patients [N (%)].

Group	N	MN		UN		CPN	TN	SN
		MCV	SCV	MCV	SCV	MCV	MCV	SCV
Left	353	103 (29.4)	91 (25.8)	53 (15.0)	92 (26.1)	162 (45.9)	184 (52.1)	190 (53.8)
Right	353	143 (40.5)	121 (34.2)	60 (17.0)	80 (22.7)	181 (51.3)	184 (53.5)	208 (58.9)
	P	<0.05	0.01	0.48	0.30	0.15	1.00	0.17

Note: NCV, nerve conduction velocity; MCV, Motor nerve conduction velocity; SCV, Sensory nerve conduction velocity; MN, Median nerve; UN, Ulnar nerve; CPN, Common peroneal nerve; TN, Tibial nerve; SN, Sural nerve.

Table 3. Comparison of abnormal rate of sensory nerve conduct velocity between male and female diabetics [N (%)].

Gender	N	Left-MN	Right-MN	Left-UN	Right-UN	Left-SN	Right-SN
Male	192	41 (21.3)	56 (29.2)	43 (22.5)	44 (22.9)	101 (52.6)	109 (56.8)
Female	161	50 (31.1)	65 (40.4)	49 (30.4)	36 (22.4)	89 (55.3)	99 (61.5)
	P	0.04	0.03	0.09	0.90	0.67	0.37

Note: SCV, Sensory nerve conduction velocity; MN, Median nerve; UN, Ulnar nerve; SN, Sural nerve.

Here, all the T2DM cases were thoroughly examined, irrespective of their CTS diagnosis. Of the 353 patients, 235 had DPN, and 139 had CTS with a prevalence of 39.3%. In this cohort, 28 patients were reported with typical symptoms of CTS (BCTSQ scores), compared with 49 patients who showed typical clinical signs of DPN (NSS and NDS scores). The high prevalence rate in this study might be attributed to the selection bias of all inpatients with chronic T2DM symptoms. The abnormal nerve conduction of CTS patients usually first affects the sensory fibers of the median nerve first, followed by focal demyelination potentially combined with axonal impairment. As the condition worsens, motor fibers may be severely damaged, leading to prolonged latency of motor nerve conduction along with reduced amplitude [15, 16]. Here, we revealed that abnormal NCV rates in T2DM patients were mainly manifested as slowed down conduction velocity of the median sensory nerve and reduced amplitude of evoked potential, followed by prolonged median motor nerve distal latency, suggesting that the SNI precedes the MNI in T2DM patients during CTS pathogenesis. At the same time, it also indicates that the median nerve injury is in fact a form of coexisting demyelination and axonal nerve injury of T2DM individuals with CTS. Furthermore, NCV examination in T2DM patients exhibited that the rate of median MNI was higher than that of the SNI. However, in T2DM patients diagnosed with CTS the rate of median SNI was higher than that of the MNI of 353 T2DM cases, some patients had the median nerve injury caused by the proximal injury rather due to the abnormal NCVs across the wrist. Notably, DPN should be considered when assessing the median nerve injury, rather than attributing all impairments to the CTS, to strategize an effective treatment plan. Here, we discovered that the dominant hands were most likely to be injured. However, a considerable number of cases involved injuries in both hands, suggesting that T2DM patients should avoid over-exertion and wrist movement in any circumstances. Additionally, while many patients seek out medical services for numbness and weakness in the right hand, we found that many patients also presented with bilateral CTS, suggesting that non-dominant hand and asymptomatic hand assessments should be conducted to avoid missed diagnoses.

Besides, we showed that the rates of SCV and MCV of the right median nerve were higher than those of the left median nerve in T2DM patients. However, there were no significant differences in other nerves between the hands. This might have been caused by increased use of the right wrist or hand. Interestingly, only the rate of abnormal bilateral median nerve SCV was higher in females than in males, and there were no

Table 4. Comparison of abnormal rate of motor nerve conduct velocity between male and female diabetics [N (%)].

Gender	N	Left-MN	Right-MN	Left-UN	Right-UN	Left-CPN	Right-CPN	Left-TN	Right-TN
Male	192	62 (32.3)	79 (41.1)	27 (14.1)	35 (18.2)	97 (50.5)	101 (52.6)	96 (50.0)	96 (50.0)
female	161	41 (25.5)	64 (39.8)	26 (16.1)	25 (15.5)	65 (40.4)	80 (49.7)	88 (54.7)	88 (54.7)
P		0.16	0.79	0.59	0.50	0.06	0.59	0.38	0.38

Note: MCV, Motor nerve conduction velocity; MN, Median nerve; UN, Ulnar nerve; CPN, Common peroneal nerve; TN, Tibial nerve.

significant differences in functions of other nerves between males and females, which was consistent with the finding of Moon HI et al. [3], indicating that female DM individuals may suffer from a higher risk of CTS due to the lifestyle and physiological differences between the genders. Since the incidence of CTS development in women reaches its maximum around menopause, clinical investigations involving specific etiological risk factors and effects of hormonal changes should be conducted in the future to better reveal the crosstalk of DM with CTS in women [17]. Reportedly T2DM patients are frequently diagnosed with metabolic syndromes, which is in turn considered a potential risk factor for CTS pathogenesis. These patients present lower action potential amplitudes in the median compound muscles and increased sensory thresholds, which have been shown to increase during the ulnar and median nerve stimulations, suggesting broader changes in the peripheral nerve excitability in DM patients with metabolic syndromes [18].

DPN is the most predominant secondary complication in DM, with a prevalence rate ranging between 23% and 54% [19, 20]. In 2020, a nationwide population studies have indicated that DM patients with DPN are more likely to suffer from CTS than those without DPN [3]. In DPN, a length-dependent axonopathy, the median nerve becomes susceptible to the compression effect in the carpal tunnel [3]. Notably, a study has demonstrated that similar metabolic and vascular syndromes can be responsible for inducing both DPN and CTS in DM patients [21]. Moreover, both these neuropathic conditions may exhibit overlapping symptoms [3, 21]. Therefore, diagnostically segregating these two diseases could be a critical measure in treating CTS with a background of T2DM and DPN, irrespective of the presence of diffuse neuropathy. When CTS occurs in the absence of DM, its pathogenesis is mostly related to anatomical factors, while disturbances in the local nerve conduction caused by the traction of the median nerve in the CT, high expressions of growth factors [like Transforming Growth Factor beta (TGF- β), Vascular Endothelial Growth Factor (VEGF), and interleukins], or enhanced vascular permeability could be a possible etiopathological factor of CTS onset in T2DM patients. Additionally, non-inflammatory fibrosis involving the subsynovial connective tissue (SCCT) can cause demyelination and axonopathy of the median nerve [22, 23, 24]. The pathological mechanism of T2DM-associated CTS is distinct from that of non-DM-linked CTS. The rate of neovascularization following the ischemia-reperfusion (I/R) is significantly higher in DM patients with CTS, compared to that in non-DM CTS patients, indicating that pathological I/R, due to diabetic microangiopathy and increased expression of VEGF in the SCCT, could be an inducing factor for CTS in DM patients [25]. Furthermore, increased mechanical pressure can also cause microvascular changes in the nerve structure, leading to decreased blood flow and edema in nerve intima, further aggravating ischemia and hypoxia in this subset of patients.

In diabetic patients, the diagnostic application of electrophysiological examinations are still controversial for CTS diagnosis in DM patients. This is because electrodiagnostic examinations (EDX) may not inform about the exact anatomy of the injured nerve and can be uncomfortable at some points, however, this method is widely practiced for clinical evaluation of CTS as the gold standard [26]. Surprisingly, with the recent development of ultrasound imaging, Singla M, et al has reported that abnormal echo graphic parameters can be observed in clinical CTS despite the normal range of NCV values [27]. A precise diagnosis of CTS can be made by calculating the wrist-to-forearm ratio (WFR) of the cross-sectional area of the median nerve, where WFR should be greater

than 1.4 [28]. In cases where CTS patients show classic symptoms and a markedly enlarged median nerve at the carpal tunnel inlet, standard EDX may be omitted. However, EDX should be seriously considered if the patient presents obscure symptoms of CTS or poor treatment response. Overall, a combination of EDX and ultrasound examinations should be critically considered for the CTS diagnosis.

CTS can be treated both medically and surgically [29, 30]. While the medical approach involves natural therapies, oral doses of steroids, and carpal bone mobilization [30], surgical procedures engage endoscopy and/or opening of the CTT [29]. In both procedures, an increase in the perioperative level of haemoglobin-A1c (HbA1c) may induce post-operative infections at the surgery site but do not impact the long-term benefit of the treatment [31, 32]. Surgeons often use surgery to relieve nerve compressions while ignoring blood sugar levels, thus undercutting the effect of nerve decompression in T2DM patients and increasing the incidence of infection. Therefore, surgical decompression and blood sugar control are imperative to deliver timely and effective treatment for T2DM patients complicated with nerve compression syndromes like CTS.

Our research has some limitations. It was a retrospective, single-center study with a small sample size that might affect the outcome. The research of retrospective data collection referred to patients who were hospitalized and might have led to a certain selection bias. The occupation was found to be a significant modulator of CTS pathogenesis. We have recorded the occupations of almost all patients, but everyone's occupation was almost different, so that it was difficult to statistically correlate occupational hazards with CTS risks. Due to the limitations of medical equipment and technologies, we were unable to explore the implication of ultrasound examination to EDX for CTS diagnosis.

Early screening of NCV is crucial for T2DM patients to detect CTS with a high prevalence rate. This study suggests that early detection of NCV can identify CTS in the absence of clinical conditions, and SNI may occur earlier in chronic and long-term T2DM patients complicated with CTS. Therefore, early diagnosis and treatment of T2DM with CTS should be attempted to slow down the development of the illness, protect hand functions, and improve the quality of life.

Declarations

Author contribution statement

Defu Dong and Hongwei Liu: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Funding statement

This study was funded by by Shanxi Province "136 Revitalization Medical Project Construction Funds".

Data availability statement

No data was used for the research described in the article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

Supplementary content related to this article has been published online at <https://doi.org/10.1016/j.heliyon.2022.e12615>.

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