Subclinical Nerve Conduction Abnormalities in Asymptomatic Type 2 Diabetes Mellitus: A Cross-Sectional Comparative Study

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Abstract

Background: Diabetic peripheral neuropathy (DPN) is a common and debilitating complication of type 2 diabetes mellitus (T2DM), often diagnosed only after significant nerve damage has occurred. Early detection of subclinical neuropathy is crucial for implementing preventative strategies. Nerve conduction studies (NCS) are objective measures of peripheral nerve function, but their utility in asymptomatic T2DM patients is still being characterized.

Methodology: A cross-sectional comparative study was conducted with 50 asymptomatic T2DM subjects (mean age 54.2 ± 6.8 years) and 50 healthy controls (mean age 53.8 ± 7.1 years). Participants underwent bilateral nerve conduction studies of the median (motor and sensory) and sural (sensory) nerves. Parameters including distal motor latency (DML), motor nerve conduction velocity (MNCV), compound muscle action potential (CMAP) amplitude, sensory nerve conduction velocity (SNCV), and sensory nerve action potential (SNAP) amplitude were recorded. Glycated hemoglobin (HbA1c) and duration of diabetes were documented for the T2DM group. Independent t-tests were used for group comparisons, and Pearson correlation analysis was performed to assess associations.

Results: The T2DM group showed significantly prolonged DML (Median nerve: 3.9 ± 0.5 ms vs. 3.2 ± 0.4 ms, $p<0.001$), reduced MNCV (Median nerve: 48.5 ± 4.1 m/s vs. 55.2 ± 3.8 m/s, $p<0.001$), and lower SNAP amplitudes (Sural nerve: 8.2 ± 2.9 µV vs. 15.6 ± 3.5 µV, $p<0.001$) compared to controls. In the T2DM group, sural SNAP amplitude showed a significant negative correlation with both HbA1c ($r = -0.58$, $p<0.001$) and duration of diabetes ($r = -0.64$, $p<0.001$). Similarly, median MNCV was negatively correlated with HbA1c ($r = -0.51$, $p<0.001$) and diabetes duration ($r = -0.55$, $p<0.001$).

Conclusions: Asymptomatic T2DM subjects exhibit significant subclinical electrophysiological abnormalities consistent with early-stage neuropathy. The severity of these changes correlates with the duration of diabetes and the degree of glycemic control. NCS can serve as a valuable, objective tool for the early detection of DPN, potentially enabling timely intervention to prevent or delay clinical progression.

Keywords: Neuropathy, Motor Latency, Conduction Velocity, Action Potential, Diabetes Mellitus

Introduction

Type 2 diabetes mellitus (T2DM) represents a formidable global health crisis, with its prevalence projected to affect over 780 million people by 2045 (1). This chronic metabolic disorder leads to a host of long-term complications, severely impacting patient quality of life and imposing a substantial economic burden on healthcare systems (2). Among these complications, diabetic peripheral neuropathy (DPN) is one of the most common and devastating, affecting up to 50% of individuals with diabetes (3). DPN is a leading cause of neuropathic pain, foot ulcerations, and non-traumatic lower limb amputations (4).

The pathophysiology of DPN is multifactorial and complex. Chronic hyperglycemia is the primary driver, initiating a cascade of metabolic and vascular derangements. Key mechanisms include the activation of the polyol pathway, increased formation of advanced glycation end-products (AGEs), oxidative stress, and activation of inflammatory pathways, all of which contribute to

neuronal and Schwann cell damage (5,6). This damage manifests as a combination of axonal degeneration and segmental demyelination, typically beginning in the longest sensory fibers and progressing in a length-dependent manner—the classic "stocking-glove" distribution (3).

The insidious nature of DPN presents a major diagnostic challenge. By the time patients report clinical symptoms such as pain, numbness, or tingling, significant and often irreversible nerve fiber loss has already occurred (7). This highlights a critical research gap: the need to identify robust, objective biomarkers for detecting neuropathy in its preclinical or subclinical stage. Nerve conduction studies (NCS) are considered the gold standard for evaluating peripheral nerve function, providing quantitative measures of nerve integrity (8). While numerous studies have demonstrated NCS abnormalities in diabetic populations, many have included symptomatic patients or failed to systematically correlate findings with both disease duration and glycemic control in a strictly asymptomatic cohort (9). Establishing this relationship is vital for validating NCS as a proactive screening tool rather than a purely diagnostic one.

This study was therefore designed to address this gap. Our research hypothesis is that T2DM subjects without any clinical signs or symptoms of neuropathy will demonstrate significant subclinical abnormalities in nerve conduction parameters compared to matched healthy controls. We further hypothesize that the magnitude of these electrophysiological deficits will be directly correlated with both the duration of diabetes and the level of long-term glycemic control (HbA1c). The significance of this work lies in its potential to support the integration of NCS into routine surveillance for high-risk diabetic patients, enabling earlier, targeted interventions aimed at preserving nerve function and preventing the transition to debilitating clinical disease (10).

Methods

A total of 100 participants were recruited and divided into two groups:

- **T2DM Group (n=50):** Patients with a confirmed diagnosis of T2DM according to American Diabetes Association criteria, aged 40–65 years.
- **Control Group (n=50):** Age- and sex-matched healthy volunteers with no personal or family history of diabetes.

Inclusion and Exclusion Criteria

- **Inclusion Criteria (T2DM Group):** Diagnosed T2DM for at least one year; absence of neuropathic symptoms, confirmed using the Neuropathy Symptom Score (NSS) with a

score <3 (11); and absence of clinical signs on examination (normal vibration perception, 10-g monofilament testing, and ankle reflexes).

- **Inclusion Criteria (Control Group):** Normal fasting blood glucose and HbA1c levels; no known chronic medical conditions.

- **Exclusion Criteria (Both Groups):** History of alcoholism, vitamin B12 deficiency, hypothyroidism, chronic kidney disease (eGFR <60 ml/min/1.73m^2), exposure to neurotoxic drugs, history of trauma or entrapment neuropathy affecting the limbs to be tested, or any other known cause of peripheral neuropathy.

Data Collection Procedures

Demographic data (age, sex) and anthropometric measurements (height, weight, BMI) were collected from all participants. For the T2DM group, the duration of diabetes since diagnosis was recorded from medical records. A venous blood sample was collected after an overnight fast to measure HbA1c using high-performance liquid chromatography (HPLC).

Nerve Conduction Studies (NCS)

All NCS were performed by a single trained neurophysiologist using a Nihon Kohden Neuropack MEB-9200 machine, following standardized protocols (12). The skin temperature of the limbs was maintained at ≥32°C using an infrared lamp to ensure consistency.

- **Median Motor Nerve:** The nerve was stimulated at the wrist and elbow, with recordings taken from the abductor pollicis brevis muscle. Distal motor latency (DML), compound muscle action potential (CMAP) amplitude, and motor nerve conduction velocity (MNCV) in the forearm segment were measured.
- **Median Sensory Nerve:** The nerve was stimulated at the wrist (digit II), with recordings taken from the median nerve at the wrist. Sensory nerve action potential (SNAP) amplitude and sensory nerve conduction velocity (SNCV) were measured.
- **Sural Sensory Nerve:** This purely sensory nerve was stimulated at the posterior aspect of the calf, with recordings taken behind the lateral malleolus. SNAP amplitude and SNCV were measured.

Studies were performed bilaterally, and the average values were used for analysis.

Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp). Continuous data were expressed as mean ± standard deviation (SD) and categorical data as numbers (percentages). The normality of data distribution was assessed using the Shapiro-Wilk test. An independent samples t-test was used to compare means of normally distributed

variables between the two groups. The Chi-square test was used for categorical variables. Pearson correlation analysis was conducted to assess the relationship between NCS parameters and HbA1c and duration of diabetes in the T2DM group. A two-tailed p-value of <0.05 was considered statistically significant.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the study participants are presented in Table 1. The two groups were well-matched for age and sex distribution (p>0.05). As expected, the T2DM group had a significantly higher mean BMI, fasting blood glucose, and HbA1c compared to the control group (p<0.001 for all). The mean duration of diabetes in the T2DM group was 6.8 ± 3.5 years.

Table 1: Demographic and Clinical Characteristics of Study Participants

Characteristic	T2DM Group (n=50)	Control Group (n=50)	p-value
Age (years)	54.2 ± 6.8	53.8 ± 7.1	0.762
Sex (Male/Female)	28 (56%) / 22 (44%)	26 (52%) / 24 (48%)	0.681
BMI (kg/m^2)	29.5 ± 4.1	24.8 ± 3.2	<0.001
Fasting Blood Glucose (mg/dL)	145.7 ± 25.3	88.4 ± 8.1	<0.001
HbA1c (%)	8.1 ± 1.3	5.4 ± 0.4	<0.001
Duration of Diabetes (years)	6.8 ± 3.5	N/A	N/A
Data are presented as mean ± SD or n (%). *BMI: Body Mass Index.*			

Nerve Conduction Parameters

The results of the nerve conduction studies are summarized in Table 2. The T2DM group demonstrated statistically significant abnormalities in all measured parameters compared to the control group. Specifically, the T2DM group had prolonged distal motor latency in the median nerve, reduced motor and sensory conduction velocities in both median and sural nerves, and

markedly reduced CMAP and SNAP amplitudes. The most pronounced difference was observed in the sural SNAP amplitude, which was nearly 50% lower in the T2DM group.

Table 2: Comparison of Nerve Conduction Study Parameters Between Groups

Parameter	T2DM Group (n=50)	Control Group (n=50)	p-value
Median Motor Nerve			
DML (ms)	3.9 ± 0.5	3.2 ± 0.4	<0.001
CMAP Amp (mV)	6.8 ± 1.9	9.5 ± 2.1	<0.001
MNCV (m/s)	48.5 ± 4.1	55.2 ± 3.8	<0.001
Median Sensory Nerve			
SNAP Amp (µV)	16.3 ± 4.5	24.1 ± 5.2	<0.001
SNCV (m/s)	46.1 ± 3.9	52.8 ± 4.3	<0.001
Sural Sensory Nerve			
SNAP Amp (µV)	8.2 ± 2.9	15.6 ± 3.5	<0.001
SNCV (m/s)	41.5 ± 3.7	47.3 ± 3.4	<0.001
Data are presented as mean ± SD. DML: Distal Motor Latency; CMAP: Compound Muscle Action Potential; MNCV: Motor Nerve Conduction Velocity; SNAP: Sensory Nerve Action Potential; SNCV: Sensory Nerve Conduction Velocity.			

Correlation Analysis

In the T2DM group, several NCS parameters showed significant negative correlations with both HbA1c and the duration of diabetes. As illustrated in Figure 1, sural SNAP amplitude demonstrated a strong negative correlation with HbA1c ($r = -0.58$, $p<0.001$) and an even stronger correlation with diabetes duration ($r = -0.64$, $p<0.001$). Median MNCV also correlated negatively with HbA1c ($r = -0.51$, $p<0.001$) and diabetes duration ($r = -0.55$, $p<0.001$). These findings suggest that both the cumulative time of exposure to the diabetic state and the

severity of hyperglycemia contribute to the decline in nerve function. The presentation style of the figure follows established guidelines for clarity (13).

Discussion

This study provides clear electrophysiological evidence of subclinical peripheral neuropathy in T2DM patients who are asymptomatic and have normal clinical neurological examinations. Our primary finding is that these individuals exhibit significant reductions in nerve conduction velocities (indicative of demyelination) and amplitudes (indicative of axonal loss) across both motor and sensory nerves compared to healthy controls. These results strongly support our hypothesis and align with the concept of DPN as a progressive disorder with a long subclinical phase (7,9).

The observed pattern of abnormalities, particularly the profound reduction in sural SNAP amplitude, is consistent with the classic length-dependent pathophysiology of DPN, where the longest sensory fibers are affected first (3). The sural nerve's vulnerability makes it a highly sensitive marker for early neuropathy (14). Our findings corroborate previous research by Partanen et al., who also identified early NCS abnormalities in diabetic subjects (9), but our study strengthens this evidence by focusing exclusively on an asymptomatic cohort, thereby isolating the electrophysiological changes that precede clinical manifestation.

A key contribution of our study is the strong correlation found between the severity of these subclinical nerve deficits and two major risk factors: the duration of diabetes and the degree of glycemic control. This finding is powerfully supported by landmark clinical trials such as the UK Prospective Diabetes Study (UKPDS), which demonstrated that intensive glycemic control in T2DM significantly reduces the long-term risk of microvascular complications, including neuropathy (15). Our data provide a cross-sectional snapshot of this process, illustrating that the cumulative hyperglycemic burden (a product of both duration and HbA1c level) is directly associated with the degree of subclinical nerve injury.

Limitations

This study has several limitations. First, its cross-sectional design prevents the inference of causality; we can demonstrate association but not prove that hyperglycemia over time causes the observed nerve damage. A longitudinal study is needed to establish a definitive temporal relationship. Second, this was a single-center study with a relatively modest sample size, which may limit the generalizability of our findings. Third, we did not assess other potentially confounding metabolic factors, such as dyslipidemia or markers of inflammation, which are also implicated in DPN pathophysiology (6). Finally, our NCS protocol was not exhaustive; a more comprehensive assessment including nerves of different fiber types and lengths could provide a more complete picture.

Implications

Despite these limitations, our findings have important theoretical and practical implications. Theoretically, they reinforce the model of DPN as a continuum of nerve injury beginning long before symptoms emerge. Practically, they advocate for the use of NCS as a screening tool in high-risk T2DM patients, even in the absence of symptoms. Professional bodies like the American Diabetes Association recommend annual screening for DPN, but this often relies on clinical tests that may lack sensitivity for early damage (10). Our results suggest that incorporating NCS could identify individuals at a much earlier stage, prompting more aggressive management of glucose levels and other risk factors to potentially slow or halt the progression to clinical neuropathy and its devastating consequences (4,15).

Conclusion

In conclusion, this study demonstrates that asymptomatic individuals with T2DM have significant subclinical deficits in peripheral nerve function detectable by NCS. The severity of these electrophysiological abnormalities is strongly correlated with both the duration of diabetes and the level of chronic glycemic control. These findings underscore the value of NCS as an objective biomarker for the early detection of diabetic neuropathy. Future research should focus on longitudinal studies to track the progression of these subclinical changes and on randomized controlled trials to determine whether early interventions based on NCS findings can alter the natural history of DPN and improve patient outcomes.

References

1. International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Brussels, Belgium: IDF; 2021.
2. American Diabetes Association. Economic Costs of Diabetes in the U.S. in 2017. Diabetes Care. 2018 May;41(5):917-928.
3. Pop-Busui R, Boulton AJM, Feldman EL, Bril V, Freeman R, Malik RA, et al. Diabetic Neuropathy: A Position Statement by the American Diabetes Association. Diabetes Care. 2017 Jan;40(1):136-154.
4. Boulton AJM, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. Lancet. 2005 Nov 12;366(9498):1719-24.
5. Feldman EL, Callaghan BC, Pop-Busui R, Zochodne DW. Diabetic neuropathy. Nat Rev Dis Primers. 2019 Jun 13;5(1):41.
6. Vincent AM, Callaghan BC, Smith AL, Feldman EL. Diabetic neuropathy: cellular mechanisms as therapeutic targets. Nat Rev Neurol. 2011 Sep 13;7(10):573-83.

7. Tesfaye S, Boulton AJ, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010 Oct;33(10):2285-93.
8. England JD, Gronseth GS, Franklin G, Miller RG, Asbury AK, Carter GT, et al. Practice Parameter: Evaluation of distal symmetric polyneuropathy: Role of autonomic testing, nerve biopsy, and skin biopsy (an evidence-based review). Report of the American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation. Neurology. 2009 Jan 13;72(2):177-84.
9. Partanen J, Niskanen L, Lehtinen J, Mervaala E, Siitonen O, Uusitupa M. Natural history of peripheral neuropathy in patients with non-insulin-dependent diabetes mellitus. N Engl J Med. 1995 Jul 6;333(2):89-94.
10. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 12. Retinopathy, Neuropathy, and Foot Care: Standards of Care in Diabetes—2023. Diabetes Care. 2023 Jan 1;46(Suppl 1):S203-S215.
11. Meijer JW, van der Meer J, van der Krans HJ, van der Wiel TW, Brunt ER. The value of the Neuropathy Symptom Score (NSS) and the Neuropathy Disability Score (NDS) in the diagnosis of diabetic polyneuropathy. The Netherlands Journal of Medicine. 2000;57(1):18-26.
12. Preston DC, Shapiro BE. Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations. 3rd ed. Philadelphia: Elsevier Saunders; 2013.
13. Lang TA, Secic M. How to Report Statistics in Medicine: Annotated Guidelines for Authors, Editors, and Reviewers. 2nd ed. Philadelphia: American College of Physicians; 2006.
14. Dyck PJ, Carter RE, Litchy WJ. Modeling nerve conduction criteria for diagnosis of polyneuropathy. Muscle Nerve. 2011 Nov;44(5):760-8.
15. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998 Sep 12;352(9131):837-53.