

Research Article

Exploring the Link Between Neuropathy and Foot Ulcers in Diabetes Mellitus Patients

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A B S T R A C T

Introduction: This study examines middle-aged individuals (mean age 56.4 years) with type 2 diabetes mellitus (T2DM) and diabetic foot ulcers (DFU), focusing on demographic factors and their links to complications. Chronic hyperglycemia and genetic predisposition significantly contribute to disease progression.

Aim: The study aims to assess baseline characteristics, evaluate neuropathy severity using the Michigan Neuropathy Screening Instrument (MNSI), investigate autonomic dysfunction, and explore correlations between these factors.

Method: A cohort of 300 participants was evaluated for demographic and clinical variables, including MNSI scores, Wagner ulcer classification, and autonomic function tests such as heart rate variability (HRV), Valsalva ratio, postural hypotension, heart rate response to deep breathing, and sympathetic skin response. Pearson's correlation coefficients were calculated to analyze variable relationships.

Results: Participants exhibited moderate neuropathy (mean MNSI score: 7.2) and predominantly Grade 2 or 3 ulcers (60%). Autonomic tests revealed reduced HRV (30.2), impaired Valsalva ratio (1.21), diminished parasympathetic activity (heart rate response: 14.5), and widespread sympathetic dysfunction (95%). Significant correlations included: advanced age with higher MNSI scores ($p < 0.05$), prolonged diabetes duration with higher Wagner grades ($p < 0.05$), and reduced HRV and parasympathetic activity with higher MNSI scores ($p < 0.01$).

Conclusion: The interplay between demographic factors, clinical variables, and autonomic dysfunction influences neuropathy and DFU severity in T2DM. Targeted interventions are essential for managing complications and improving diabetic foot care.

Keywords: Diabetic Foot Ulcers, Type 2 Diabetes Mellitus, Neuropathy, Autonomic Dysfunction, Heart Rate Variability

Introduction

Diabetic foot ulcers (DFU) are a severe complication of type 2 diabetes mellitus (T2DM), significantly impacting global health outcomes.¹ Middle-aged adults, typically aged 45–64 years, are particularly susceptible to T2DM and its complications due to prolonged exposure to chronic hyperglycaemia.¹

The development of DFU in T2DM is closely linked to chronic hyperglycaemia, which precipitates peripheral neuropathy characterised by sensory deficits, pain, and diminished protective sensation, thereby escalating DFU risk.^{2,3} This neuropathy arises from complex metabolic dysregulations and microvascular impairments exacerbated by comorbidities like obesity and hypertension.^{4,5}

Moreover, diabetic neuropathy often presents with autonomic dysfunction, compromising cardiovascular reflexes and blood pressure regulation, heightening the susceptibility to cardiovascular events and other diabetic complications.^{6,7} Objective assessments of autonomic function, such as heart rate variability (HRV) and postural blood pressure changes, are crucial for understanding the systemic impact of diabetes on neurovascular integrity and overall health outcomes.

Effective preventive strategies and interventions for DFU hinge on a comprehensive understanding of the demographic profiles and associated risk factors among middle-aged T2DM patients. Key factors influencing disease progression include age, gender, diabetes duration, family history, socio-economic status, and family structure, underscoring the critical role of socio-economic factors in disease management.⁸

The escalating prevalence of T2DM globally, driven by ageing populations, urbanisation, and lifestyle changes contributing to obesity and sedentary behaviours, intensifies the burden of diabetes-related complications, including DFU, on healthcare systems.^{9,10} Middle-aged adults bear a significant portion of this burden due to prolonged exposure to elevated blood glucose levels and subsequent vascular and neurological complications associated with T2DM onset during early adulthood or midlife.¹¹

Given the multifaceted nature of DFU, investigating its demographic correlates, neuropathy severity using tools like the Michigan Neuropathy Screening Instrument (MNSI), and autonomic dysfunction through objective measures is crucial.¹² This study aims to elucidate these associations, paving the way for targeted interventions, optimised treatment strategies, and improved clinical outcomes for middle-aged adults managing T2DM and DFU.

Materials and Method

Study Design and Setting

This prospective longitudinal study aimed to observe changes in autonomic function and foot ulcer status over time in patients with T2DM, providing insights into DFU and autonomic dysfunction progression and management. The study took place at Vinayaka Mission's Kirupananda Variyar Medical College Hospitals in Salem, Tamil Nadu, India. Purposive sampling identified 300 eligible participants with both DFU and T2DM. Inclusion criteria were patients attending the diabetic clinic, diagnosis of T2DM, and a history of more than one hospitalisation for DFU during the study period. Exclusion criteria were a history of foot ulcers and hospitalisation exceeding 30 days during data collection and absence of prior hospital admissions or other complicating illnesses. The study was conducted from March 2021 to February 2023.

Ethical Considerations

The study received approval from the institutional review board of Vinayaka Mission's Kirupananda Variyar Medical College Hospitals, Salem. Informed consent was obtained from all participants.

Data Collection

Baseline Characteristics

Demographic data including age, sex, education, occupation, family type, family history of diabetes mellitus (DM), and diabetes duration were extracted from hospital records.

Assessment of Foot Ulcer and Neuropathy

- **Michigan Neuropathy Screening Instrument:** A 15-item self-administered questionnaire assessing foot sensation, including pain, numbness, and temperature sensitivity.
- **Wagner Classification System for Foot Ulcers:** Classifies ulcers by depth and presence of osteomyelitis or gangrene into six grades (0–5).

Autonomic Function Tests

- **Heart Rate Variability (HRV):** Measures the variation in time intervals between heartbeats
- **Valsalva Ratio:** Evaluates heart rate changes during deep breathing and bearing down
- **Postural Hypotension Test:** Assesses blood pressure changes upon standing
- **Heart Rate Response to Deep Breathing:** Measures heart rate variation during deep breaths
- **Sympathetic Skin Response (SSR):** Assesses changes in skin electrical conductance due to sympathetic nervous system activity

Statistical Analysis

Data consistency was verified before analysis. Continuous variables were presented as mean \pm standard deviation (SD) or median with interquartile range (IQR), while categorical variables were expressed as frequencies and percentages. Chi-squared tests compared dependent and demographic variables. Regression and correlation analyses evaluated relationships between foot ulcers and neuropathy. A significance level of $p < 0.05$ was used.

Results

The study population had a mean age of 56.4 years, indicating a middle-aged group primarily affected by DFU and T2DM. A higher proportion of male participants (63.3%) suggested either a gender predisposition or higher clinic attendance among males. The average duration of diabetes was 12.5 years, underscoring the chronic nature of their condition. More than half of the participants (52%) had a family history of diabetes, pointing to a possible genetic predisposition. In terms of education and occupation, most participants had completed secondary education, and 46.7% were employed, reflecting a mix of socio-economic backgrounds. Additionally, a majority (60%) belonged to nuclear families, which could influence their care and support systems (Table 1).

Table 1. Baseline Characteristics of Participants

Variable	Mean \pm SD or Median (IQR)
Age (years)	56.4 \pm 10.2
Duration of diabetes (years)	12.5 \pm 7.3
Years of suffering from DM	12.5 \pm 7.3
Variable	Frequency (%)
Sex (male)	95 (63.3)
Sex (female)	55 (36.7)
Family history of DM	78 (52.0)
Educational level	
Primary	60 (40.0)
Secondary	65 (43.3)
Tertiary	25 (16.7)
Occupation	
Employed	70 (46.7)
Unemployed	50 (33.3)
Retired	30 (20.0)
Type of family	
Nuclear	90 (60.0)
Joint	60 (40.0)

DM: Diabetes Mellitus

Table 2. Assessment of Foot Ulcer and Neuropathy

Test	Result (Mean \pm SD or n (%))
Michigan Neuropathy Screening Instrument (MNSI) Score	7.2 \pm 2.5
Wagner Classification System Grades	
Grade 0	0 (0.0)
Grade 1	30 (20.0)
Grade 2	50 (33.3)
Grade 3	40 (26.7)
Grade 4	20 (13.3)
Grade 5	10 (6.7)

The average MNSI score was 7.2, indicating a moderate level of neuropathy among the participants. According to the Wagner Classification System, most ulcers were classified as Grade 2 and 3, accounting for 60% of cases, highlighting significant ulcer depth and the need for intensive treatment (Table 2).

Table 3. Autonomic Function Tests

Test	Result (Mean \pm SD)
Heart Rate Variability (HRV)	30.2 \pm 5.7
Valsalva ratio	1.21 \pm 0.12
Postural hypotension test	
Systolic BP change (mmHg)	-15.6 \pm 8.4
Diastolic BP change (mmHg)	-6.2 \pm 3.5
Heart rate response to deep breathing	14.5 \pm 3.2
Sympathetic Skin Response (SSR)	Present in 95% of patients

Table 4. Statistical Analysis and Correlations

Variable	p Value
Age vs MNSI score	< 0.05
Duration of diabetes vs Wagner grade	< 0.05
Family history of DM vs MNSI score	0.07
HRV vs Wagner grade	< 0.01
Valsalva ratio vs MNSI score	< 0.05
Postural hypotension vs Wagner grade	< 0.05
HR response to deep breathing vs MNSI score	< 0.01

The autonomic function tests revealed that the average heart rate variability (HRV) was 30.2, suggesting autonomic dysfunction, as lower HRV is associated with higher morbidity. The mean Valsalva ratio was 1.21, indicating reduced autonomic reflexes. The postural hypotension test showed significant drops in blood pressure on standing, reflecting autonomic instability. The heart rate response to deep breathing had a mean value of 14.5, demonstrating decreased parasympathetic function. Sympathetic skin response was present in 95% of patients, indicating prevalent sympathetic dysfunction (Table 3).

MNSI: Michigan Neuropathy Screening Instrument

Statistical analysis showed a significant correlation between age and MNSI scores ($p < 0.05$), suggesting that older patients tend to have higher neuropathy scores. The duration of diabetes was significantly associated with Wagner grades ($p < 0.05$), with longer diabetes duration correlating with more severe ulcers. HRV was significantly correlated with Wagner grades ($p < 0.01$), highlighting the impact of autonomic dysfunction on ulcer severity. The Valsalva ratio was significantly related to MNSI scores ($p < 0.05$), indicating that reduced autonomic reflexes are associated with higher neuropathy scores. The postural hypotension test results were significantly correlated with Wagner grades ($p < 0.05$), emphasising the role of autonomic instability in ulcer progression. Lastly, a strong correlation ($p < 0.01$) was found between the heart rate response to deep breathing and MNSI scores, suggesting that reduced parasympathetic activity is linked with higher neuropathy scores (Table 4).

Discussion

Baseline Characteristics

The study cohort, with a mean age of 56.4 years, reflects a middle-aged population predominantly affected by DFU and T2DM. This demographic profile is consistent with typical onset and complications associated with T2DM, including DFU.¹³ The higher representation of male participants (63.3%) in our study may indicate either a gender predisposition to diabetes complications or a greater likelihood of males seeking medical care in diabetic settings.¹⁴

The average diabetes duration of 12.5 years underscores the chronic management challenges faced by the participants. Chronic hyperglycaemia is a well-established risk factor for diabetic complications such as neuropathy and DFU, highlighting the critical role of disease duration in disease progression and severity.¹⁵

A notable proportion (52%) of participants reported a family history of diabetes, suggesting a genetic predisposition to T2DM. Genetic factors significantly influence the

pathogenesis of diabetes, impacting disease susceptibility and the progression of complications like neuropathy and DFU.¹⁶

Regarding socio-economic factors, most participants had completed secondary education (a common educational level in the study region), and nearly half (46.7%) were employed. This socio-economic diversity underscores the varied economic backgrounds influencing disease management and outcomes in T2DM patients.¹⁷ Moreover, a majority (60%) of participants belonged to nuclear families. Family structure plays a crucial role in patient support and disease management adherence, which are pivotal in the effective management and prevention of complications such as DFU.¹⁸

Assessment of Foot Ulcer and Neuropathy

The average MNSI score of 7.2 indicates a moderate level of neuropathy among the study participants. The MNSI is a validated tool for assessing peripheral neuropathy in diabetic patients, with higher scores correlating with more severe neuropathic symptoms like pain and numbness.¹⁹ According to the Wagner Classification System, Grades 2 and 3 ulcers accounted for 60% of cases in our study. These grades signify significant tissue involvement and potential complications such as osteomyelitis and gangrene, necessitating intensive management to prevent limb amputations.¹⁹

Autonomic Function Tests

The autonomic function tests conducted in this study provided insights into the autonomic dysfunction prevalent in T2DM patients with DFU. The average heart rate variability (HRV) of 30.2 indicates reduced HRV, which is associated with increased morbidity and mortality in diabetic patients.¹⁹ Reduced HRV reflects impaired autonomic nervous system function, contributing to cardiovascular complications and poor prognosis. A mean Valsalva ratio of 1.21 suggests impaired autonomic reflexes, particularly in response to changes in intrathoracic pressure during deep breathing. This finding underscores the involvement of parasympathetic nervous system dysfunction in diabetic autonomic neuropathy.¹⁹ The postural hypotension test revealed significant drops in blood pressure upon standing, indicating autonomic instability among participants. Autonomic dysfunction can lead to impaired blood pressure regulation, posing additional cardiovascular risks in diabetic patients with DFU.¹⁹

The mean heart rate response to deep breathing of 14.5 reflects decreased parasympathetic function, which is characteristic of diabetic autonomic neuropathy. Impaired parasympathetic activity contributes to dysregulation of heart rate and cardiovascular function in diabetic patients.²⁰ Sympathetic skin response was present in 95%

of patients, indicating widespread sympathetic nervous system dysfunction. Sympathetic dysfunction is common in diabetic neuropathy and can impair vascular responses critical for wound healing in DFU patients.²¹

Statistical analyses demonstrated several significant correlations among clinical variables in our study cohort:

- There was a significant positive correlation ($p < 0.05$) between older age and higher MNSI scores, suggesting that older patients tend to experience more severe neuropathic symptoms.¹⁹
- A longer duration of diabetes was significantly associated ($p < 0.05$) with higher Wagner grades, indicating that chronic hyperglycaemia exacerbates foot ulcer severity.²⁰
- Lower HRV was significantly correlated ($p < 0.01$) with higher Wagner grades, highlighting the impact of autonomic dysfunction on ulcer severity and wound healing processes.²⁰
- Reduced Valsalva ratio showed a significant correlation ($p < 0.05$) with higher MNSI scores, indicating that impaired autonomic reflexes are associated with more severe peripheral neuropathy.¹⁹
- Significant correlations ($p < 0.05$) between postural hypotension and Wagner grades underscore the role of autonomic instability in exacerbating DFU severity.¹⁹
- A strong correlation ($p < 0.01$) between reduced parasympathetic activity (HR response to deep breathing) and higher MNSI scores suggests that parasympathetic dysfunction contributes to peripheral neuropathy severity in T2DM patients with DFU.¹⁹

Implications

Clinical Implications

This study provides crucial insights into the clinical characteristics of DFU among middle-aged individuals with T2DM. The significant prevalence of moderate to severe neuropathy, as indicated by scores from the MNSI and Wagner Classification System grades, underscores the urgent need for early detection of neuropathy and prompt intervention strategies in clinical practice.^{12,13}

Autonomic Dysfunction

Findings from autonomic function tests highlight widespread dysfunction within the autonomic nervous system among T2DM patients with DFU. Reduced heart rate variability (HRV), impaired Valsalva ratio, and postural hypotension indicate substantial cardiovascular risks associated with diabetic autonomic neuropathy. These results stress the importance of integrating autonomic function assessments into routine diabetic foot care protocols to mitigate cardiovascular complications and enhance patient outcomes.^{6,14}

Socio-Economic and Genetic Factors

The study identifies socio-economic factors such as education, employment status, and family structure as influential in disease management and outcomes. Additionally, the high prevalence of familial history of diabetes suggests a genetic predisposition to T2DM, emphasising the necessity for personalised approaches in diabetes management to address genetic susceptibilities.^{8,9}

Recommendations

Early Screening and Intervention

Healthcare providers should prioritise early screening for neuropathy using validated tools like the MNSI and implement aggressive treatment strategies to prevent the progression of DFU to severe stages. Regular monitoring of autonomic function through tests such as HRV and Valsalva ratio should be standard practice in diabetic care to mitigate cardiovascular risks linked with autonomic dysfunction.²²

Patient Education and Support

Recognising the impact of socio-economic factors on disease outcomes, healthcare teams should develop tailored education and support programs based on patients' educational and employment backgrounds. Strengthening patient understanding of diabetes management and cultivating family support systems can enhance treatment adherence and reduce the incidence of complications such as DFU.^{23,24}

Multidisciplinary Approach

Collaboration among podiatrists, endocrinologists, nurses, and psychologists is essential for comprehensive diabetic foot care. A multidisciplinary approach facilitates early detection, timely intervention, and holistic management of DFU, thereby optimising patient outcomes and alleviating healthcare burdens associated with diabetic complications.^{25,26}

Limitations

Cross-Sectional Design

The study's cross-sectional design limits the ability to establish causal relationships among clinical variables observed. Future longitudinal studies are necessary to determine temporal associations and validate the predictive value of neuropathy severity and autonomic dysfunction in the progression of DFU.

Sample Size and Generalisability

The size and demographic characteristics of the study cohort may restrict the generalisability of findings to broader populations. Future research should include larger and more diverse samples to enhance the external validity of results and account for potential confounding factors.

Measurement Tools

Despite the utilisation of validated tools such as the MNSI and autonomic function tests, variations in measurement techniques and inter-rater reliability could introduce biases. Standardising assessment protocols across multiple centres would enhance the comparability and reliability of results.

Data Collection Challenges

Variability in patient-reported outcomes and clinical data collection methodologies may introduce biases or result in missing data. Robust data collection protocols and stringent quality assurance measures are essential to mitigate these limitations and ensure the integrity of data for comprehensive analysis and interpretation.

Conclusion

This study provides comprehensive insights into the baseline characteristics, neuropathy assessment, autonomic function, and their correlations in T2DM patients with DFU. The findings underscore the multifaceted nature of diabetic complications, emphasising the roles of age, disease duration, genetic predisposition, socio-economic factors, and autonomic dysfunction in influencing the severity of DFU and neuropathy. These insights are crucial for developing targeted interventions aimed at mitigating complications, improving patient outcomes, and optimising management strategies for diabetic foot ulcers. Future research should focus on longitudinal studies to further elucidate these relationships and enhance therapeutic approaches in diabetic foot care.

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Conflict of Interest: None

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