ORIGINAL RESEARCH

Correlating Blood Selenium Levels in Type 2 Diabetes Mellitus with Peripheral Neuropathy and Factors Contributing to Associated Lesion Development

Hui Xu, MM; Qian Wen, MM; Mao Ye, MD

ABSTRACT

Background • Diabetic peripheral neuropathy (DPN) is a prevalent complication of type 2 diabetes mellitus (T2DM). A comprehensive understanding of DPN's causal factors is pivotal for effective prevention and treatment, but the precise clinical pathogenesis remains unclear.

Objective • To investigate the correlation between blood selenium (Se) levels and DPN in T2DM patients and analyze factors contributing to lesion development.

Methods • We selected 51 patients with DPN and 57 with T2DM alone between June 2021 and August 2022. Blood glucose, lipid, and Se levels were assessed. Electromyographic evoked potentials measured motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) in DPN patients.

Results • DPN patients exhibited lower Se, MNCV, and SNCV compared to DM patients, with higher glucose and lipid levels ($P < .05$). Logistic regression analysis identified age (95%CI 1.256-9.631), disease duration (95%CI 2.160-11.816), fasting blood glucose (95%CI 2.160-11.816), and HbA_{1c} (95%CI 1.064-7.632) as independent risk factors for DPN in T2DM, while Se (95%CI 0.324-1.126) emerged as an independent protective factor ($P < .05$).

Conclusions • Blood selenium levels and DPN are closely related, with selenium emerging as a significant factor in DPN occurrence among T2DM patients. (*Altern Ther Health Med.* 2024;30(4):180-184)

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) continues to be one of the most prevalent chronic diseases globally.[1-2] It results from the persistent elevation of blood glucose levels and is responsible for more than 425 million cumulative T2DM cases worldwide, as reported by the International Diabetes Federation (IDF) in 2017.[1] Notably, China holds the highest number of T2DM cases globally, with approximately 114.4 million cases.[2] The global number of T2DM cases is projected to exceed 600 million by 2045.[3]

Presently, the prevalence of T2DM in individuals over 50 is approximately 8-12%, with a rising trend in recent years.[4] No clinical protocol currently exists for the complete cure of T2DM, and individuals diagnosed with this condition require lifelong glucose-lowering therapy to manage the progression of T2DM once it manifests.[5] T2DM poses significant risks to the overall health of an individual as it can disrupt organs and tissues, potentially leading to their failure. It includes conditions such as retinopathy, cardiovascular disease, and nephropathy, all associated with T2DM.[6]

Diabetic peripheral neuropathy (DPN), a prevalent complication of T2DM, involves lesions affecting spinal and cranial nerves, accounting for approximately 8.4% to 61.8% of T2DM cases.[7] DPN most commonly presents as abnormal sensations in patients, including heightened pain sensitivity, limb numbness, and unusual cold or burning sensations. These symptoms significantly impact patients' daily lives.[8] An in-depth understanding of the causative factors of DPN is essential for developing effective prevention and treatment strategies. However, the precise clinical pathogenesis of DPN remains incompletely understood.[9]

Selenium (Se) is a vital nutrient in the human body, known for its significant antioxidant properties that are believed to play a role in preventing and managing the progression of T2DM.[10] While various studies have established a positive correlation between elevated Se levels and the prevalence of T2DM,[11,12] research on DPN is relatively scarce. Previous studies have also indicated a strong connection between Se and neurodevelopmental disorders and neurotoxicity,[13,14] raising the possibility that Se could be relevant in assessing DPN. However, there is a lack of studies to confirm this hypothesis.

Therefore, this study conducted a preliminary analysis of the relationship between Se and DPN and investigated the factors associated with the occurrence of DPN, aiming to provide a reliable reference for future prevention and treatment.

MATERIALS AND METHODS

Study Design

A total of 51 patients diagnosed with DPN and 57 patients with T2DM without DPN were selected for retrospective analysis, covering the period from June 2021 to August 2022. The study strictly adhered to the principles outlined in the Declaration of Helsinki, and all participants provided their informed consent.

Group Allocation

Patients were divided into two groups. The DPN group, comprising 51 patients, had an average age of (66.59±7.57) years, with a gender distribution of 34 males and 17 females. Conversely, the T2DM group, consisting of 57 patients, had an average age of (66.07±6.46) years, with 32 males and 25 females. This allocation ensures a comprehensive evaluation of these two distinct patient cohorts in our study.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: (1) Participants were required to be aged over 18 years; (2) those adhered to the diagnostic guidelines for T2DM and DPN[15,16]; (3) had complete medical records; and (4) provided informed consent to participate in this study.

Exclusion criteria were as follows: (1) Individuals with acute complications such as acidosis and lactic acidosis, those suffering from other neurological lesions or neurological dysfunctional diseases; (2) patients with neuropathy attributed to surgical procedures, cervical spondylosis, or other metabolic conditions were excluded from the study.

Laboratory and Clinical Assessments

Upon admission, 4 ml of fasting venous blood was collected from both study groups. We measured fasting blood glucose (FBG), glycosylated hemoglobin (HbA_{1c}), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) levels using a fully automated biochemical analyzer (BECKMAN COULTER AU5800). Se levels were determined through inductively coupled plasma mass spectrometry (ICP-MS) using the Agilent ICP-MS 7700 instrument.

To assess motor nerve conduction velocity (MNCV) and sensory nerve conduction velocity (SNCV) in DPN patients, we utilized the electromyography evoked potential meter (NeuroExam M 800) to examine the median nerve in the upper extremity and the common peroneal nerve in the lower extremity.

Outcome Measures

Several indexes were used to measure the outcomes in this study. (1) Differences in Se, glucose, and lipid levels between DPN and T2DM patients. This measure helped us understand the variations in these critical factors between patients with DPN and those with T2DM alone. (2) The relationship between Se and blood glucose and lipid levels in patients with DPN. This assessment aimed to establish the associations between Se levels and the parameters of blood glucose and lipid profiles in DPN patients. (3) The relationship between Se and nerve conduction velocity in patients with DPN. This measure explored the correlations between Se levels and nerve conduction velocities in individuals diagnosed with DPN. (4) The diagnostic value of Se for the development of DPN in patients with T2DM. This measure assessed the utility of Se as a diagnostic indicator for predicting the onset of DPN in T2DM patients. (5) Factors associated with the occurrence of DPN in T2DM. We investigated various factors that might contribute to the development of DPN in individuals with T2DM.

Statistical Analysis

In this study, statistical analysis was performed using SPSS version 23.0 software (IBM, Armonk, NY, USA). Categorical data, represented as counts [n (%)], were compared using the chi-square test, while continuous data ($\bar{x} \pm s$), presented as mean ($\bar{x}$) and standard deviation (s), were analyzed with independent samples t tests. Receiver Operating Characteristic (ROC) curves were employed to assess the diagnostic accuracy of various parameters, with the area under the ROC curve (AUC) serving as a key measure. A higher AUC value indicated greater diagnostic precision. Correlations among normally distributed variables were determined using Pearson correlation coefficients. Additionally, logistic regression was applied to analyze factors associated with these observed correlations. A P value of .05 or lower was considered indicative of statistical significance.

RESULTS

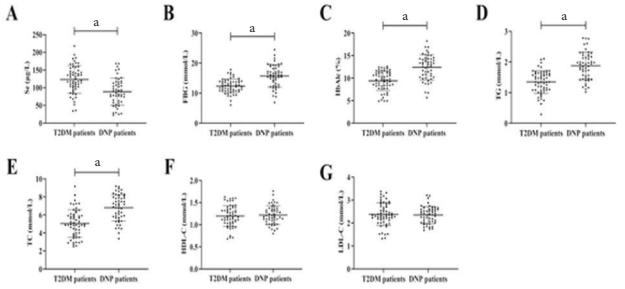
Comparison of Se, Blood Glucose, and Lipid Levels

Se levels in our study exhibited a mean value of (88.78±37.75) μg/L in patients with DPN and (125.89±49.65) μg/L in those diagnosed with T2DM. A comparison between the two groups revealed a significant decrease in Se levels among DPN patients compared to T2DM patients ($P < .05$), as illustrated in Figure 1A. Furthermore, the analysis revealed higher levels of FBG, HbA_{1c}, TG, and TC in DPN patients compared to T2DM patients ($P < .05$), represented in Figure 1B to 1E. In contrast, the differences in LDL-C and HDL-C levels did not reach statistical significance ($P > .05$), as indicated in Figures 1F and 1G.

Relationship between Se and Blood Glucose and Lipids in DPN Patients

Pearson correlation coefficients unveiled a significant negative correlation between Se levels in patients with DPN and FBG, HbA_{1c}, TG, and TC (r=-0.658, -0.712, -0.578, -0.629, $P < .05$), as illustrated in Figure 2A to 2D. This result indicates that higher Se levels in DPN patients were associated with lower blood glucose levels and lipids.

Figure 1. Comparison of Se, Blood Glucose, and Lipid Levels

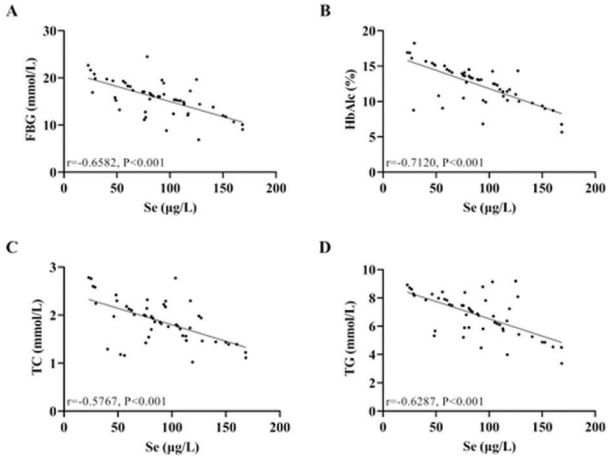


#Significant at $P < .05$.

Note: (A) Comparison of Se; (B) Comparison of FBG; (C) Comparison of HbA_{1c}; (D) Comparison of TG; (E) Comparison of TC; (F) Comparison of HDL-C; (G) Comparison of LDL-C.

Abbreviations: FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; TC,: total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus.

Figure 2. Relationship Between Se and Blood Glucose and Lipids in DPN Patients.



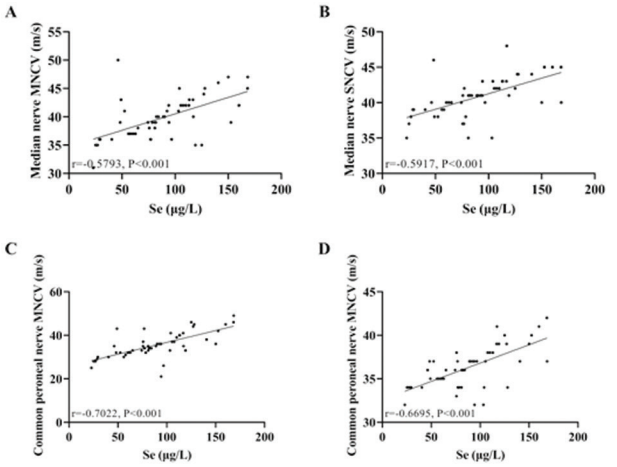
Note: (A) Correlation of Se with FBG; (B) Correlation of Se with HbA_{1c} (C) Correlation of Se with TG; (D) Correlation of Se with TC.

Abbreviations: FBG, fasting blood glucose; HbAlc, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus.

Relationship between Se and Nerve Conduction Velocity in DPN Patients

In DPN patients, the MNCV measured (39.86±3.78) m/s, and the SNCV) measured (40.76±2.80 m/s. For the common peroneal nerve, MNCV was (35.51±5.86) m/s, and SNCV was (36.33±2.37) m/s. Pearson correlation coefficients demonstrated a notable negative correlation between Se levels in DPN patients and MNCV and SNCV for both the median and common peroneal nerves (r=-0.579, -0.592, -0.702, -0.670, $P < .05$), as illustrated in Figure 3A to 3D. This finding indicates that higher Se levels were associated with faster nerve conduction velocities.

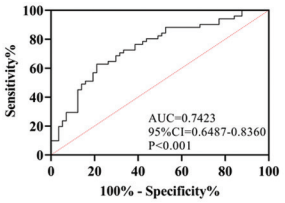
Figure 3. Relationship Between Se and Nerve Conduction Velocity in DPN Patients



Note: (A) Correlation of Se with the median nerve MNCV; (B) Correlation of Se with the median nerve SNCV; (C) Correlation of Se with the common peroneal nerve MNCV; (D) Correlation of Se with the common peroneal nerve SNCV.

Abbreviations: MNCV, motor nerve conduction velocity; SNCV, sensory nerve conduction velocity; DPN, diabetic peripheral neuropathy.

Figure 4. Efficacy of ROC Analysis of Se in Diagnosing the Occurrence of DPN in Patients with T2DM



Abbreviations: AUC: area under curve; 95%CI: 95% confidence interval.

Diagnostic Effect of Se on DPN

We conducted ROC analysis utilizing Se levels in DPN patients compared to those in T2DM patients. The outcomes revealed that for Se levels below 96.79 μg/L, the sensitivity of diagnosing the onset of DPN in T2DM patients reached 62.75%, accompanied by a specificity of 78.95%. The AUC was calculated as 0.742 ($P < .001$), as illustrated in Figure 4, indicating a robust diagnostic efficacy.

Univariate Analysis of Factors Affecting the Occurrence of DPN in T2DM

In our analysis, we observed that differences in gender ($P = .63$), blood pressure ($P = .835$ and $.795$), smoking ($P = .408$), and drinking ($P = .948$), among other factors, between DPN patients and T2DM patients were not statistically significant ($P > .05$). However, DPN patients exhibited higher age ($P < .001$), a longer duration of diabetes mellitus ($P < .001$), and a higher prevalence of family history compared to T2DM patients ($P = .041$), as presented in Table 1.

Table 1. Univariate Analysis Affecting the Occurrence of DPN in T2DM

Variables	T2DM Patients (n = 57)	DPN patients (n = 51)	*t* (or χ^2)	*P* value
Age	59.49±7.64	66.59±7.57	4.842	<.001
Duration of DM Disease (years)	6.47±1.88	8.43±2.03	5.209	<.001
DBP (mmHg)	91.18±11.13	90.73±11.16	0.210	.835
SBP (mmHg)	145.14±16.11	144.24±19.72	0.261	.795
Sex			1.255	.263
Male	32(56.14)	34(66.67)		
Female	25(43.86)	17(33.33		
Smoking			0.686	.408
Yes	29(50.88)	30(58.82)		
No	28(49.12)	21(41.18)		
Drinking			0.004	.948
Yes	22(38.60)	20(39.2)		
No	35(61.40)	31(60.78)		
Family History of T2DM			4.162	.041
Yes	16(28.07)	24(47.06)		
No	41(71.93)	27(52.94)		
Place of Residence			0.248	.618
City	34(59.65)	28(54.90)		
Rural	23(40.35)	23(45.10)		

Note: The table presents univariate analysis results of various factors affecting the occurrence of DPN in T2DM patients. $P < .05$ indicate statistical significance.

Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure; DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus.

Table 2. Multivariate Analysis of Factors Affecting the Occurrence of DPN in T2DM

Variables	β	S.E.	Wald χ^2	*P* value	OR	95% CI
Age	1.216	0.621	5.263	.000	3.262	1.256-9.631
Duration of T2DM disease	1.626	0.448	13.626	.000	4.624	2.160-11.816
Se	0.711	0.405	6.262	.000	0.726	0.324-1.126
FBG	0.741	0.563	2.631	.004	2.162	0.842-6.263
HbA_{1c}	1.034	0.496	4.393	.000	2.816	1.064-7.632
TG	1.623	0.622	1.626	.076	1.426	0.713-5.612
TC	1.262	0.757	1.062	.273	1.630	0.531-10.841
Family history of T2DM	1.437	0.512	1.222	.167	1.063	0.812-1.359

Abbreviations: FBG, fasting blood glucose; HbA_{1c}, glycosylated hemoglobin; TC, total cholesterol; TG, triglycerides; DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus.

Multivariate Analysis of Factors Affecting the Occurrence of DPN in T2DM

In this comprehensive analysis, we assigned values to the previously mentioned univariate indicators and Se (0 for no family history and 1 for a family history; all other indicators were measured and analyzed using raw data). These values were then entered into SPSS as covariates for logistic regression analysis, with the occurrence of DPN in patients as the dependent variable.

The results indicated that family history ($P = .167$), TG ($P = .076$), and TC ($P = .273$) were not independent factors influencing the development of DPN in patients with T2DM ($P > .05$). In contrast, factors such as age (95% CI 1.256-9.631, $P < .001$), duration of the disease (95% CI 2.160-11.816, $P < .001$), FBG (95% CI 2.160-11.816, $P < .001$), HbA_{1c} (95% CI 1.064-7.632, $P < .001$), and Se (95% CI 0.324-1.126, $P < .001$) were identified as independent factors influencing the development of DPN in T2DM ($P < .05$), as detailed in Table 2. Notably, the ORs for age, duration of the disease, FBG, and HbA_{1c} were greater than 1 (OR >1), designating them as independent risk factors, while the OR for Se was less than 1 (OR <1), signifying it as an independent protective factor.

DISCUSSION

DPN is recognized as a prevalent complication in T2DM and substantially impacts the quality of life of affected individuals. In severe cases, it can result in irreversible nerve damage, ultimately leading to limb paralysis.[17] Considering the absence of a definitive cure for DPN, it is crucial to thoroughly understand the fundamental mechanisms and key indicators associated with DPN. This understanding plays a vital role in shaping the development and improvement of future clinical treatments, ensuring that they are better equipped to address this challenging condition.

Se, an essential trace element, significantly influences metabolic pathways. It stimulates glucose uptake, regulates glycolysis, and influences fatty acid synthesis. Furthermore, its antioxidant properties have demonstrated a notably positive impact on the prevention and treatment of T2DM.[18] Consequently, investigations into the relationship between Se and DPN hold the potential to be a pivotal breakthrough in future diagnostics and therapeutic strategies.

In the present study, we observed significantly lower levels of Se in patients with DPN compared to those with T2DM alone, suggesting that Se is potentially associated with the occurrence and development of DPN.[19] Furthermore, glucose and lipid levels were found to be further elevated in patients with DPN compared to those with T2DM, aligning with the pathological manifestations of DPN.[20,21]

In correlation analysis, we observed that Se levels in patients with DPN exhibited a negative correlation with blood glucose and lipids, while they displayed a positive correlation with nerve conduction velocity. This finding supports the close relationship between Se and the pathological progression of DPN. Notably, it is widely recognized that the development of T2DM is linked to the generation of excessive reactive oxygen species in the hyperglycemic state.[22]

Se constitutes an integral component of the active center of glutathione peroxidase (GSH-Px), imparting anti-lipid peroxidation effects. Consequently, elevated Se levels under normal conditions can strengthen the body's antioxidant system, mitigating the detrimental impacts of T2DM and oxidative stress damage.[23] Moreover, Se has found application in clinical practice for nerve repair following spinal cord injuries, demonstrating its potential to enhance the regeneration of neuromodulatory factors.[24]

However, certain studies have noted that excessive enhancement of GSH-Px activity can potentially disrupt insulin signaling by scavenging hydrogen peroxide. It may lead to the emergence of insulin resistance and hyperinsulinemia, ultimately facilitating the progression of T2DM and DPN.[25] A study conducted by Al-Salmi et al.[26] highlighted that prolonged Se supplementation led to continuous increases in body fat in mice and a noticeable development of insulin resistance. Subsequently, upon discontinuation of Se supplementation, body fat levels and insulin sensitivity gradually returned to normal. This finding emphasizes the dual role of Se in the development of DPN, where both excessively high and low levels may have adverse effects on the human body.

In this study, ROC and logistic regression analyses demonstrated that Se exhibited superior diagnostic efficacy for the development of DPN in patients with T2DM. It also emerged as an independent protective factor for DPN. This finding holds substantial significance for DPN, which lacks a dependable clinical assessment index. Furthermore, Se supplementation as a therapeutic approach may represent a novel avenue for preventing and treating DPN.

Our findings indicate that the Se role in DPN may have multiple aspects. However, this assertion requires further substantiation by including a more extensive dataset encompassing additional DPN cases. Cohort studies should be undertaken to define the ideal Se range for managing DPN effectively. Such research could offer valuable clinical references for diagnosing and treating DPN.

Moreover, the link between the duration of T2DM and DPN highlights the importance of vigilance from both clinicians and patients. Early detection of potential DPN in the early stages of T2DM is vital, enabling timely therapeutic interventions that significantly enhance patients' quality of life. It is worth noting that the interrelationship between FBG, HbA_{1c}, age, T2DM, and its various complications, including DPN, has been well-established in prior research.[27-29] Therefore, these relationships were not repeated within this study. This study identified that Se exhibits potential both as a protective factor and a diagnostic marker for DPN. This multifaceted role necessitates further exploration.

Study Limitations

We acknowledge a few limitations in this study. First, the sample size was relatively small, which may limit the generalizability of the findings. Secondly, this was a cross-sectional study, and causality cannot be established. Longitudinal studies are needed to explore the dynamic relationship between Se levels and DPN over time. Additionally, while this study focused on Se, other potential confounding factors were not extensively examined. Future research should consider a broader range of variables that could influence the development of DPN. Lastly, our study did not explore the potential interactions of Se with other medications or treatments that patients may have been receiving. Despite these limitations, this study provides valuable insights into the association between Se and DPN, laying the foundation for further research in this important area of diabetes management.

CONCLUSION

In conclusion, our study reveals a remarkable relationship between Se levels and DPN in individuals with T2DM. Se levels exhibited negative correlations with blood glucose and lipids while demonstrating positive associations with nerve conduction velocity. The excellent diagnostic capacity of Se for identifying the occurrence of DPN in T2DM patients underscores its potential as a valuable clinical marker. Our findings highlight age, the duration of the disease, FBG, and HbA_{1c} as independent risk factors for DPN in T2DM, with Se emerging as an independent protective factor. These results open the door to a promising avenue for DPN management through Se supplementation, offering fresh perspectives on future prevention and treatment strategies.

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None

CONFLICT OF INTERESTS

The authors report no conflict of interest.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study are available from the corresponding author upon request, subject to reasonable conditions.

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