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**EDITORIAL**

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## Observational Study

## Increased blood urea nitrogen levels and compromised peripheral nerve function in patients with type 2 diabetes

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**Abstract****BACKGROUND**

Increased blood urea nitrogen (BUN) levels have been demonstrated to be associated with broader metabolic disturbances and the incidence of type 2 diabetes (T2D), potentially playing a role in the development of diabetic complications, including diabetic peripheral neuropathy.

**AIM**

To examine the relationship between BUN levels and peripheral nerve function in patients with T2D.

**METHODS**

This observational study involved the systematic recruitment of 585 patients with T2D for whom BUN levels and estimated glomerular filtration rate were measured. Electromyography was used to assess peripheral motor and sensory nerve function in all patients, and overall composite Z-scores were subsequently calculated for nerve latency, amplitude, and conduction velocity (NCV) across the median, ulnar, common peroneal, posterior tibial, superficial peroneal, and sural

nerves.

## RESULTS

Across the quartiles of BUN levels, the overall composite Z-score for latency ( $F = 38.996$ ,  $P$  for trend  $< 0.001$ ) showed a significant increasing trend, whereas the overall composite Z-scores for amplitude ( $F = 50.972$ ,  $P$  for trend  $< 0.001$ ) and NCV ( $F = 30.636$ ,  $P$  for trend  $< 0.001$ ) exhibited a significant decreasing trend. Moreover, the BUN levels were closely correlated with the latency, amplitude, and NCV of each peripheral nerve. Furthermore, multivariate linear regression analysis revealed that elevated BUN levels were linked to a higher overall composite Z-score for latency ( $\beta = 0.166$ ,  $t = 3.864$ ,  $P < 0.001$ ) and lower overall composite Z-scores for amplitude ( $\beta = -0.184$ ,  $t = -4.577$ ,  $P < 0.001$ ) and NCV ( $\beta = -0.117$ ,  $t = -2.787$ ,  $P = 0.006$ ) independent of the estimated glomerular filtration rate and other clinical covariates. Additionally, when the analysis was restricted to sensory or motor nerves, elevated BUN levels remained associated with sensory or motor peripheral nerve dysfunction.

## CONCLUSION

Increased BUN levels were independently associated with compromised peripheral nerve function in patients with T2D.

**Key Words:** Blood urea nitrogen; Metabolic disturbance; Peripheral nerve function; Electromyography; Type 2 diabetes

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**Core Tip:** Blood urea nitrogen (BUN) is a well-established biomarker utilized in clinical diagnostic evaluations. When renal function is relatively normal, an increase in BUN may indicate a negative nitrogen balance, underlying metabolic disorders, and potential adverse outcomes. In the present study, our findings indicated that increased BUN levels were independently associated with compromised peripheral nerve function in patients with type 2 diabetes and may serve as a potential risk factor for peripheral nerve dysfunction in these patients. Future interventions to lower BUN levels by improving nutritional status and balancing protein metabolism may alleviate peripheral nerve dysfunction in patients with type 2 diabetes.

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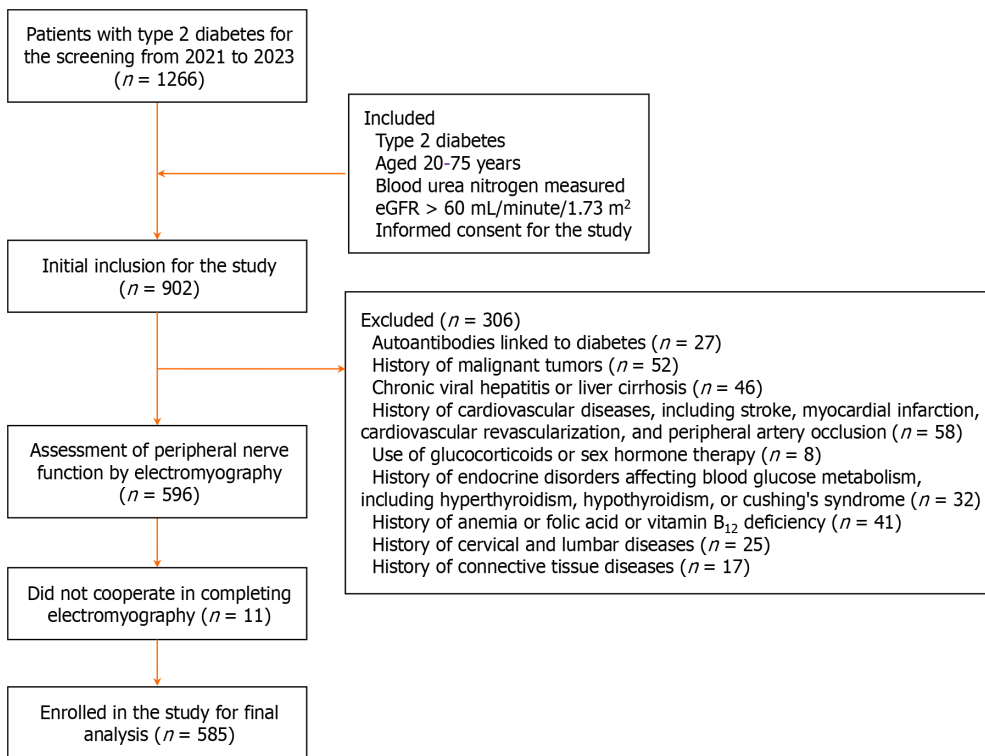
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## INTRODUCTION

Diabetic peripheral neuropathy (DPN) represents a prevalent and debilitating complication among individuals with type 2 diabetes (T2D)[1]. It is characterized by damage to peripheral nerves that manifests as various symptoms, including pain, tingling, numbness, and weakness in the extremities[2]. This condition is a significant contributor to increased morbidity and mortality in this patient population[3,4]. While the etiology and pathogenesis of DPN in T2D remain inadequately understood, its development is recognized as a multifactorial process resulting from an interplay of metabolic disturbances, oxidative stress, and inflammatory responses[5]. Consequently, identifying potential risk factors and devising appropriate interventions for DPN in clinical practice are of paramount importance.

Currently, there are a variety of screening methods for DPN, including physical examination scoring systems, quantitative sensory tests, and neurophysiological examination assessments by electromyography (EMG)[6]. Nerve conduction function studies by EMG are the most sensitive, objective, and reliable methods for testing DPN and quantifying nerve function, particularly in asymptomatic patients[7].

Blood urea nitrogen (BUN) is the main end product of human protein catabolism. After being produced in the liver, urea nitrogen enters the blood and is excreted through glomerular filtration. In the context of relatively normal renal function and the absence of excessive protein intake, elevated BUN levels may serve as an indicator of poor nutritional status and imbalances in protein metabolism in humans[8,9]. BUN is increasingly acknowledged as a crucial marker for a series of metabolic disturbances, including insulin resistance, oxidative stress, and inflammation, which can lead to endothelial dysfunction and vascular damage[10-12] and negatively impact peripheral nerve function[13]. This condition is particularly pertinent in the context of diabetes, where insulin resistance is a major concern. Moreover, in clinical studies, elevated baseline BUN levels are also considered a predictor of the occurrence of gestational diabetes and T2D [14,15]. Furthermore, an increase in BUN levels has been identified as a significant risk factor for the onset of diabetic retinopathy in individuals with T2D[16]. On the basis of these findings, we hypothesized that increased BUN levels may play a role in the development of DPN in patients with T2D and could contribute to compromised peripheral nerve function in these patients.



**Figure 1 Study diagram.** eGFR: Estimated glomerular filtration rate.

Therefore, we conducted a clinical observational study to measure BUN levels in T2D patients, assess peripheral nerve conduction function *via* EMG, and analyze the associations between BUN levels and peripheral nerve function in these patients.

## MATERIALS AND METHODS

### Study design and patient recruitment

We designed a series of studies to explore the potential clinical risk factors for the pathogenesis of DPN[17,18], and the present study is a part of that series. The study diagram is displayed in Figure 1. From January 2021 to December 2023, we recruited eligible T2D patients from the Department of Endocrinology at Nantong First People's Hospital, and the inclusion criteria were as follows: (1) Diagnosed with T2D according to the 2020 Diabetes Management Guidelines from the American Diabetes Association[19]; (2) Aged 20-75 years; (3) Estimated glomerular filtration rate (eGFR) > 60 mL/minute/1.73 m<sup>2</sup>; and (4) Fully comprehended the study procedures and consented to participate. The exclusion criteria were as follows: (1) History of autoantibodies linked to diabetes; (2) History of malignant tumors; (3) History of chronic viral hepatitis or liver cirrhosis; (4) History of cardiovascular diseases (CVD), including stroke, myocardial infarction, cardiovascular revascularization, and peripheral artery occlusion; (5) Use of glucocorticoids or sex hormone therapy; (6) History of endocrine disorders affecting blood glucose metabolism, including hyperthyroidism, hypothyroidism, or Cushing's syndrome; (7) History of anemia or folic acid or vitamin B<sub>12</sub> deficiency; (8) History of cervical and lumbar diseases; and (9) History of connective tissue diseases. Finally, 585 eligible T2D patients with complete data were enrolled in the study. All participants provided informed consent, and the study was approved by the Medical Ethics Committee of Nantong First People's Hospital under reference number 2017XJS008.

### Data collection

Comprehensive clinical information, including human parameters (such as age, sex, height, weight, and systolic/diastolic blood pressure), course of diabetes, medication prescriptions (such as statins and hypoglycemic drugs), and biochemical indicators, was collected. Body mass index (BMI) was also calculated (kg/m<sup>2</sup>).

After an 8-h fast, peripheral venous blood samples were collected to measure the levels of BUN, alanine aminotransferase, albumin (ALB), triglyceride, total cholesterol, uric acid (UA), cystatin C (CysC), hemoglobin, glycosylated hemoglobin A1c (HbA1c), and fasting C-peptide. Morning urine was collected to measure the ALB and creatinine levels, and the urinary ALB/creatinine ratio was subsequently calculated. The eGFR was also determined *via* the MDRD equation [20]. BUN levels were measured *via* the urease-glutamate dehydrogenase method with a fully automatic biochemical analyzer (Labospect 008AS, Hitachi, Japan).

### Peripheral nerve function assessment

EMG (MEB-9200K, Nihon Kohden, Japan) was used to assess peripheral motor and sensory nerve function in all patients, and nerve latency, amplitude, and conduction velocity (NCV) were measured in the median (MN), ulnar (UN), common peroneal, posterior tibial, superficial peroneal, and sural nerves.

After standardization of the functional data related to motor and sensory nerves using Z-scores, overall composite Z-scores for latency, amplitude, and NCV were calculated. This calculation was achieved by averaging the respective functional parameters across all motor and sensory nerves. Specifically, the composite Z-score for latency was derived by calculating the mean of the latency Z-scores across all peripheral nerves, a methodology that has been previously documented in the literature[7,17].

In addition, we computed the composite Z-scores for motor nerves (MN, UN, common peroneal nerve, and posterior tibial nerve) as well as the composite Z-scores for sensory nerves (MN, UN, superficial peroneal nerve, and sural nerve).

### Statistical analysis

All the statistical analyses were performed using SPSS software (IBM SPSS Statistics, Version 25.0). A  $P < 0.05$  was considered to indicate statistical significance.

First, a descriptive statistical analysis was performed. Normally distributed continuous data were presented as the means and standard deviations, skewed continuous data as medians and interquartile ranges, and categorical data as frequencies and percentages. In the subsequent univariate and multivariate analyses, the skewed data were further subjected to natural logarithmic transformation.

Second, we employed one-way analysis of variance with linear polynomial contrasts, the Jonckheere-Terpstra test, or the  $\chi^2$  test with linear-by-linear associations to examine trend changes in the normally distributed, skewed, and categorical data, respectively, between subgroups of BUN quartiles.

Third, Pearson's correlation analysis was performed to evaluate the relationships between BUN levels and peripheral nerve functional indices.

Finally, multivariate linear regression analyses were further used to adjust for other clinical variables to determine whether an abnormal BUN level was an indicator of peripheral nerve dysfunction in patients with T2D.

## RESULTS

### Clinical characteristics of patients

The clinical data for the enrolled T2D patients categorized by quartile levels of BUN (Q1, Q2, Q3, and Q4) are presented in [Table 1](#). The BUN levels were 2.03-4.56 mmol/L in the Q1 group (147 patients), 4.57-5.65 mmol/L in the Q2 group (147 patients), 5.66-6.86 mmol/L in the Q3 group (146 patients), and 6.87-16.28 mmol/L in the Q4 group (145 patients). From the BUN quartile groups Q1 to Q4, age, duration of diabetes, and CysC and HbA1c significantly increased ( $P < 0.05$ ), whereas the proportion of females, BMI, systolic blood pressure, diastolic blood pressure, alanine aminotransferase, triglyceride, and eGFR significantly decreased ( $P < 0.05$ ). Trend changes were not observed in the proportions of statin use, the incidence of hypertension, or the levels of ALB, total cholesterol, UA, hemoglobin, urinary albumin/creatinine ratio (ACR), or fasting C-peptide among the four BUN quartile groups ( $P > 0.05$ ). As the BUN quartiles increased, the overall composite Z-score for latency significantly increased ( $P < 0.001$ ), whereas the overall composite Z-scores for amplitude and NCV significantly decreased ( $P < 0.001$ ).

### Univariate analysis of the associations between BUN levels and peripheral nerve functional indices

Pearson's correlation analysis revealed that BUN levels positively contributed to the overall composite Z-score for latency ( $r = 0.288$ ,  $P < 0.001$ ) and inversely contributed to the overall composite Z-scores for amplitude and NCV ( $r = -0.325$  and  $-0.243$ , respectively;  $P < 0.001$ ). The graphical correlations between BUN levels and overall peripheral nerve functional indices are shown in [Figure 2](#).

Given the asynchronous progression of sensory and motor nerves in the limbs during T2D, we further examined the correlation between BUN levels and the functions of all peripheral nerves ([Table 2](#)). Significant correlations were identified between BUN levels and functional indices, specifically nerve latency, amplitude, and NCV, for each peripheral nerve. Despite being relatively weak, these correlations reached statistical significance. BUN levels were consistently correlated with the latency, amplitude, and NCV of each peripheral nerve. Moreover, in peripheral motor nerves, BUN levels positively contributed to the composite Z-score for motor latency ( $r = 0.266$ ,  $P < 0.001$ ) and inversely contributed to the composite Z-scores for motor amplitude and NCV ( $r = -0.287$  and  $-0.202$ , respectively;  $P < 0.001$ ). Moreover, in peripheral sensory nerves, BUN levels were also positively correlated with the composite Z-score for sensory latency ( $r = 0.242$ ,  $P < 0.001$ ) and negatively correlated with the composite Z-scores for sensory amplitude and NCV ( $r = -0.268$  and  $-0.229$ , respectively,  $P < 0.001$ ; [Table 2](#)). The graphical associations between BUN levels and functional indices of motor and sensory nerves are presented in [Figure 3](#).

### Multivariate linear regression analysis of whether BUN levels are independent indicators of peripheral nerve dysfunction

Multivariate linear regression analysis was performed to adjust for various factors, including age, sex, BMI, blood pressure, diabetes duration, use of statins and diabetes medications, liver function indicators, lipid parameters, the ACR, the eGFR, and UA, CysC, hemoglobin, HbA1c, and fasting C-peptide levels. We found that an increase in BUN was

Table 1 Clinical features of the recruited patients with type 2 diabetes, *n* (%)

Variables	Total	Quartiles of BUN levels				Test statistic	P for trend
		Q1	Q2	Q3	Q4		
BUN (mmol/L) (range)	5.79 ± 1.64 (2.03-16.28)	3.94 ± 0.49 (2.03-4.56)	5.08 ± 0.31 (4.57-5.65)	6.16 ± 0.36 (5.66-6.86)	8.00 ± 1.17 (6.87-16.28)	-	-
<i>n</i>	585	147	147	146	145	-	-
Age (year)	54.7 ± 12.9	51.5 ± 13.6	51.6 ± 13.6	56.5 ± 11.3	59.0 ± 11.6	34.779 <sup>1</sup>	< 0.001
Female	210 (35.9)	69 (46.9)	56 (38.1)	47 (32.2)	38 (26.2)	14.701 <sup>2</sup>	< 0.001
BMI (kg/m <sup>2</sup> )	25.3 ± 3.9	25.8 ± 4.1	25.3 ± 3.8	25.1 ± 3.7	24.8 ± 3.8	5.232 <sup>1</sup>	0.023
SBP (mmHg)	135 ± 19	137 ± 19	135 ± 20	135 ± 19	133 ± 17	4.081 <sup>1</sup>	0.044
DBP (mmHg)	83 ± 12	85 ± 10	84 ± 14	83 ± 13	81 ± 10	10.324 <sup>1</sup>	0.001
Diabetes duration (year)	5.0 (1.0-10.0)	3.0 (0.2-10.0)	4.0 (0.9-10.0)	6.0 (2.0-10.0)	8.0 (3.0-15.0)	5.638 <sup>3</sup>	< 0.001
Hypoglycemic drugs							
Insulin	265 (45.3)	55 (37.4)	64 (43.5)	58 (39.7)	88 (60.7)	12.757 <sup>2</sup>	< 0.001
Secretagogues	55 (9.4)	13 (8.8)	17 (11.6)	9 (6.2)	16 (11.0)	0.011 <sup>2</sup>	0.916
Metformin	302 (51.6)	88 (59.9)	77 (52.4)	80 (54.8)	57 (39.3)	10.213 <sup>2</sup>	0.001
TZDs	94 (16.1)	22 (15.0)	21 (14.3)	24 (16.4)	27 (18.6)	0.927 <sup>2</sup>	0.336
AGIs	21 (3.6)	5 (3.4)	6 (4.1)	4 (2.7)	6 (4.1)	0.015 <sup>2</sup>	0.901
DPP-4Is	82 (14.0)	19 (12.9)	21 (14.3)	23 (15.8)	19 (13.1)	0.025 <sup>2</sup>	0.874
SGLT-2Is	265 (45.3)	63 (42.9)	61 (41.5)	81 (55.5)	60 (41.4)	0.277 <sup>2</sup>	0.599
GLP-1RAs	156 (26.7)	41 (27.9)	41 (27.9)	44 (30.1)	30 (20.7)	1.383 <sup>2</sup>	0.240
Hypertension	235 (40.2)	54 (36.7)	63 (42.9)	62 (42.5)	56 (38.6)	0.087 <sup>2</sup>	0.768
Statins uses	141 (24.1)	27 (18.4)	32 (21.8)	46 (31.5)	36 (24.8)	3.404 <sup>2</sup>	0.065
ALT (U/L)	20 (14-31)	25 (14-41)	20 (14-31)	19 (15-28)	20 (13-28)	-2.395 <sup>3</sup>	0.017
ALB (g/L)	39.2 ± 4.0	39.0 ± 3.6	39.7 ± 4.1	39.3 ± 4.1	38.7 ± 4.3	0.738 <sup>1</sup>	0.391
TG (mmol/L)	1.65 (1.16-2.71)	1.95 (1.29-3.17)	1.60 (1.14-2.98)	1.65 (1.11-3.00)	1.48 (1.07-2.22)	-3.019 <sup>3</sup>	0.003
TC (mmol/L)	4.59 ± 1.27	4.70 ± 1.01	4.67 ± 1.44	4.46 ± 1.25	4.52 ± 1.32	2.500 <sup>1</sup>	0.114
UA (μmol/L)	323 ± 155	311 ± 100	337 ± 261	309 ± 89	333 ± 100	0.422 <sup>1</sup>	0.516
CysC (mg/L)	0.73 (0.57-0.92)	0.66 (0.52-0.83)	0.71 (0.54-0.90)	0.76 (0.63-0.94)	0.85 (0.66-1.03)	5.043 <sup>3</sup>	< 0.001
eGFR (mL/minute/1.73 m <sup>2</sup> )	113.23 ± 29.74	122.46 ± 33.15	116.43 ± 31.23	109.98 ± 24.00	103.68 ± 26.48	33.962 <sup>1</sup>	< 0.001
ACR (mg/g/cr)	15.3 (8.5-42.5)	13.4 (8.0-33.9)	21.8 (9.8-50.7)	15.6 (7.8-45.4)	13.5 (7.3-39.2)	0.012 <sup>3</sup>	0.990
Fasting C-peptide (ng/mL)	1.67 ± 1.15	1.75 ± 1.21	1.56 ± 0.96	1.70 ± 1.12	1.69 ± 1.30	0.007 <sup>1</sup>	0.934
Hemoglobin (g/L)	140 ± 18	138 ± 18	140 ± 19	142 ± 16	141 ± 17	2.633 <sup>1</sup>	0.105
HbA1c (%)	8.35 ± 1.56	8.03 ± 1.47	8.19 ± 1.66	8.38 ± 1.49	8.41 ± 1.60	5.197 <sup>1</sup>	0.023
Overall composite Z-score for latency	0.04 ± 0.66	-0.18 ± 0.56	0.01 ± 0.64	-0.01 ± 0.57	0.32 ± 0.77	38.996 <sup>1</sup>	< 0.001
Overall composite Z-score for amplitude	-0.03 ± 0.58	0.18 ± 0.49	0.06 ± 0.59	-0.09 ± 0.55	-0.27 ± 0.61	50.972 <sup>1</sup>	< 0.001
Overall composite Z-score for NCV	-0.03 ± 0.75	0.20 ± 0.64	-0.01 ± 0.77	0.01 ± 0.73	-0.31 ± 0.79	30.636 <sup>1</sup>	< 0.001

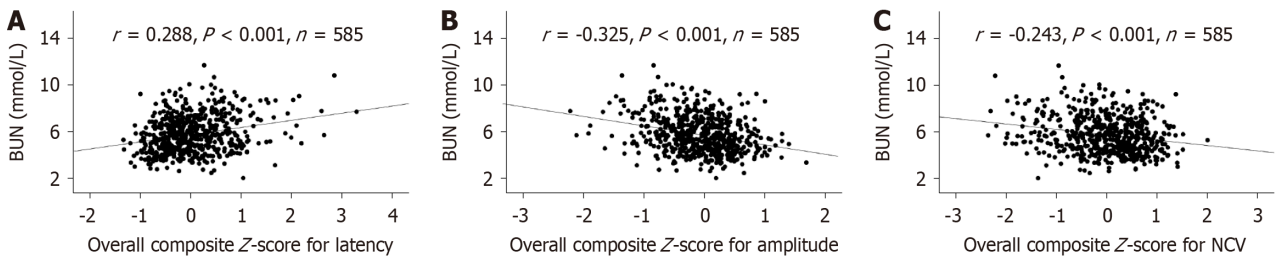
<sup>1</sup>Linear polynomial contrasts of analysis of variance (*F* value).

<sup>2</sup>Linear-by-linear association of  $\chi^2$  test ( $\chi^2$  value).

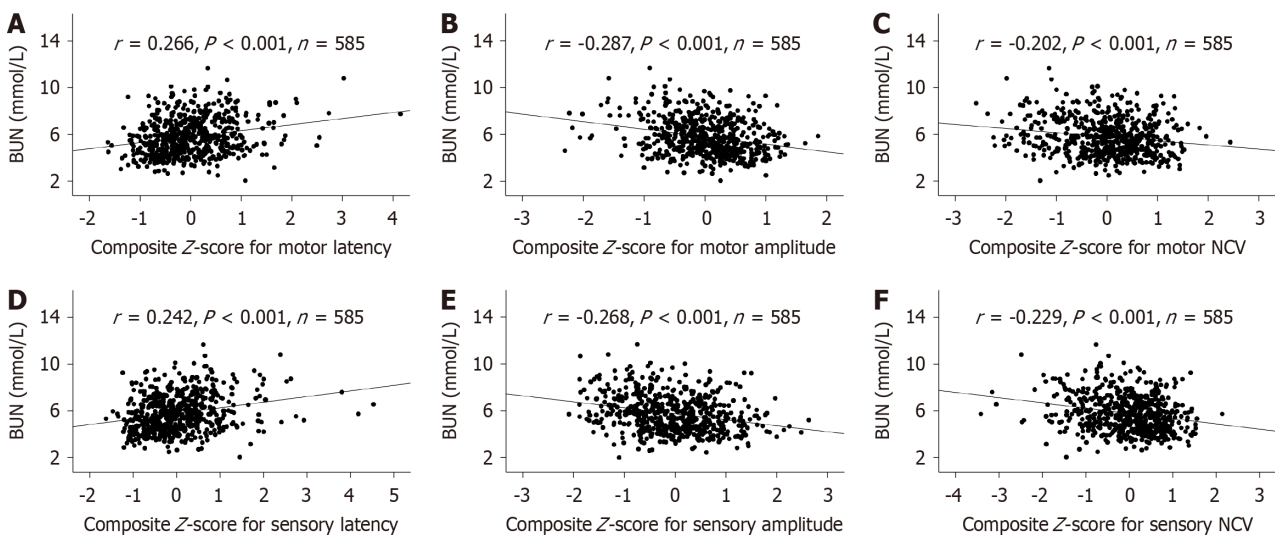
<sup>3</sup>Jonckheere-Terpstra test (*Z* value).

BUN: Blood urea nitrogen; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; TZDs: Thiazolidinediones; AGIs:  $\alpha$ -glucosidase inhibitors; DPP-4Is: Dipeptidyl peptidase-4 inhibitors; SGLT-2Is: Sodium-glucose cotransporter 2 inhibitors; GLP-1RAs: Glucagon-like peptide 1 receptor agonists; ALT: Alanine aminotransferase; ALB: Albumin; TG: Triglyceride; TC: Total cholesterol; UA: Uric acid; CysC: Cystatin C; eGFR:

Estimated glomerular filtration rate; ACR: Urinary albumin /creatinine ratio; HbA1c: Glycosylated hemoglobin A1c; NCV: Nerve conduction velocity.



**Figure 2 Graphical correlations between blood urea nitrogen levels and overall peripheral nerve functional indices.** Pearson's correlation coefficient (*r*) and the corresponding *P* value were based on total data (*n* = 585). A: Overall nerve latency; B: Overall nerve amplitude; C: Overall nerve conduction velocity (NCV). BUN: Blood urea nitrogen.



**Figure 3 Graphical correlations between blood urea nitrogen levels and functional indices of motor and sensory nerves.** Pearson's correlation coefficient (*r*) and the corresponding *P* value were based on total data (*n* = 585). A: Motor nerve latency; B: Motor nerve amplitude; C: Motor nerve conduction velocity (NCV); D: Sensory nerve latency; E: Sensory nerve amplitude; F: Sensory nerve NCV. BUN: Blood urea nitrogen.

independently linked to an increase in the overall composite Z-score for latency ( $\beta = 0.166, t = 3.864, P < 0.001$ ) and a decrease in the overall composite Z-scores for amplitude ( $\beta = -0.184, t = -4.577, P < 0.001$ ) and NCV ( $\beta = -0.117, t = -2.787, P = 0.006$ ; Table 3).

Moreover, when we further analyzed the correlations of BUN levels with the functions of different sensory and motor nerves, we found that elevated BUN levels remained independently associated with impaired peripheral sensory and motor nerve functional parameters (Tables 4 and 5).

## DISCUSSION

BUN, a routine biomarker used in the process of clinical diagnosis and treatment, was included in the database of our DPN clinical study, which included 585 patients with T2D and a normal to mildly reduced eGFR. Our key findings were as follows: (1) BUN levels correlated well with the latency, amplitude, and NCV of each peripheral nerve; (2) After standardization of nerve functional indices *via* Z-scores, higher BUN levels were positively correlated with the overall composite Z-score for latency and negatively correlated with the overall composite Z-scores for amplitude and NCV; (3) After adjusting for demographic data, glycemic control, eGFR, and other clinical variables, higher BUN levels independently contributed to higher overall composite Z-scores for latency and lower overall composite Z-scores for amplitude and NCV; and (4) When the analysis was restricted to sensory or motor nerves, higher BUN levels remained associated with peripheral sensory or motor nerve dysfunction. Elevated BUN levels may increase the risk of compromised peripheral nerve function in patients with T2D.

Table 2 Pearson's correlation analysis for associations between blood urea nitrogen levels and peripheral nerve functional indices

Item	BUN levels	
	<i>r</i>	<i>P</i> value
Motor nerves		
MN motor latency	0.163	< 0.001
MN motor amplitude	-0.191	< 0.001
MN motor NCV	-0.135	0.001
UN motor latency	0.222	< 0.001
UN motor amplitude	-0.196	< 0.001
UN motor NCV	-0.123	0.003
CPN motor latency	0.202	< 0.001
CPN motor amplitude	-0.187	< 0.001
CPN motor NCV	-0.194	< 0.001
PTN motor latency	0.213	< 0.001
PTN motor amplitude	-0.201	< 0.001
PTN motor NCV	-0.190	< 0.001
Composite Z-score for motor latency	0.266	< 0.001
Composite Z-score for motor amplitude	-0.287	< 0.001
Composite Z-score for motor NCV	-0.202	< 0.001
Sensory nerves		
MN sensory latency	0.139	< 0.001
MN sensory amplitude	-0.226	< 0.001
MN sensory NCV	-0.125	0.003
UN sensory latency	0.240	< 0.001
UN sensory amplitude	-0.271	< 0.001
UN sensory NCV	-0.228	< 0.001
SPN sensory latency	0.200	< 0.001
SPN sensory amplitude	-0.206	< 0.001
SPN sensory NCV	-0.190	< 0.001
SN sensory latency	0.215	< 0.001
SN sensory amplitude	-0.195	< 0.001
SN sensory NCV	-0.216	< 0.001
Composite Z-score for sensory latency	0.242	< 0.001
Composite Z-score for sensory amplitude	-0.268	< 0.001
Composite Z-score for sensory NCV	-0.229	< 0.001
Overall		
Overall composite Z-score for latency	0.288	< 0.001
Overall composite Z-score for amplitude	-0.325	< 0.001
Overall composite Z-score for NCV	-0.243	< 0.001

BUN: Blood urea nitrogen; NCV: Nerve conduction velocity; MN: Median nerve; UN: Ulnar nerve; CPN: Common peroneal nerve; PTN: Posterior tibial nerve; SPN: Superficial peroneal nerve; SN: Sural nerve.

**Table 3** Effects of blood urea nitrogen levels on overall peripheral nerve function according to multivariable linear regression analysis

Models	B (95%CI)	$\beta$	t	P value	R <sup>2</sup>
Overall composite Z-score for latency					
Model 0	0.117 (0.085, 0.148)	0.288	7.263	< 0.001	0.081
Model 1	0.056 (0.024, 0.088)	0.137	3.433	< 0.001	0.196
Model 2	0.071 (0.036, 0.106)	0.172	4.032	< 0.001	0.257
Model 3	0.069 (0.034, 0.104)	0.166	3.864	< 0.001	0.256
Overall composite Z-score for amplitude					
Model 0	-0.115 (-0.142, -0.088)	-0.325	-8.289	< 0.001	0.104
Model 1	-0.052 (-0.078, -0.025)	-0.142	-3.785	< 0.001	0.287
Model 2	-0.070 (-0.098, -0.041)	-0.193	-4.777	< 0.001	0.336
Model 3	-0.067 (-0.095, -0.038)	-0.184	-4.577	< 0.001	0.353
Overall composite Z-score for NCV					
Model 0	-0.112 (-0.148, -0.076)	-0.243	-6.055	< 0.001	0.058
Model 1	-0.041 (-0.078, -0.004)	-0.087	-2.170	0.030	0.188
Model 2	-0.060 (-0.098, -0.021)	-0.126	-3.023	0.003	0.285
Model 3	-0.055 (-0.094, -0.016)	-0.117	-2.787	0.006	0.289

Model 0: Unadjusted; Model 1: Adjusted for age, sex, diabetes duration, body mass index, systolic/diastolic blood pressure, hypertension and statin treatment; Model 2: Additionally adjusted for alanine aminotransferase, albumin, triglyceride, total cholesterol, uric acid, cystatin C, estimated glomerular filtration rate, albumin/creatinine ratio, C-peptide, hemoglobin and glycosylated hemoglobin A1c; Model 3: Additionally adjusted for hypoglycemic drugs. CI: Confidence interval; NCV: Nerve conduction velocity.

DPN develops as a result of the combined influence of multiple risk factors[21]. These risk factors include but are not limited to metabolic disorders of nutrients (glucose, lipids, and protein), CVD risk factors, and imbalances in immune and inflammatory factors[21]. An accurate indicator for measuring glycemic control is the time in range, which is derived from continuous glucose monitoring. Recent studies have indicated that a low time in range is independently linked to compromised peripheral nerve function in T2D patients[7]. Glycemic fluctuations are also risk factors for the pathogenesis of DPN. Xu *et al*[17] reported that lower levels of 1,5-anhydro-D-glucitol, a marker for short-term glycemic fluctuation, were significantly associated with compromised peripheral nerve function. Su *et al*[18] reported that HbA1c variability, which is indicative of long-term glycemic fluctuations, is strongly associated with the development of DPN. Additional risk factors, including smoking, hypertension, obesity, dyslipidemia, and insulin resistance status, and proinflammatory cytokines, such as C-reactive protein, tumor necrosis factor- $\alpha$ , and interleukin-6, may contribute to the progression of DPN[5]. In addition to the various risk factors associated with diabetes described above, poor nutritional status is also associated with the development of DPN. Previous studies have shown that low BMI, hypoalbuminemia status, and decreased hemoglobin levels (anemia) are potential risk factors for peripheral nerve injury[1,22,23]. In the present study, we identified elevated BUN levels as a potential risk factor for the development of DPN in T2D patients. Elevated BUN levels usually indicate a negative nitrogen balance due to a protein catabolic state, which may suggest impaired nutrition and a metabolic disorder. Our study revealed that BUN levels were positively correlated with neural latency and negatively correlated with neural amplitude and NCV, independent of eGFR, glycemic control, and other clinical covariates. Elevated BUN levels were found to be independently associated with compromised peripheral nerve function in patients with T2D. Future longitudinal studies are necessary to establish a causal relationship between increased BUN levels and impaired peripheral nerve function in this population, which may further elucidate the clinical implications of our findings.

In clinical practice, BUN levels are generally used to reflect the amount of nitrogen derived from the catabolism of proteins and amino acids and can be used to evaluate the equilibrium of nutrition and the homeostasis of protein metabolism in individuals with relatively normal renal function[9,24]. Notably, elevated BUN levels are indicative of a cluster of cardiovascular risk factors and reflect a constellation of metabolic dysfunctions. Higher BUN levels are reportedly related to adverse CVD outcomes across asymptomatic populations and individuals with chronic diseases. In the general population of American adults, increased BUN levels are linked to increased long-term mortality due to CVD and all-cause mortality[25]. In the prospective Dongfeng-Tongji cohort from China, elevated BUN levels were linked to an increased risk of incident coronary heart disease[26] as well as total and ischemic stroke[27]. Moreover, higher BUN levels independently predicted poor discharge outcomes and all-cause in-hospital mortality in patients with CVD, including congestive heart failure[28] and acute ischemic stroke[29]. Furthermore, elevated BUN levels in patients with metabolic diseases such as hyperlipidemia and diabetes were linked to a greater risk of all-cause and cardiovascular mortality[30, 31]. Additionally, higher BUN levels were not only shown to potentially predict T2D and gestational diabetes develop-

**Table 4 Effects of blood urea nitrogen levels on motor nerve function according to multivariable linear regression analysis**

Models	B (95%CI)	$\beta$	t	P value	R <sup>2</sup>
Composite Z score of motor latency					
Model 0	0.117 (0.082, 0.152)	0.266	6.651	< 0.001	0.069
Model 1	0.054 (0.019, 0.089)	0.122	3.056	0.002	0.197
Model 2	0.072 (0.034, 0.109)	0.160	3.772	< 0.001	0.266
Model 3	0.070 (0.032, 0.108)	0.155	3.623	< 0.001	0.262
Composite Z score of motor amplitude					
Model 0	-0.112 (-0.142, -0.081)	-0.287	-7.224	< 0.001	0.081
Model 1	-0.054 (-0.084, -0.023)	-0.135	-3.393	< 0.001	0.209
Model 2	-0.078 (-0.112, -0.044)	-0.193	-4.491	< 0.001	0.243
Model 3	-0.076 (-0.110, -0.042)	-0.188	-4.395	< 0.001	0.263
Composite Z score of motor NCV					
Model 0	-0.100 (-0.139, -0.060)	-0.202	-4.990	< 0.001	0.039
Model 1	-0.041 (-0.071, -0.011)	-0.060	-1.447	0.148	0.147
Model 2	-0.056 (-0.097, -0.014)	-0.110	-2.598	0.010	0.263
Model 3	-0.049 (-0.091, -0.007)	-0.098	-2.299	0.022	0.271

Model 0: Unadjusted; Model 1: Adjusted for age, sex, diabetes duration, body mass index, systolic/diastolic blood pressure, hypertension and statin treatment; Model 2: Additionally adjusted for alanine aminotransferase, albumin, triglyceride, total cholesterol, uric acid, cystatin C, estimated glomerular filtration rate, albumin/creatinine ratio, C-peptide, hemoglobin and glycosylated hemoglobin A1c; Model 3: Additionally adjusted for hypoglycemic drugs. CI: Confidence interval; NCV: Nerve conduction velocity.

ment[15,32] but were also linked to a greater risk of developing diabetes-related complications, including diabetic retinopathy[33] and peripheral arterial disease[34]. In the present study, we observed elevated BUN levels in elderly individuals and those with long-term diabetes, which were positively correlated with poor glycemic control, as indicated by increased HbA1c levels, and with kidney injury, as evidenced by elevated CysC and urinary ACR levels. Furthermore, our findings demonstrated that an elevated BUN level was independently linked to compromised peripheral nerve function in T2D patients. These findings suggest that interventions aimed at reducing BUN levels through the enhancement of nutritional status and the regulation of protein metabolism may mitigate peripheral nerve dysfunction in this patient population.

There may be potential mechanistic links between increased BUN levels and compromised peripheral nerve function in individuals with T2D. First, increased BUN levels may suggest the presence of a metabolic disorder. Amino acid catabolism, gluconeogenesis, and urea cycle activity are increased in T2D patients with a deficiency of insulin action and poor metabolic control[9]. In contrast, strict glycemic control by insulin therapy in individuals with diabetes may partially normalize nitrogen metabolism[24]. Therefore, increased BUN levels indicate poor glycemic control. Huang *et al*[35] revealed that increased BUN levels were well correlated with short-term and long-term glycemic variability. In the present study, BUN levels were inversely related to BMI and positively related to HbA1c. These metabolic disorders are strongly linked to peripheral nerve dysfunction in T2D. Second, increased BUN levels may be somewhat toxic to the nervous system[36]. Third, elevated BUN levels can impair pancreatic  $\beta$  cells, inhibit insulin secretion[37], and induce insulin resistance[10], adversely affecting peripheral nerve function in T2D patients. Fourth, increased BUN levels could cause arterial endothelial dysfunction[38], stimulate proatherogenic pathways, and promote senescence in endothelial progenitor cells[39], which subsequently could contribute to peripheral nerve dysfunction in patients with T2D. However, as these mechanisms are currently supported by indirect evidence, we propose that fundamental research be performed to elucidate the specific pathways through which BUN contributes to nerve damage in T2D patients.

Our study had several limitations. First, this was an observational study. Therefore, the causal relationship between increased BUN levels and impaired peripheral nerve function in T2D patients remains inconclusive, and cohort follow-up studies are needed for further clarification. Second, the present study was limited to T2D patients in a single center in China; therefore, the results may not be generalizable. Third, in this study, we identified a clinical correlation, but basic research is needed to investigate the role of high BUN levels in the progression of DPN. Fourth, we did not examine the association of BUN with the risk of DPN. In future studies, we will investigate the associations of BUN with the risk of DPN and the severity of DPN. During follow-up, we can explore the relationship between BUN and the incidence of DPN. Fifth, dietary protein intake, which could potentially influence BUN levels, was not assessed in our study. Sixth, the use of hypoglycemic drugs in the present study may influence peripheral nerve function. The recruitment of a large sample of drug-naïve patients is challenging in clinical practice.

**Table 5** Effects of blood urea nitrogen levels on sensory nerve function according to multivariable linear regression analysis

Models	B (95%CI)	$\beta$	t	P value	R <sup>2</sup>
Composite Z score of sensory latency					
Model 0	0.123 (0.083, 0.163)	0.242	6.023	< 0.001	0.057
Model 1	0.052 (0.012, 0.091)	0.102	2.586	0.010	0.216
Model 2	0.065 (0.022, 0.108)	0.127	2.972	0.003	0.252
Model 3	0.063 (0.019, 0.106)	0.123	2.845	0.005	0.252
Composite Z score of sensory amplitude					
Model 0	-0.141 (-0.182, -0.099)	-0.268	-6.698	< 0.001	0.070
Model 1	-0.056 (-0.095, -0.016)	-0.105	-2.763	0.006	0.269
Model 2	-0.080 (-0.122, -0.037)	-0.150	-3.668	< 0.001	0.319
Model 3	-0.076 (-0.118, -0.033)	-0.143	-3.495	< 0.001	0.331
Composite Z score of sensory NCV					
Model 0	-0.116 (-0.156, -0.076)	-0.229	-5.670	< 0.001	0.051
Model 1	-0.050 (-0.090, -0.010)	-0.099	-2.449	0.015	0.188
Model 2	-0.061 (-0.104, -0.018)	-0.120	-2.786	0.006	0.242
Model 3	-0.059 (-0.102, -0.015)	-0.116	-2.660	0.008	0.241

Model 0: Unadjusted; Model 1: Adjusted for age, sex, diabetes duration, body mass index, systolic/diastolic blood pressure, hypertension and statin treatment; Model 2: Additionally adjusted for alanine aminotransferase, albumin, triglyceride, total cholesterol, uric acid, cystatin C, estimated glomerular filtration rate, albumin/creatinine ratio, C-peptide, hemoglobin and glycosylated hemoglobin A1c; Model 3: Additionally adjusted for hypoglycemic drugs. CI: Confidence interval; NCV: Nerve conduction velocity.

## CONCLUSION

Increased BUN levels were independently associated with compromised peripheral nerve function in patients with T2D. Future clinical treatment strategies aimed at decreasing BUN levels by improving nutritional status and balancing protein metabolism may subsequently alleviate peripheral nerve dysfunction in patients with T2D.

## FOOTNOTES

**Author contributions:** Wang R and Xu YX contributed significantly to the study design, patient recruitment, collection of demographic data and medical history, biochemical and urinary indicator testing, electromyography for all participants, peripheral nerve function assessment, and statistical analysis for data interpretation; Wang R was responsible for drafting the initial manuscript and revising it in response to feedback from co-authors, peer reviewers, and editors; Xu F, Wang CH, Zhao LH, and Wang LH assisted in the collection of demographic data and medical history as well as the analysis of biochemical and urinary indicators; Wang LH also contributed to securing funding and interpreting the study's findings; Chen WG contributed to the study design and conducted a critical review of the manuscript; Wang XQ was responsible for reviewing the manuscript and overseeing the study process; All authors participated in the review and approval of the final version of the manuscript; Su JB initiated a series of studies on diabetic peripheral neuropathy. The conceptualization and design of the current study's protocol were collaboratively undertaken by Duan CW and Su JB, who also assumed responsibility for securing funding, data interpretation, manuscript review, and overall study supervision, thereby qualifying as the co-corresponding authors of this manuscript.

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**Informed consent statement:** All participants provided informed consent to take part in the study.

**Conflict-of-interest statement:** All the authors report no relevant conflicts of interest for this article.

**Data sharing statement:** It is reasonable to request that the principal investigators make the data available for this study at [sujbjzx@163.com](mailto:sujbjzx@163.com).

**STROBE statement:** The authors have reviewed the STROBE Statement checklist and have prepared and revised the manuscript in accordance with its guidelines.

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