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Observational Study

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

Wang R *et al.* BUN and peripheral nerve function.

Rui Wang, Yu-xian Xu, Feng Xu, Chun-hua Wang, Li-hua Zhao, Li-Hua Wang, Wei-Guan Chen, Xue-Qin Wang, Cheng-wei Duan, Jian-bin Su

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 (eGFR) 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 eGFR 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 type 2 diabetes.

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

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 indicate that increased BUN levels are independently associated with compromised peripheral nerve function in patients with type 2 diabetes (T2D) 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 T2D.

INTRODUCTION

Diabetic peripheral neuropathy (DPN) represents a prevalent and debilitating complication among individuals with type 2 diabetes (T2D)[1], 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. 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[10,11,12] 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 (GDM) 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 type 2 diabetes (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.

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 ADA[19]; (2) aged 20–75 years; (3) estimated glomerular filtration rate (eGFR) > 60 mL/min/1.73 m²; 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, 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 B12 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 (SBP/DBP)), course of diabetes, medication prescriptions (such as statins and hypoglycemic drugs), and biochemical indicators, was collected. Body mass index (BMI) was also calculated (kg/m²).

After an 8-hour fast, peripheral venous blood samples were collected to measure the levels of BUN, alanine aminotransferase (ALT), albumin (ALB), triglyceride (TG), total cholesterol (TC), 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 (UACR) 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

Electromyography (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 (CPN), posterior tibial (PTN), superficial peroneal (SPN), and sural (SN) nerves.

After standardization of the functional data related to motor and sensory nerves using Z-scores, overall composite Z-scores for latency, amplitude, and nerve conduction velocity (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, CPN, and PTN) as well as the composite Z-scores for sensory nerves (MN, UN, SPN, and SN).

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 are 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 ANOVA with linear polynomial contrasts, the Jonckheere-Terpstra test, or the χ^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, SBP, DBP, ALT, TG 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, TC, UA, hemoglobin, 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 nerve conduction velocity (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 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, and 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. (4) Finally, 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.

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), cardiovascular disease (CVD) risk factors, and imbalances in immune and inflammatory factors[21]. An accurate indicator for measuring glycemic control is the time in range (TIR), which is derived from continuous glucose monitoring (CGM). Recent studies have indicated that a low TIR 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, TNF- α , and IL-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 cardiovascular disease 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 (DFTJ) 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 predict 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 are 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 GDM development[15, 32] but were also linked to a greater risk of developing diabetes-related complications, including diabetic retinopathy[33] and peripheral arterial disease (PAD)[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- 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 β 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 has 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, and 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-naive patients is challenging in clinical practice.

CONCLUSION

In summary, 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.

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