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Assessing the diagnostic utility of urinary albumin-to-creatinine ratio as a potential biomarker for diabetic peripheral neuropathy in type 2 diabetes mellitus patients

Hui Zhang^{1,7}, Shufang Yang^{2,3,7}, Hongxiao Wang^{4,7},
Huzaifa Fareeduddin Mohammed Farooqui³, Wenwen Zhu³, Tong Niu³, Zhen Zhang⁵,
Yang Chen⁵, Ling Huang⁵, Ya Zhang⁵, Mengting He⁵, Bing Song⁴✉, Songtao Feng⁶✉ &
Haoqiang Zhang⁵✉

Background and aims Diabetic peripheral neuropathy (DPN) and diabetic nephropathy (DN) both have microcirculation dysfunction. Urinary albumin-to-creatinine ratio (UACR) is a biomarker for DN. We aimed to explore the links between DPN and UACR in patients with type 2 diabetes mellitus (T2DM). **Methods** A total of 195 T2DM patients were defined as Control or DPN group. Clinical parameters were compared, and the association between HbA1c (or UACR) and DPN was analyzed. Risk factors for DPN were observed, and the diagnostic values of HbA1c and UACR were assessed.

Results Compared with 104 participants without DPN, 91 individuals with DPN exhibited higher HbA1c and UACR levels. In all patients, increased HbA1c and UACR were identified as risk factors for DPN in individuals with T2DM. Moreover, increased HbA1c was a risk factor for DPN in volunteers without DN, whereas elevated UACR was determined as a risk factor for DPN in participants with DN. The cut-off point for HbA1c (7.65%) in patients without DN had a sensitivity of 86.0% and specificity of 44.6%, while the cut-off point for UACR (196.081 mg/g) in patients with DN had a sensitivity of 52.9% and specificity of 76.2%.

Conclusion Elevated HbA1c and UACR levels are risk factors for DPN and may serve as potential biomarkers for DPN in T2DM patients.

Keywords Type 2 diabetes mellitus, Diabetic peripheral neuropathy, Urinary albumin-to-creatinine ratio

The rising prevalence of diabetes and its complications¹, such as diabetic peripheral neuropathy (DPN), significantly impact the quality of life for patients with diabetes². While some individuals experience severe clinical symptoms of painful neuropathy, many diabetic patients only exhibit mild or even no symptoms³. Due to the unclear mechanism and concealed onset of DPN, early diagnosis still requires extensive development to meet clinical practice needs.

Various factors contribute significantly to the occurrence and progression of DPN. These factors include metabolic disorders⁴, insulin resistance⁵, oxidative stress^{6,7}, neuroinflammation^{8,9}, nerve demyelination¹⁰, lack of neurotrophic factors¹¹, and vascular factors¹². Our previous research has revealed that uncontrolled plasma

¹Luoyang Key Laboratory of Clinical Multiomics and Translational Medicine, Henan Key Laboratory of Rare Diseases, Endocrinology and Metabolism Center, The First Affiliated Hospital, and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, China. ²Department of Endocrinology, The Affiliated Taizhou People's Hospital of Nanjing Medical University, Taizhou, China. ³Department of Endocrinology, Affiliated Zhongda Hospital of Southeast University, Nanjing, China. ⁴Department of Endocrinology, The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, China. ⁵Department of Endocrinology, Institute of Endocrine and Metabolic Diseases, Centre for Leading Medicine and Advanced Technologies of IHM, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, China. ⁶Department of Nephrology, Jiangsu University Affiliated People's Hospital, Zhenjiang, China. ⁷Hui Zhang, Shufang Yang and Hongxiao Wang contributed equally to this work. ✉email: songbing1978@163.com; fengsongtao@126.com; drhqzhang@ustc.edu.cn

glucose levels may mediate the effect of increased low-density lipoprotein cholesterol (LDL-C) upon DPN in individuals with type 2 diabetes mellitus (T2DM)¹³. Additionally, uric acid, plays a crucial role in enhancing the body's antioxidant capacity to combat oxidative stress¹⁴. Another study conducted by our team demonstrated that low levels of serum uric acid (SUA) increase the risk of DPN, particularly affecting the functionality of the nerve conduction velocity of tibial nerve motor fiber independently of glycosylated hemoglobin (HbA1c) levels in patients with T2DM¹⁵.

Vascular lesions, especially macrovascular ones, combined with nerve pathology contribute to the symptoms experienced by patients with T2DM and DPN. However, limited study focused on the link between microvascular pathology and DPN. A population-based study revealed that DPN and diabetic microvascular lesions, which include both diabetic retinopathy and diabetic nephropathy (DN), share similar risk factors¹⁶. Furthermore, it was suggested that DPN and DN not only exhibit distinct characteristics but also share common pathogenic mechanisms¹⁷. Moreover, increased levels of urinary albumin-to-creatinine ratio (UACR) serve as a biomarker for DN. The information above indicates a possible association between DPN and UACR in diabetic individuals.

In this current study, our primary objective is to investigate the potential associations between DPN and plasma glucose (or UACR) in individuals with T2DM. Additionally, we aim to observe the risk factors for DPN in these volunteers. Furthermore, we have divided the patients into subgroups based on the absence or presence of DN to observe the diagnostic values of HbA1c (or UACR) for DPN in participants with T2DM.

Methods

Study design and ethics approval

This present cross-sectional research was performed at The First Affiliated Hospital of USTC. A total of 195 patients were recruited, all of whom met the criteria for T2DM. Among these volunteers, 91 were diagnosed with DPN, while 104 patients were without DPN. Before their participation of this research, all volunteers were informed about the cross-sectional study procedures, and they provided their informed consent by signing the necessary documents. Research involving human research participants were performed in accordance with the Declaration of Helsinki. The Ethics Committee in the first affiliated hospital of USTC approved this research (2023-RE-013).

Inclusion and exclusion criteria

Every patient included in the research met the standard for T2DM of the World Health Organization¹⁸. Decreased eGFR levels have been linked to DPN¹⁹. Therefore, T2DM participants with a value of eGFR > 45 ml/min/1.73 m² were enrolled in this study. The exclusion standards were described as follows: (a) other types of diabetes except for T2DM; (b) diabetic volunteers with values of eGFR ≤ 45 ml/min/1.73 m²; (c) diabetes with acute complications (including diabetic ketoacidosis, lactic acidosis, and Diabetes hyperglycemia hyperosmolar state); (d) severe hypoglycemia; (e) neuropathy caused by other reason (including disease, injury or drugs); (f) serious cardiovascular disease and cerebrovascular disease; (g) other vascular disease; (h) venous embolism, lymphangitis; (i) the usage of neurotoxicity drugs; (j) any amputation; (k) thyroid function disorder; (l) smoking and drinking; (m) any other undefined factors may affect neurophysiological performance.

Groups

The diagnosis of DPN relies on the Toronto Consensus criteria². The definition of confirmed DPN was used in this research. Patients with T2DM but without DPN were assigned to the control group, whereas diabetic volunteers diagnosed as DPN were categorized into the DPN group.

Clinical data collection

Age, gender, systolic pressure, diastolic pressure and duration of diabetes and hypertension were collected. Body mass index (BMI) were calculated with recorded information of height and weight by weight (kg)/height (m)². Indexes from blood were also isolated from the medical records. The above information including fasting plasma glucose (FPG), HbA1c, total cholesterol (TC), LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG). Serum creatinine (Scr) was used to evaluate the glomerular filtration rate (eGFR), while fasting serum C-peptide (FCP) was used to get HOMA-IR. The data of uric Albumin and creatinine were used to calculate UACR.

Neurophysiological data

The results of conduction velocity of nerve fiber were extracted from the medical records of recruited patients. The aforementioned neurophysiological tests were performed in our Electrophysiology chamber by skilled staff by the equipment named electromyographic evoked potential meter (Natus Neurology, USA). The average velocities of both nerves on each side were utilized for analysis.

Sample size calculation

The suitable minimum sample size for this current study was evaluated using PASS software (version 11.0.7). After completing the participant enrollment process, the minimum sample size was estimated based on the mean and standard deviation of UACR levels. Assuming a 1:1 ratio between the control group and the DPN group, the minimum participant number for each group was determined to be 86.

Statistical methods

In this study, the data was analyzed by IBM SPSS Statistics (26.0 Version). Systolic pressure, diastolic pressure, LDL-C, nerve conduction velocities of median and tibial nerve motor fibers, as well as ulnar nerve, radial nerve, and sural nerve sensory fibers conduction velocities are normal distribution variables. Mean ± standard deviation

was used to describe these data. The difference of these information between the 2 groups were compared using Student's t-tests. Median and interquartile range were used to describe the data of age, BMI, duration of DM and HBP, HbA1c, HOMA-IR, eGFR, TG, TC, HDL-C, UACR, and ulnar nerve, radial nerve and common peroneal nerve motor fibers conduction velocities, as well as median nerve sensory fibers conduction velocity for they are symmetrically distributed variables. The difference of these data between patients with and without DPN were analyzed by nonparametric Mann-Whitney U tests. Gender information of diabetic participants with or without DPN were binary variables and described as numbers and percentages. The differences in these 2 groups were analyzed by the χ^2 test. The associations between HbA1c (or UACR) and nerve conduction velocities were analyzed by Pearson correlations and partial correlations. The risk factors of DPN in diabetic individuals were demonstrated by the analysis of binary logistic regression. Factors influencing the nerve conduction velocities of T2DM patients were observed by using the analysis of multiple linear regression. Finally, the diagnosis cut-off point and diagnosis values were also evaluated by ROC curve. The statistical significance was defined as $P < 0.05$.

Results

Comparison between clinical information of T2DM individuals in control group and DPN group

In Table 1, we have summarized the clinical information of all the enrolled diabetic participants. In order to observe their differences, the clinical data between patients in the DPN group and control group were compared. Age, gender, BMI, duration of DM and HBP, diastolic pressure, HOMA-IR, eGFR, TG, LDL-C, HDL-C, and TC did not show any statistically significant differences in the 2 groups (all $P > 0.05$). However, T2DM individuals with DPN exhibited increased levels of HbA1c and UACR, as well as increased systolic pressure, compared to those patients did not diagnosed with DPN (all $P < 0.05$).

	Control group (n = 104)	DPN group (n = 91)	p
Age (years)	50.25 (57.00–64.75)	58.00 (52.00–68.00)	0.962 ^b
Female (n, %)	38, 36.54	37, 40.66	0.555 ^c
BMI (m ² /kg)	24.56 (22.49–26.34)	24.86 (21.84–27.91)	0.947 ^b
Duration of DM (years)	7.00 (3.00–11.75)	10.00 (3.00–15.00)	0.102 ^b
Duration of HBP (years)	0.05 (0.00–10.00)	0.00 (0.00–7.00)	0.103 ^b
Systolic pressure	129.60 ± 15.56	135.42 ± 19.57	0.024 ^{a*}
Diastolic pressure	80.65 ± 9.37	83.47 ± 12.04	0.073 ^a
HbA1c (%)	8.45 (6.92–9.68)	9.80 (8.50–11.80)	0.001 ^{b*}
HOMA-IR	0.15 (0.08–0.24)	0.12 (0.08–0.25)	0.427 ^b
eGFR	99.10 (87.05–108.34)	100.42 (90.53–111.50)	0.723 ^b
TG (mmol/l)	1.74 (1.24–2.25)	1.42 (1.02–2.31)	0.427 ^b
TC (mmol/l)	4.54 (3.75–5.06)	4.59 (3.90–5.23)	0.625 ^b
HDL-C (mmol/l)	0.95 (0.74–1.17)	0.93 (0.79–1.15)	0.811 ^b
LDL-C (mmol/l)	2.50 ± 0.87	2.68 ± 0.95	0.150 ^a
UACR (mg/g)	12.70 (7.18–22.02)	18.70 (11.46–65.93)	0.008 ^{b*}
Motor conduction			
Ulnar nerve (m/s)	59.35 (53–78–63.00)	57.00 (52.80–61.00)	0.000 ^{b*}
Radial nerve (m/s)	64.30 (62.66–66.15)	63.80 (61.50–65.85)	0.002 ^{b*}
Median nerve (m/s)	58.09 ± 4.00	52.82 ± 4.67	0.000 ^{a*}
Tibial nerve (m/s)	46.29 ± 3.96	41.63 ± 3.66	0.000 ^{a*}
Common peroneal nerve (m/s)	45.98 (43.41–48.34)	43.90 (41.00–45.95)	0.000 ^{b*}
Sensory conduction			
Ulnar nerve (m/s)	56.29 ± 5.03	50.12 ± 6.34	0.000 ^{a*}
Radial nerve (m/s)	58.05 ± 7.17	52.65 ± 7.11	0.000 ^{a*}
Median nerve (m/s)	58.88 (55.41–62.53)	48.35 (43.10–54.00)	0.000 ^{b*}
Sural nerve (m/s)	52.09 ± 5.36	46.06 ± 6.32	0.000 ^{a*}

Table 1. Comparison of clinical parameters and neurophysiological test results between control and DPN group. a Student's t test was employed for normally distributed variables. b The Mann-Whitney U test was employed for asymmetrically distributed variables. c The Chi-square test was employed for categorical variables. * $P < 0.05$. Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; DM, diabetes mellitus; HBP, high blood pressure, HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment-insulin resistance; eGFR, estimated glomerular filtration rate; TG, triglycerides; TC, Total cholesterol; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Ucr, uric creatinine; UACR, urinary albumin-to-creatinine ratio.

Comparison between nerve conduction velocity of T2DM patients with or without DPN

To confirm the diagnosis of DPN in participants with T2DM, the neurophysiological examination was performed to assess the nerve conduction of the participants. The study observed lower nerve conduction velocities in patients with DPN for all motor fibers, including ulnar, radial, median, and tibial nerves, as well as all sensory nerves, encompassing ulnar, radial, median, and sural fibers, compared to those patients did not diagnosed with DPN (all $P < 0.05$).

Association between HbA1c levels and nerve conduction velocity

To investigate the links between HbA1c and nerve conduction velocity in T2DM patients, Pearson association analysis was performed. The results revealed significant associations between HbA1c levels and ulnar, median, tibial, and common peroneal nerves motor fibers, as well as ulnar, radial, median, and sural nerves sensory fibers conduction velocities (all $P < 0.05$). To further account for the differences in systolic pressure and UACR between these 2 groups, partial correlation was performed to examine the relationship between HbA1c and nerve conduction velocity. These findings showed that even after adjusting for systolic pressure and UACR, there were still significant associations between HbA1c levels and the mentioned motor and sensory nerve fibers conduction velocities (all $P < 0.05$) (see Table 2).

Association between nerve conduction velocity and UACR levels

To investigate the correlation between UACR and nerve conduction velocity of individuals diagnosed with T2DM, the Pearson correlation analysis was performed. The results revealed significant correlations between UACR levels and the motor fibers conduction velocities of ulnar, median, tibial, and common peroneal nerves, as well as the sensory fibers' conduction velocities of ulnar, median, and sural nerves (all $P < 0.05$). Moreover, to explore the variations in systolic pressure and HbA1c level between T2DM volunteers with or without DPN, a partial correlation analysis between HbA1c level and nerve conduction velocity was also performed. The findings indicated that UACR levels remained significantly linked to the conduction velocities of ulnar, median, tibial, and common peroneal nerves' motor fibers, as well as ulnar, median, and sural nerves' sensory fibers, even after adjusting for systolic pressure and HbA1c (all $P < 0.05$) (Table 3).

Risk factors for DPN in patients with T2DM

To assess the risk factors for DPN in T2DM individuals, a binary logistic regression was carried out. Among all patients, elevated HbA1c ($P = 0.000$, OR = 1.329) and increased UACR ($P = 0.040$, OR = 1.003) were identified as risk factors for DPN in diabetic participants, alongside systolic pressure, HbA1c, and UACR as predictor variables (Table 4). Further subgroup analysis involved dividing the patients into two groups: those with DN and those without DN. In patients without DN, elevated HbA1c emerged as one of the risk factors for DPN in T2DM individuals independent from systolic pressure and UACR ($P = 0.001$, OR = 1.361). However, in patients with DN, increased UACR was identified as one of the risk factors for DPN in participants with diabetes ($P = 0.042$, OR = 1.004) (Table 5).

Diagnosis values of HbA1c for DPN in patients without DN and UACR for PDN in patients without DN

Elevated HbA1c was identified as one of the risk factors for DPN in patients without DN. On the other hand, increased UACR was found to be as one of the risk factors for DPN in patients with DN. The diagnostic values for HbA1c and UACR in relation to DPN were determined using ROC curves. In patients without DN, the ROC curve analysis revealed a cut-off point of 7.65% for HbA1c, achieving a sensitivity of 86.0% and a specificity of

	Model 1		Model 2	
	R	P	R	P
Motor conduction				
Ulnar nerve	-0.150	0.037*	-0.122	0.092*
Radial nerve	-0.061	0.397	-0.052	0.476
Median nerve	-0.307	0.000*	-0.286	0.000*
Tibial nerve	-0.361	0.000*	-0.341	0.000*
Common peroneal nerve	-0.383	0.000*	-0.363	0.000*
Sensory conduction				
Ulnar nerve	-0.233	0.001*	-0.209	0.004*
Radial nerve	-0.277	0.000*	-0.262	0.000*
Median nerve	-0.205	0.004*	-0.174	0.016*
Sural nerve	-0.306	0.000*	-0.283	0.000*

Table 2. Correlation between HbA1c and nerve conduction velocity. Model 1 showed Pearson association between HbA1c and nerve conduction velocity in patients with T2DM. Model 2 showed partial association between HbA1c and nerve conduction velocity in patients with T2DM adjusting for UACR and systolic pressure. * $P < 0.05$. Abbreviations: HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus; UACR, urinary albumin-to-creatinine ratio.

	Model 1		Model 2	
	R	P	R	P
Motor conduction				
Ulnar nerve	-0.280	0.000*	-0.262	0.000*
Radial nerve	-0.041	0.565	-0.003	0.964
Median nerve	-0.248	0.000*	-0.201	0.005*
Tibial nerve	-0.251	0.000*	-0.196	0.006*
Common peroneal nerve	-0.362	0.000*	-0.324	0.000*
Sensory conduction				
Ulnar nerve	-0.209	0.003*	-0.144	0.046*
Radial nerve	-0.122	0.090	-0.036	0.662
Median nerve	-0.269	0.000*	-0.197	0.006*
Sural nerve	-0.257	0.000*	-0.196	0.006*

Table 3. Correlation between UACR and nerve conduction velocity. Model 1 showed Pearson association between UACR and nerve conduction velocity in patients with T2DM; Model 2 showed partial association between UACR and nerve conduction velocity in patients with T2DM adjusting for HbA1c and systolic pressure. * $P < 0.05$. Abbreviations: UACR, urinary albumin-to-creatinine ratio; HbA1c, glycosylated hemoglobin; T2DM, type 2 diabetes mellitus.

	p	OR	95% CI of OR	
Systolic pressure	0.347	1.009	0.991	1.027
HbA1c	0.000*	1.329	1.147	1.540
UACR	0.040*	1.003	1.000	1.006

Table 4. Binary logistic regression analysis for risk factors of DPN in T2DM patients. * $P < 0.05$. Abbreviations: DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus; HbA1c, glycosylated hemoglobin; UACR, urinary albumin-to-creatinine ratio.

	p	OR	95% CI of OR	
Without DN				
Systolic pressure	0.152	1.015	0.994	1.037
HbA1c	0.001*	1.361	1.140	1.626
UACR	0.085	1.050	0.993	1.110
With DN				
Systolic pressure	0.370	0.981	0.940	1.023
HbA1c	0.102	1.247	0.957	1.625
UACR	0.042*	1.004	1.000	1.007

Table 5. Binary logistic regression analysis for risk factors of DPN in T2DM patients. * $P < 0.05$. Abbreviations: DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus; DN, diabetic nephropathy; HbA1c, glycosylated hemoglobin; UACR, urinary albumin-to-creatinine ratio.

44.6% (Fig. 1A). Similarly, in patients with DN, the ROC curve analysis indicated a cut-off point of 196.081 mg/g for UACR, resulting in a sensitivity of 52.9% and a specificity of 76.2% (Fig. 1B).

Discussion

DPN is one of the main significant complications that impact the quality of life for diabetic patients². Although it primarily involves neuronal injury, microvascular disorders also play a crucial role in its onset and progression²⁰. Therefore, urinary albumin was primarily analyzed since it results from DN, which represents a microvascular dysfunction.

Like many other diabetic complications, plasma glucose control can influence the occurrence and development of DPN²¹. In the current study, we detected higher HbA1c levels in individuals with DPN than those patients did not diagnosed with DPN, consistent with our last published research findings¹⁵. These studies have shown that poorly controlled plasma glucose is not only correlated to peripheral neuropathy in individuals with T2DM²² but also in those with type 1 diabetes²³. In fact, our recently published research has demonstrated a clear link

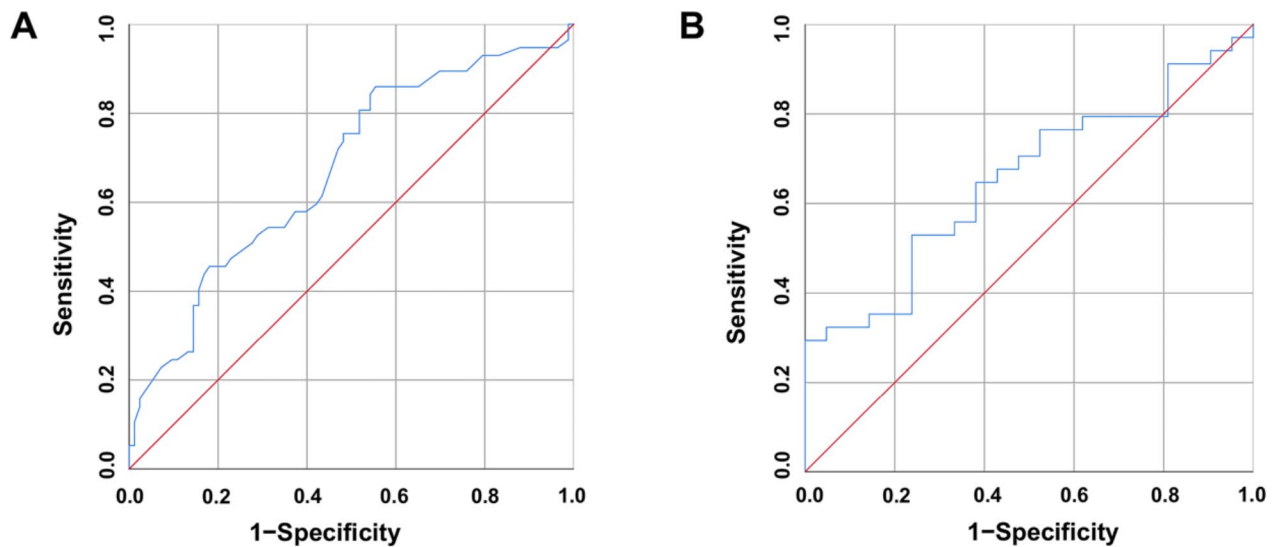


Fig. 1. ROC curve of HbA1c and UACR for the sensitivity and specificity of DPN in patients with T2DM (A) Showed the ROC curve of HbA1c for the sensitivity and specificity of DPN in T2DM patients without DN; the AUC is 0.673; The cut-off point for HbA1c (7.65%) achieved a sensitivity of 86.0% with a specificity of 44.6% in patients without DN. (B) Showed the ROC curve of UACR for the sensitivity and specificity of DPN in T2DM patients with DN; the AUC 0.654; The cut-off point for UACR (196.081 mg/g) yielded a sensitivity of 52.9% with a specificity of 76.2% in patients with DN. Abbreviations: ROC, receiver operating characteristic; HbA1c, glycosylated hemoglobin; UACR, urinary albumin-to-creatinine ratio; DPN, diabetic peripheral neuropathy; T2DM, type 2 diabetes mellitus; DN, diabetic nephropathy.

between uncontrolled HbA1c levels and DPN in T2DM individuals. Furthermore, HbA1c also appears to play a role in the impact of LDL-C upon conduction velocity of nerves in T2DM patients¹³. In addition to plasma glucose control, we also observed increased systolic blood pressure in T2DM individuals with DPN, compared to those patients did not diagnosed with DPN. This finding is consistent with a recent published research, which suggested that DPN is correlated to elevated systolic blood pressure in Chinese Han adults with T2DM²⁴.

For the main focus of this study, it was observed that T2DM patients with DPN exhibited elevated UACR levels, compared to those diabetic patients did not diagnosed with DPN. Interestingly, a previous study suggested that even mildly abnormal albuminuria serves as a warning sign for DPN in T2DM patients²⁵. Furthermore, a recent retrospective cohort research showed that changes in UACR are among the risk factors for DPN in T2DM patients²⁶.

The above information indicates that elevated HbA1c, systolic pressure, and UACR may play their roles in the occurrence of DPN in individuals diagnosed with T2DM, acting as risk factors. Therefore, we performed a binary logistic regression, and surprisingly, we discovered that increased HbA1c and UACR are indeed risk factors for DPN in T2DM patients. Moreover, an in-depth correlation analysis corroborates this finding. It demonstrates that HbA1c levels are linked to ulnar, median, tibial, and common peroneal nerves motor fiber, as well as ulnar, radial, median, and rural nerves sensory fiber conduction velocities—both with or without adjusting for UACR and systolic pressure. Similarly, UACR levels are associated with motor fiber conduction velocities of the ulnar, median, tibial, and common peroneal nerves, as well as sensory fiber conduction velocities of the ulnar, median, and rural nerves—again with or without adjusting for HbA1c and systolic pressure.

As one of the most important characteristics of DN, the elevated level of UACR was further analyzed in subgroups. Based on the presence or absence of DN, all individuals were divided into two groups. Interestingly, the results showed that only an increased HbA1c is one of the risk factors for DPN in patients did not diagnosed with DN. However, elevated UACR is the sole risk factor for DPN in diabetic patients diagnosed with DN. These findings are consistent with a previous study that suggested higher UACR might be correlated to the risk for DPN, even normal or mildly abnormal UACR levels were found to be one of the predictive factors for DPN²⁵. Additionally, a retrospective cohort study indicated that change in UACR is one of the risk factors for the occurrence DPN in participants with T2DM²⁶. Considering the above results, the diagnostic utility of UACR for DPN in T2DM patients with DN and HbA1c for patients without DN was evaluated. The cut-off point for UACR (196.081 mg/g) yielded a sensitivity of 52.9% with a specificity of 76.2% in patients with DN, whereas HbA1c (7.65%) in patients without DN achieved a sensitivity of 86.0% with a specificity of 44.6%.

Generally, previous researches mainly focused on elucidating the risk factors for DPN in diabetic individuals. However, our research extends beyond that by investigating the risk factors for DPN in all T2DM individuals. Moreover, we have determined that HbA1c serves as one of the risk factors for DPN in diabetic patients without DN, while UACR is one of the risk factors for DPN in diabetic patients with DN. While numerous earlier studies have reported the relationship between UACR (or HbA1c) and DPN, as well as the diagnostic value of UACR for

DPN in all diabetic patients^{27–30}, our research stands out as the first to assess the diagnostic value of HbA1c and UACR separately in T2DM patients without DN and with DN, respectively.

Despite the novel findings in this study, several limitations still need to be addressed. Firstly, it is essential to note that this study is cross-sectional and is based on small sample size, allowing us to establish only the association rather than the causal relationship between HbA1c (or UACR) and DPN. Although we utilized ROC curves in subgroup analyses to evaluate the diagnostic value of UACR and HbA1c in patients with and without diabetic nephropathy and calculated the optimal diagnostic cut-off points using the Youden index in our analysis. However, as a single-center, small-sample cross-sectional study, we must acknowledge that there is still a gap between our findings and clinical practice. Larger, multi-center studies are needed to further investigate our findings. To avoid exaggerating our research conclusions, we described UACR and HbA1c as “potential biomarkers” rather than “biomarkers” in this study. Secondly, we excluded smokers from this study, as previous research has shown a significant effect of smoking upon neuropathy in patients with diabetes³¹. Likewise, we also excluded patients with alcohol abuse from the current research, as there may be a relationship between drinking and DPN^{32,33}. However, we did not consider individuals exposure to tobacco directly, as research suggests that second-hand smoke may also affect the nervous system of human³⁴. Thirdly, Thirdly, we must pay attention to the effect of blood pressure on DPN²⁴, and therefore, in this study, we considered the duration of hypertension and systolic blood pressure. Nevertheless, incorporating more details, such as ambulatory blood pressure monitoring, may be a better choice.

Conclusion

In conclusion, elevated levels of HbA1c and UACR represent risk factors for DPN in individuals without DN and with DN, respectively. Furthermore, these markers may also serve as potential biomarkers for DPN in individuals diagnosed with T2DM. The primary focus of this study centers on the analysis of the correlation between DPN and various risk factors in individuals from diverse demographics. For non-DN patients, uncontrol plasma glucose may be associated with DPN. Conversely, in T2DM patients with DN, increased UACR levels may be linked to the occurrence of DPN. While this investigation assessed the diagnostic potential of HbA1c and the UACR in DPN, it is imperative to emphasize that their utilization as diagnostic biomarkers is contingent upon further evaluation through large-scale studies to ascertain their precise diagnostic value and applicability in clinical diagnoses. Additionally, aside from describing the potential diagnostic value of UACR and HbA1c, our study also suggests that for patients with T2DM without DN, DPN may be related to poor plasma glucose control. However, for patients with both T2DM and DN, merely controlling plasma glucose may not prevent the occurrence of DPN. In these patients, an elevated UACR, rather than HbA1c, is an independent risk factor for DPN.

Data availability

All data in this manuscript have been submitted to The First Affiliated Hospital of USTC for records. Additionally, all ID of recruited patients were also collected for further using. All data are available on reasonable request from corresponding authors.

Received: 5 September 2023; Accepted: 4 November 2024

Published online: 08 November 2024

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Acknowledgements

We are grateful to all staffs and participants involved in the study.

Author contributions

All authors made a significant contribution to the work reported. Haoqiang Zhang, Songtao Feng, and Bing Song contributed to the idea. Hui Zhang, Shufang Yang, Hongxiao Wang, Huzaifa Fareeduddin Mohammed Farooqui, Wenwen Zhu, Tong Niu, Zhen Zhang, Yang Chen, Ling Huang, Ya Zhang, and Mengting He collected the data, and (or) performed the statistical analysis and (or) wrote the draft, and (or) revised the manuscript. All authors gave final approval of the version to be submitted. Hui Zhang, Shufang Yang and Hongxiao Wang contribute equally to this work and considered as co-first authors for this manuscript.

Funding

This work was partially supported by National Natural Science Foundation of China (Haoqiang Zhang, 82400950), China Postdoctoral Science Foundation (Haoqiang Zhang, 2024M753132), Chinese Cardiovascular Association-Natural lipid-lowering drugs fund (Haoqiang Zhang, 2023-CCA-NLD-820), China Endocrine Metabolism Talent Research Project from China International Medical Foundation (Haoqiang Zhang, 2023-N-03-12), and Research Funds of Center for Leading Medicine and Advanced Technologies of IHM (Haoqiang Zhang, 2023IHM02006), Scientific Research Start-up Funds of The First Affiliated Hospital of USTC (Haoqiang Zhang, RC2021178), Zhenjiang Jinshan Talent Medical High Level Talent Project (Songtao Feng, JSYC2023-11), and Taizhou People's Hospital Hospital-level Scientific Research Fund Project (Shufang Yang, ZL202219).

Competing interests

The authors declare no competing interests.

Ethical approval

All volunteers were informed about the cross-sectional study procedures, and they provided their informed consent by signing the necessary documents. The Ethics Committee in the first affiliated hospital of USTC approved this research (2023-RE-013).

Additional information

Supplementary Information The online version contains supplementary material available at <https://doi.org/10.1038/s41598-024-78828-y>.

Correspondence and requests for materials should be addressed to B.S., S.F. or H.Z.

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