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ORIGINAL RESEARCH

Neuropad Assessment of Sudomotor Function Across Glycemic Levels in Adults

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Purpose: To evaluate the impact of metabolic indicators on plantar sudomotor function and to explore the relationships between metabolic and non-metabolic indicators and sudomotor function in a physical examination cohort using Neuropad.

Methods: In this cross-sectional study, 481 participants were randomly enrolled. Sudomotor function was evaluated using Neuropad and a handheld color analyzer for both qualitative (visual Neuropad) and quantitative (quantitative Neuropad) analyses. The slope (Slope[1–10]) was used as a quantitative measure of sudomotor function.

Additional data included age, BMI (body mass index), FPG (fasting plasma glucose), HbA1c (hemoglobin A1c), blood pressure, lipid levels, and liver and kidney function. Participants were categorized into four blood glucose groups: normoglycemia (FPG <6.1 mmol/L and HbA1c <6%), prediabetes (FPG 6.1–6.9 mmol/L or HbA1c 6.0–6.4%), newly diagnosed diabetes (FPG ≥7.0 mmol/L or HbA1c ≥6.5% with no prior diagnosis, diabetes was diagnosed on the day of the physical examination), and previously diagnosed diabetes.

Results: (1) The previously diagnosed diabetes group presented a lower slope than the normoglycemia group (6.96 vs 8.73) and a greater rate of incomplete color change (71.11% vs 49.01%). With increasing FPG and HbA1c levels, the 10-minute slope decreased progressively (P =0.003, P=0.006). (2) A multivariable linear mixed-effects model adjusted for confounders indicated that previously diagnosed diabetes was an independent predictor of reduced sudomotor function. (3) Adjusting for the same confounders, previously diagnosed diabetes was associated with a 3.480-fold greater risk of incomplete color change than was normoglycemia (OR = 3.480, 95% CI = 1.506–8.042). (4) Age, BMI, ALB, eGFR, and alcohol consumption history were closely associated with sudomotor function.

Conclusion: There is a progressive decline in sudomotor function with increasing blood glucose levels in a physical examination cohort, and previously diagnosed diabetes emerges as an independent risk factor for sudomotor dysfunction.

Keywords: neuropad, sudomotor dysfunction, sudomotor function, physical examination cohort, DPN

Introduction

Although the underlying pathogenesis of diabetic peripheral neuropathy (DPN) remains incompletely understood, it is one of the most common chronic complications of diabetes, predominantly affecting sensory, motor, and autonomic nerves.[1] Impairment of autonomic nerve function often leads to abnormal sweat secretion, which can result in systemic complications affecting multiple organs.[2] Specifically, reduced sweat secretion in the feet causes skin dryness, increasing the risk of cutaneous injuries. This autonomic dysfunction significantly contributes to the pathogenesis of foot ulcers in patients with diabetes.[3]

Sudomotor dysfunction is recognized as an early and sensitive indicator of autonomic neuropathy. Throughout the progression from normoglycemia to diabetes, the autonomic nervous system is often compromised, leading to impaired sudomotor function.[4] The initial signs of DPN are often subtle and nonspecific, making early detection challenging. Research suggests that DPN may develop even before a formal diagnosis of diabetes is established.[5] As a result, neuropathy in the prediabetic state has received growing attention. Prediabetes is defined by elevated blood glucose levels that do not meet the diagnostic criteria for diabetes, including impaired glucose tolerance (IGT) and impaired

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fasting glucose (IFG).[6] Patients in this phase may be asymptomatic or symptomatic, and nerve conduction may remain normal or show signs of impairment.[7]

Chronic hyperglycemia profoundly affects sudomotor function through multiple physiological mechanisms. A major factor in this process is the formation of advanced glycation end products (AGEs). AGEs promote oxidative stress, which worsens endothelial dysfunction and disrupts nerve signaling, contributing to nerve damage. Previous studies have shown that these mechanisms impair peripheral nerve function, including the nerves regulating sweat glands, resulting in sudomotor dysfunction.[8] Similarly, Lee et al investigated the role of oxidative stress in autonomic nerve dysfunction and emphasized its role in peripheral neuropathy among diabetic patients.[9] These findings highlight the significance of understanding the molecular mechanisms behind sudomotor dysfunction in diabetes and provide a rationale for this study. Concerning autonomic nerve or sudomotor dysfunction in prediabetes, most studies suggest that the incidence of peripheral neuropathy is higher in prediabetic patients than in the general population, mainly attributed to small nerve fiber damage.[10] The prevalence of cardiac autonomic dysfunction is higher in patients with prediabetes.[11] Subclinical autonomic dysfunction is more common in prediabetic individuals than in those with normal blood glucose levels.[12] However, a study has found no significant differences in the incidence of small fiber neuropathy, abnormal skin biopsy results, or intraepidermal nerve fiber density between prediabetic individuals and those with normal blood sugar levels.[13]

Sweat production is regulated by the sympathetic nervous system and plays a vital role in thermoregulation. The secretory function of sweat glands is strongly associated with the autonomic nervous system.[14] Peripheral neuropathy, commonly associated with chronic diseases such as diabetes, exposure to toxins (eg, alcohol), human immunodeficiency virus (HIV), connective tissue diseases, sarcoidosis, certain medications (eg, antiretroviral therapy, chemotherapy), and idiopathic conditions,[15,16] may disrupt this function.

Sudomotor function testing is a vital tool for detecting abnormalities in peripheral or autonomic nerve function, enabling the evaluation of sweat secretion irregularities in diabetic individuals.[17] Sudomotor dysfunction is recognized as a clinical marker of autonomic nerve impairment that affects sweat gland activity. The assessment of sudomotor function through various methods facilitates the early detection of diabetic autonomic neuropathy and helps prevent subsequent complications, such as diabetic foot ulcers.

At present, clinical evaluations of sweat secretion function primarily include the Sudoscan and Neuropad tests.[18] The Sudoscan assesses the ability of sweat glands to release chloride ions in response to electrochemical stimulation. Sudoscan demonstrates the ability to quantitatively assess sudomotor function within 3 minutes, with sensitivity levels comparable to those of Neuropad. However, it requires bulky equipment and professional expertise for operation.[19] Meanwhile, Neuropad provides a semiquantitative screening approach, although results may be influenced by individual visual interpretation. It is characterized by low cost, high repeatability, and ease of operation with minimal training. As a simple, convenient, and rapid screening tool in clinical practice, it considers an incomplete color change of the test strip within 10 minutes as indicative of sudomotor dysfunction, demonstrating a sensitivity of up to 80% for detecting small fiber neuropathy.[19] To enhance precision, our study employed two handheld color analyzers (diabetic autonomic neuropathy testers) to simultaneously and quantitatively measure Neuropad color changes. Using photometric colorimetry, we carefully assessed Neuropad color changes to evaluate sweat secretion function. This research investigated the impact of varying glucose metabolism levels on sudomotor function, with a particular focus on the effects of prediabetes and diabetes on sweat production. As an early and non-invasive screening tool for autonomic dysfunction, Neuropad may guide early interventions or monitoring strategies in individuals with prediabetes or diabetes. Despite existing studies on autonomic dysfunction in diabetes, there is limited understanding of how sudomotor function changes progressively across glycemic levels, including normoglycemia, prediabetes, and diabetes. This study aims to evaluate the influence of varying levels of glucose metabolism on sudomotor function, with a focus on the progression from normoglycemia to prediabetes and diabetes. Variables such as age, BMI, alcohol consumption history and renal function are potential confounders influencing sudomotor function beyond glycemic control.[20] Therefore, in addition to diabetes-related indicators, we aimed to examine the influence of various other metabolic and non-metabolic factors on sudomotor function.

Materials and Methods

General Information

The study was carried out from November 2020 to December 2021. A total of 481 participants (a total of 648 participants were initially enrolled, and 167 were excluded based on the exclusion criteria) from the Health Examination Center at Tongliang People's Hospital were enrolled, including 224 females and 257 males, with an average age of 57.67 ± 13.54 years. The study population included 302 individuals in the normoglycemia group (aged 22–83 years), 95 in the prediabetes group (aged 25–90 years), 39 in the newly diagnosed diabetes group (aged 39–80 years), and 45 in the previously diagnosed diabetes group (aged 46–86 years). The diagnostic criteria for type 2 diabetes, as established by the Chinese Diabetes Society (CDS) in 2020, were used. Sudomotor function was evaluated using Neuropad test strips, and colorimetric quantification was conducted with a handheld color analyzer. During the study, a dedicated room was used, and temperature and humidity were maintained under strict control.

Inclusion and Exclusion Criteria

All participants who met the eligibility criteria obtained informed consent, underwent Neuropad quantitative testing, and had relevant clinical data collected. The inclusion criteria were: (1) age over 18 years; and (2) signed informed consent.

The exclusion criteria were foot skin lesions (such as scars, rashes, scaling, or infections; lesions affecting both feet simultaneously were excluded), peripheral arterial occlusive disease, heavy smoking (smoking 20 cigarettes per day for over 10 years), chronic alcohol abuse (men consuming over 60 g of pure alcohol per day or women consuming over 40 g of pure alcohol per day, persisting for several years or more), thyroid disease, hepatic impairment (liver enzyme levels exceeding three times the upper limit of normal), renal impairment (eGFR below 30 mL/min/1.73 m^2), acute or chronic infections, cervical/lumbar spine disease, osteoarticular disease, other neurological disorders (such as neurodegenerative disorders or those directly impacting sudomotor function), autoimmune disease, infectious disease, malignancy, mental or psychological disorders (all mental illnesses, regardless of their impact on autonomic function or research participation), medications influencing autonomic function (such as antihypertensives or psychotropic drugs), and other conditions associated with peripheral neuropathy (such as chronic inflammatory demyelinating, polyradiculoneuropathy). Additionally, participants unable to comply with the study requirements were excluded. The study adhered to the tenets of the Declaration of Helsinki and was approved by the Ethics Committees of Tongliang People's Hospital in Chongqing (approved NO 2020–37).

Measurement Parameters

The data collected included general demographics (age and gender), medical history, weight, height (used to calculate BMI), and blood pressure. Fasting plasma glucose (FPG) was measured using the hexokinase method (Cobas c701, Roche, Tokyo, Japan). Hemoglobin A1c (HbA1c) was quantified via high-performance liquid chromatography (Premier Hb9210, Trinity Biotech, Kansas City, Missouri, USA). Albumin levels were detected using the bromocresol green method (Cobas 8000, Roche, Tokyo, Japan). Thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), and free thyroxine (FT4) were measured by chemiluminescence (Modular DDP, Roche, Tokyo, Japan). Lipid profiles, including triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were determined through colorimetric and enzymatic methods (Cobas c701, Roche, Tokyo, Japan). Serum creatinine (Scr) was measured enzymatically (Cobas c701, Roche, Tokyo, Japan), and the estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. The CKD-EPI equation is as follows: For females: If Scr concentration ≤ 0.7 mg/dL: $eGFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$; If Scr concentration > 0.7 mg/dL: $eGFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$.

For males: If Scr concentration ≤ 0.9 mg/dL: $eGFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$; If Scr concentration > 0.9 mg/dL: $eGFR = 141 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$.[21]

Sudomotor function was assessed using the Neuropad test (Omino diagnostic plaster; Miro VerbaDNStoffe GmbH, Germany) at a controlled room temperature of 20 to 25 °C, with humidity maintained between 40% and 60%. Before testing, the participants removed their shoes and rested in the supine position for 15 minutes. The plantar surface was cleaned with

distilled water and cotton swabs to remove sweat and other secretions, allowing the skin to dry for 5 minutes. The Neuropad strips were placed adjacent to the metatarsal heads (I/II); if calluses were present, the strips were positioned accordingly. Using two handheld color analyzers (Norsda Medical instruments, Chongqing, China), each foot was scanned every minute for 10 minutes, and the time for the strip to fully change from blue to pink (normal is within 10 minutes) was recorded. If the color change was incomplete within 10 minutes, the result was considered positive. To minimize subjective bias, the Neuropad was removed after 10 minutes of testing. Two independent physicians separately assessed whether the Neuropad had completely changed color. In cases of disagreement between the two physicians, a third physician was consulted to ensure consistency in color interpretation. To ensure impartiality, we assigned individuals who were not involved in the assessment process to perform the data analysis. To clearly illustrate the Neuropad testing procedure, a flowchart was provided in Figure 1, which outlined the key steps involved in the detection process.

Quantitative Neuropad test: Two assessors used two handheld color analyzers to measure color changes on the test strips of each foot from the 3rd to the 10th minute. We conducted an assessment of the intra-day (6 measurements per day) and inter-day (over a span of 3 days) variability of the handheld color analyzer. The analyzer is equipped with an internal D65 standard light source, which ensures consistent and uniform lighting through the test window. During the assessment, the test window was accurately aligned with the Neuropad strip, and the test button was pressed to measure the chromatic aberration value of the Neuropad.[22] The color change curve were exported via NORSDA-NCM-PC software (Norsda Medical instruments, Chongqing, China), and the slope for color change per minute was calculated as $[\text{Slope}=\sum \frac{(x-\bar{x})\ (y-\bar{y})}{(x-\bar{x})\ 2}]$, where x represents the time and y represents the color difference value. The slope (Slope[1–10]) was used as a quantitative indicator of sudomotor function: a higher slope indicated faster color change and better sudomotor function, whereas a lower slope indicated slower change and reduced sudomotor function. Data from the side

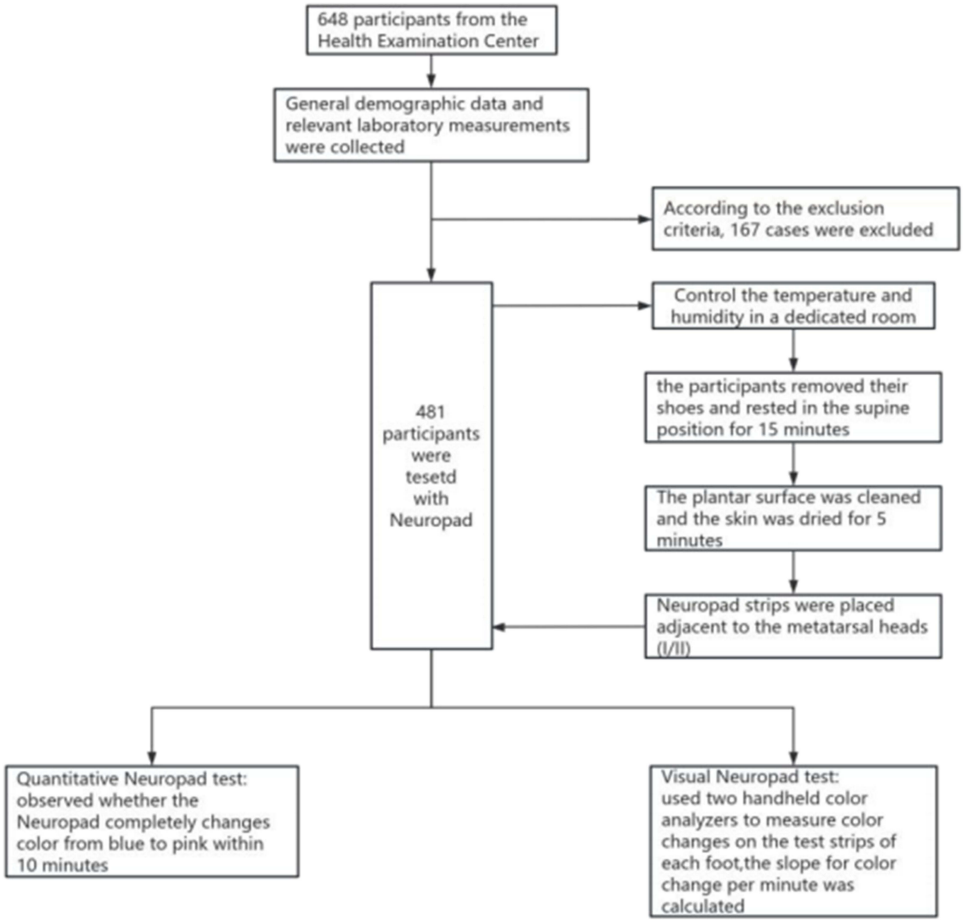

Figure 1 Flowchart for the study.

with poorer sudomotor function were used for analysis; if calluses or scaling were present, data from the opposite side were used.

Visual Neuropad test: Visual Neuropad was a categorical variable defined by whether the Neuropad completely changes color from blue to pink within 10 minutes. An abnormal Visual Neuropad test was defined as the failure of the Neuropad to achieve complete color change within 10 minutes.

Statistical Analysis

Statistical analysis was performed using SAS 9.4 software (Copyright ©2016 SAS Institute Inc. Cary, NC, USA). Continuous variables with normal distributions were presented as the means ± standard deviations and were compared across groups by analysis of variance (ANOVA), with SNK-q tests for pairwise comparisons. Skewed data were summarized as medians (interquartile ranges) and were compared via the Kruskal–Wallis test, with Dunn–Bonferroni adjustments for pairwise comparisons. Categorical data were presented as frequencies and percentages and were compared via χ^2-tests, with Bonferroni adjustments for pairwise comparisons. Slope values, which were repeated measures, were analyzed with a linear mixed-effects model to identify influencing factors. Variables including age, body mass index (BMI), waist circumference, history of alcohol consumption, previously diagnosed diabetes, albumin, globulin, eGFR, red blood cell count, white blood cell count, and high-density lipoprotein (HDL) levels were included, multivariate logistic regression analysis was performed to identify risk factors associated with incomplete color change. Variables such as age, BMI, waist circumference, systolic blood pressure, alcohol consumption history, history of hypertension, previously diagnosed diabetes, albumin, globulin, eGFR, and red blood cell count were included, a multivariate linear mixed-effects model was used for analysis to determine the independent factors influencing the slope of color change. Assumptions of logistic regression model (eg, absence of multicollinearity, linearity of the logit for continuous predictors) and linear mixed-effect model (eg, normality of residuals) were evaluated. Gender, alcohol consumption, and smoking were included in the multivariate models as dichotomous variables. The remaining confounding variables were measured as continuous data and were all included in the model with their original values. Cohen's f2 for regressions was used to represent the effect sizes. All missing values were less than 10 cases and were imputed using the mean value of the same age and sex group. Based on an examination of box plots and other analytical methods, it is evident that there are no notable outliers present. Statistical significance was defined as $P<0.05$.

Utilizing the "Tests for Multiple Proportions in a One-Way Design" feature in PASS2021 to estimate the necessary sample size, it is determined that a minimum of 300 cases are required to achieve a Type I error rate of 0.05 and a statistical power of 0.8. Additionally, each sample group must contain at least 30 cases.

Results

Associations Between Different Blood Glucose Levels and Sudomotor Function

The mean slopes across the four groups stratified by glycemic status were as follows: 8.73 ± 0.17 in the normoglycemia group, 8.61 ± 0.30 in the prediabetes group, 8.04 ± 0.46 in the newly diagnosed diabetes group, and 6.96 ± 0.43 in the previously diagnosed diabetes group (Table 1). Statistical analysis demonstrated significant differences in the mean slope of color difference value change per minute across the four groups. Post hoc analysis revealed that the slope in the previously diagnosed diabetes group was significantly lower than that in the normoglycemia group (6.96 ± 0.43 vs 8.73 ± 0.17, $P < 0.05$), as shown in Figure 2A.

Regarding the proportion of incomplete discoloration, the percentages among the four groups were as follows: 49.01% in the normoglycemia group, 49.47% in the pre-diabetes group, 53.85% in the newly diagnosed diabetes group, and 71.11% in the previously diagnosed diabetes group (Table 1). Statistical analysis also demonstrated significant differences in the rate of incomplete discoloration among these groups. Specifically, the rate of incomplete discoloration in the previously diagnosed diabetes group was higher compared to the normoglycemia group (71.11% vs 49.01%, $P < 0.05$), as shown in Figure 2B.

Table 1 Clinical Characteristics of Populations With Varied Glycemic Status

Variable	Normoglycemia Group (n=302)	Prediabetes Group (n=95)	Newly Diagnosed Diabetes Group (n=39)	Previously Diagnosed Diabetes Group (n=45)	F/χ2	P-value
Female[case (%)]	165(54.64)	36(37.89)[a]	11(28.21)[a]	12(26.67)[a]	23.220	<0.001
Age (years)	54.19±13.87[bcd]	62.92±10.92[a]	62.90±9.86[a]	65.36±10.88[a]	20.352	<0.001
BMI (kg/m^2)	23.52±3.02[bcd]	24.98±2.62[a]	25.55±3.40[a]	24.67±2.93[a]	10.290	<0.001
Waist circumference (cm)	82.69±10.10bcd	87.86±8.79[a]	89.82±8.80[a]	88.16±9.59[a]	13.175	<0.001
SBP (mmHg)	129.28±18.12[bcd]	140.16±17.91[a]	147.33±18.18[a]	145.31±20.96[a]	22.664	<0.001
DBP (mmHg)	77.43±12.31[bc]	82.55±10.99[ac]	87.05±11.61[abd]	80.02±9.18[c]	10.663	<0.001
Alcohol history[yes (%)]	72(23.84)	31(32.63)	15(38.46)	18(40.00)	8.863	0.031
Smoking history[yes (%)]	62(20.53)	26(27.37)	18(46.15)	17(37.78)	16.40	<0.001
Hypertension history[yes (%)]	47(15.56)	30(31.58)[a]	21(53.85)[ab]	26(57.78)[ab]	58.282	<0.001
TSH (mIU/L)	2.42(1.67,3.60)	2.26(1.67,3.34)	2.53(1.81,3.65)	2.377(1.65,3.56)	1.946	0.584
ALT (U/L)	17.85(13.50,25.80)[bcd]	21.20(15.90,29.80)[a]	27.30(19.80,32.00)[a]	22.80(17.70,31.10)[a]	32.697	<0.001
AST (U/L)	121.80(17.90,25.70)	22.10(19.00,26.70)	24.30(19.80,32.80)	22.60(18.80,29.20)	7.643	0.054
Total protein (g/L)	73.00±3.56	72.94±3.28	74.13±3.11	73.93±5.37	1.874	0.133
Albumin (g/L)	45.23±2.06	45.22±1.92	45.51±2.10	45.70±2.21	0.877	0.453
Globulin (g/L)	27.78±3.28	27.57±3.14	28.62±2.86	28.22±4.67	1.111	0.344
Creatinine (μmol/L)	68.13±14.28	72.74±14.23	73.37±12.41	70.27±13.84	3.625	0.013
Uric acid (mmol/L)	317.94±81.97[c]	346.89±88.70	357.90±72.55[ad]	313.07±83.65[c]	5.260	0.001
eGFR (mL·min^{-1})	96.41±15.02[bcd]	88.92±11.96[a]	90.06±10.57[a]	90.87±13.23[a]	8.942	<0.001
WBC (10^9/L)	6.03±1.46[c]	6.34±1.66	6.92±1.46a	6.51±1.72	5.077	0.002
RBC (10^12/L)	4.68±0.47[c]	4.79±0.47c	5.02±0.51[abd]	4.81±0.53c	6.448	<0.001
HGB (g/L)	144.29±15.01[c]	147.63±13.70	153.05±11.92[a]	150.38±17.11	5.985	0.001
PLT (10^9/L)	211.59±56.64[d]	212.97±59.26[d]	204.26±52.02[d]	176.98±43.00[abc]	5.381	0.001
TG (mmol/L)	1.22(0.88,1.84)[cd]	1.38(1.02,2.00)[c]	1.79(1.28,3.42)[ab]	1.52(1.19,2.23)[a]	31.700	<0.001
TC (mmol/L)	5.07±0.98	5.25±0.86	5.17±1.16	4.90±1.23	1.447	0.228
HDL-C (mmol/L)	1.54±0.36[cd]	1.47±0.34	1.34±0.29[a]	1.37±0.39[a]	6.335	<0.001
LDL-C (mmol/L)	2.98±0.76	3.15±0.67	3.02±0.89	2.80±0.84	2.357	0.071
Slope of color change (3–10 minutes)	8.73±0.17	8.61±0.30	8.04±0.46	6.96±0.43[a]	5.291	0.001
Incomplete color change at 10 minutes	148(49.01)	47(49.47)	21(53.85)	32(71.11)[a]	7.923	0.048

Notes: The values are the means ± SDs or medians (interquartile ranges). [a]$P < 0.05$ vs normoglycemia group; [b]$P < 0.05$ vs prediabetes group; [c]$P < 0.05$ vs newly diagnosed diabetes group; [d]$P < 0.05$ vs previously diagnosed diabetes group.

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TSH, thyroid-stimulating hormone; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; WBC, white blood cell; RBC, red blood cell; HGB, hemoglobin; PLT, platelet; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

Associations Between Different Blood Glucose Markers (FPG and HbA1c) and Sudomotor Function

The 10-minute slope exhibited a gradual decline with increasing fasting blood glucose levels (Figure 3A) and glycated hemoglobin levels (Figure 3B), indicating a progressive impairment of sudomotor function associated with deteriorating glycemic control.

Multivariable Analysis of Factors Influencing Sudomotor Function

Multivariable Analysis of Factors Affecting the Slope of Quantitative Neuropad

A multivariate linear mixed-effects model was employed to identify independent factors influencing the slope. After adjustment for potential confounders, previously diagnosed diabetes was independently associated with a reduced slope (Table 2).

Further multivariable analysis revealed that, the slope was negatively associated with age and previously diagnosed diabetes, whereas it was positively associated with BMI, alcohol consumption history, albumin, and eGFR (Table 3).

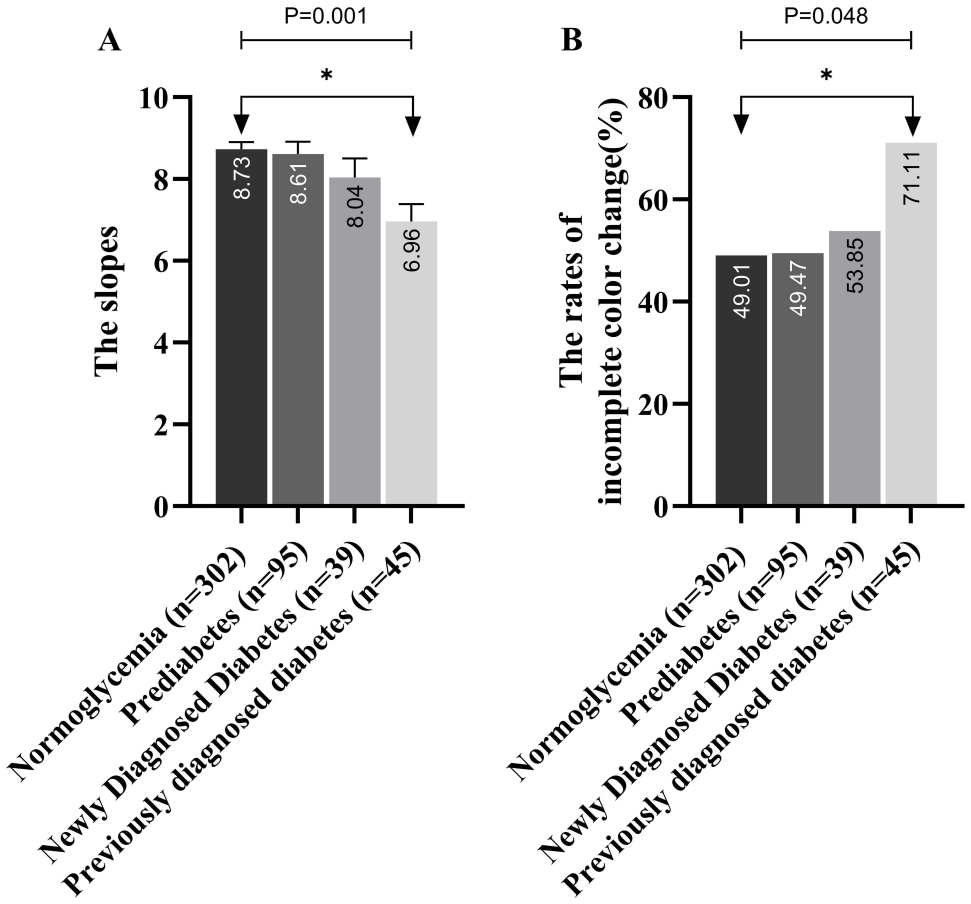

Figure 2 Associations between different blood glucose levels and sudomotor function. (**A**) blood glucose level groups and slopes, (**B**) blood glucose level groups and incomplete color change.

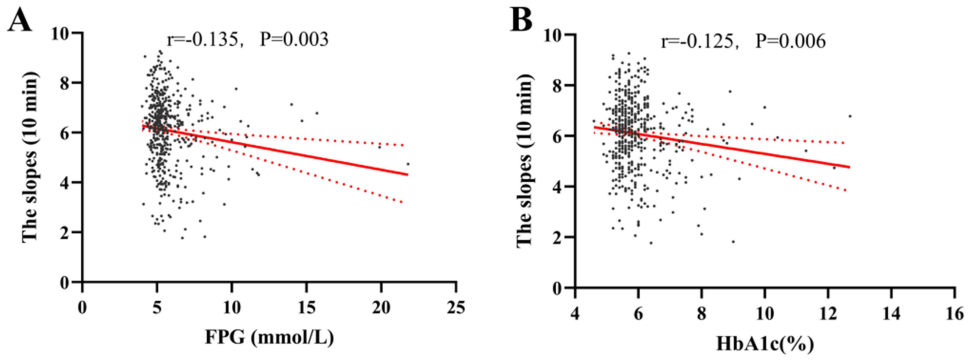

Figure 3 Associations between different blood glucose markers (FPG and HbA1c) and sudomotor function. (**A**) FBG and the 10 minute slope, (**B**) HbA1c and the 10 minute slope.

These findings suggest that both metabolic and non-metabolic factors, in addition to glycemic control, play a role in the regulation of sweat gland function.

Multivariable Analysis of Factors Affecting Visual Neuropad

Multivariable logistic regression analysis demonstrated that, after adjustment for potential confounders, individuals with previously diagnosed diabetes had a significantly higher risk of incomplete color change at 10 minutes compared to those

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Table 2 Multivariate Analysis of Quantitative Neuropad in Different Glycemic Status Groups

Model	Glycemic Status Group	β (95% CI)	SE	T-value	P-value	Cohen's f2
Model 1	Normoglycemia	0.0(reference)				0.030
	Prediabetes	−0.118(−0.781,0.545)	0.338	−0.348	0.728	
	Newly diagnosed diabetes	−0.688(−1.647,0.271)	0.489	−1.406	0.160	
	Previously diagnosed diabetes	−1.765(−2.666, −0.864)	0.459	−3.842	<0.001	
Model 2	Normoglycemia	0.0(reference)				0.027
	Prediabetes	0.125(−0.526,0.777)	0.332	0.377	0.706	
	Newly diagnosed diabetes	−0.601(−1.551,0.349)	0.484	−1.241	0.215	
	Previously diagnosed diabetes	−1.575(−2.482, −0.669)	0.462	−3.409	0.001	
Model 3	Normoglycemia	0.0(reference)				0.034
	Prediabetes	0.120(−0.532,0.773)	0.333	0.362	0.718	
	Newly diagnosed diabetes	−0.673(−1.628,0.282)	0.487	−1.381	0.167	
	Previously diagnosed diabetes	−1.868(−2.789, −0.948)	0.47	−3.978	<0.001	
Model 4	Normoglycemia	0.0(reference)				0.041
	Prediabetes	0.074(−0.577,0.725)	0.332	0.222	0.824	
	Newly diagnosed diabetes	−0.869(−1.828,0.090)	0.489	−1.778	0.076	
	Previously diagnosed diabetes	−1.993(−2.920, −1.067)	0.473	−4.217	<0.001	
Model 5	Normoglycemia	0.0(reference)				0.036
	Prediabetes	0.093(−0.563,0.748)	0.334	0.278	0.781	
	Newly Diagnosed Diabetes	−0.819(−1.796,0.158)	0.498	−1.643	0.100	
	Previously diagnosed diabetes	−1.952(−2.898, −1.006)	0.482	−4.047	<0.001	

Notes: Model 1: unadjusted; Model 2: adjusted for sex, age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, alcohol consumption, and smoking history; Model 3: adjusted as in Model 2 + thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, globulin, creatinine, and eGFR; Model 4: adjusted as in Model 3 + white blood cell count, red blood cell count, hemoglobin, and platelet count; Model 5: adjusted as in Model 4 + triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Table 3 Multivariate Analysis of Factors Influencing the Slope of Quantitative Neuropad

Variable	β (95% CI)	SE	T-value	P-value	Cohen's f2
Constant	−2.097(−10.200,6.007)	4.124	−0.508	0.611	—
Age(years)	−0.030(−0.060,0.000)	0.015	−1.980	0.048	0.007
BMI (kg/m^2)	0.166(0.083,0.248)	0.042	3.944	<0.001	0.036
Alcohol history[yes (%)]	0.762(0.216,1.307)	0.278	2.739	0.006	0.016
Hypertension history[yes (%)]	−0.141(−0.754,0.472)	0.313	−0.452	0.651	<0.001
Glycemic status group					0.029
-Normoglycemia	0.0(reference)				
-Prediabetes	0.032(−0.615,0.680)	0.330	0.098	0.922	
-Newly diagnosed diabetes	−0.790(−1.736,0.155)	0.482	−1.640	0.101	
-Previously diagnosed diabetes	−1.626(−2.524, −0.728)	0.458	−3.551	<0.001	
Albumin (g/L)	0.169(0.043,0.295)	0.064	2.634	0.008	0.015
Globulin (g/L)	−0.052(−0.124,0.021)	0.037	−1.399	0.162	0.002
eGFR (mL·min^{-1})	0.032(0.006,0.058)	0.013	2.439	0.015	0.012
RBC (10^12/L)	0.508(−0.022,1.038)	0.270	1.878	0.060	0.006

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; RBC, red blood cell count.

in the normoglycemia group (OR= 3.480, 95% CI: 1.506–8.042; $P < 0.05$), representing a 3.48-fold increased risk (Table 4).

Further multivariable analysis revealed that Visual Neuropad was negatively associated with BMI and alcohol consumption history but positively associated with a history of previously diagnosed diabetes (Table 5).

Table 4 Multivariate Analysis of Visual Neuropad in Different Glycemic Status Groups

Model	Glycemic Status Group	β	SE	P-value	OR (95% CI)	Cohen's f2
Model 1	Normoglycemia				1.0(reference)	0.026
	Prediabetes	0.019	0.235	0.937	1.019(0.642,1.616)	
	Newly diagnosed diabetes	0.194	0.341	0.570	1.214(0.622,2.369)	
	Previously diagnosed diabetes	0.941	0.348	0.007	2.561(1.294,5.071)	
Model 2	Normoglycemia				1.0(reference)	0.026
	Prediabetes	−0.020	0.262	0.941	0.981(0.586,1.640)	
	Newly diagnosed diabetes	0.385	0.388	0.322	1.469(0.686,3.145)	
	Previously diagnosed diabetes	1.071	0.395	0.007	2.917(1.346,6.325)	
Model 3	Normoglycemia				1.0(reference)	0.026
	Prediabetes	−0.004	0.269	0.987	0.996(0.587,1.688)	
	Newly diagnosed diabetes	0.333	0.394	0.397	1.395(0.645,3.018)	
	Previously diagnosed diabetes	1.166	0.414	0.005	3.208(1.425,7.223)	
Model 4	Normoglycemia				1.0(reference)	0.032
	Prediabetes	0.018	0.274	0.947	1.018(0.596,1.741)	
	Newly diagnosed diabetes	0.497	0.406	0.220	1.644(0.743,3.641)	
	Previously diagnosed diabetes	1.267	0.424	0.003	3.552(1.546,8.160)	
Model 5	Normoglycemia				1.0(reference)	0.029
	prediabetes	0.009	0.277	0.975	1.009(0.586,1.735)	
	Newly diagnosed diabetes	0.468	0.416	0.260	1.597(0.707,3.608)	
	Previously diagnosed diabetes	1.247	0.427	0.004	3.480(1.506,8.042)	

Notes: Model 1: Unadjusted; Model 2: Adjusted for sex, age, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, alcohol consumption, and smoking history; Model 3: Adjusted for Model 2 + thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total protein, albumin, globulin, creatinine, and eGFR; Model 4: Adjusted for Model 3 + white blood cell count, red blood cell count, hemoglobin, and platelet count; Model 5: Adjusted for Model 4 + triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Table 5 Multivariable Logistic Regression Analysis of Factors Influencing Visual Neuropad

Variable	β	SE	Wald $\chi 2$	P-value	OR (95% CI)	Cohen's f2
Constant	6.520	—	3.502	3.466	0.063	—
Age (years)	0.020	0.012	2.609	0.106	1.020(0.996,1.044)	0.008
BMI (kg/m^2)	−0.092	0.036	6.608	0.010	0.912(0.850,0.978)	0.020
Alcohol history[yes (%)]	−0.611	0.250	5.995	0.014	0.543(0.333,0.885)	0.018
Smoking history[yes (%)]	−0.049	0.269	0.034	0.855	0.952(0.562,1.612)	<0.001
Glycemic status group						0.030
-Normoglycemia					1.0(reference)	
-Prediabetes	0.01	0.264	0.001	0.970	1.010(0.602,1.695)	
-Newly Diagnosed Diabetes	0.496	0.384	1.672	0.196	1.642(0.774,3.483)	
-Previously diagnosed diabetes	1.131	0.392	8.315	0.004	3.098(1.436,6.681)	
Albumin (g/L)	−0.076	0.053	2.016	0.156	0.927(0.835,1.029)	0.006
Globulin (g/L)	0.047	0.031	2.292	0.130	1.048(0.986,1.114)	0.007
eGFR ($mL \cdot min^{-1}$)	−0.016	0.011	2.288	0.130	0.984(0.963,1.005)	0.007
WBC (10^9/L)	−0.125	0.070	3.173	0.075	0.883(0.770,1.013)	0.009
RBC (10^12/L)	−0.299	0.228	1.714	0.190	0.742(0.474,1.160)	0.005
HDL-C (mmol/L)	0.345	0.310	1.245	0.265	1.413(0.770,2.591)	0.004

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; WBC, white blood cell; RBC, red blood cell count; HDL-C, high-density lipoprotein cholesterol.

Discussion

Despite existing studies on autonomic dysfunction in diabetes, there is limited understanding of how sudomotor function changes progressively across glycemic levels, including normoglycemia, prediabetes, and diabetes. This study aims to evaluate the influence of varying levels of glucose metabolism on sudomotor function, with a focus on the progression

from normoglycemia to prediabetes and diabetes. In addition to diabetes-related indicators, we also investigated the impact of other metabolic and non-metabolic factors on sudomotor function. Variables including a history of previously diagnosed diabetes, age, BMI, albumin concentration, alcohol consumption history, and eGFR exhibited significant associations with sudomotor function.

Notably, previously diagnosed diabetes was identified as an independent determinant of impaired sudomotor function, demonstrated by both incomplete color change at 10 minutes and a reduced slope of color difference value change. From the normoglycemia group, through the prediabetes group and the newly diagnosed diabetes group, to the Previously diagnosed diabetes group, there was a gradual increasing trend in incomplete color change and a gradual decreasing trend in the color change slope. However, there were no significant statistical differences between the normoglycemia group, the prediabetes group, and the newly diagnosed diabetes group. Even with the more objective quantitative Neuropad assessment, the results remained consistent. However, with increasing fasting blood glucose and HbA1c levels, the rate of color change exhibited a progressive decline.

Previous studies have highlighted the presence of peripheral neuropathy even in the prediabetic state. A systematic review reported that the prevalence of peripheral neuropathy in individuals with prediabetes ranges from 2% to 77%.[10] An international, multicenter, randomized, partially double-blind, placebo-controlled clinical trial utilized SUDOSCAN to measure and calculate the foot electrochemical skin conductance (ESC) index, revealing a prevalence of peripheral neuropathy in prediabetes of 31%.[23] A study conducted in the United States found that 36 out of 107 patients (34%) with idiopathic neuropathy had impaired glucose tolerance (IGT).[24] Fujimoto et al reported that 46.2% of IGT patients had neuropathy diagnosed via neurophysiological evidence.[25] Similarly, Divisova et al reported that approximately 32.8% of IGT patients exhibited peripheral neuropathy.[26] It was indicated that 23.9% of individuals with DPN had either impaired fasting glucose (IFG) or impaired IGT.[27] Our study revealed that 49.47% of the prediabetes had sudomotor dysfunction, similar to them.

The development of DPN is thought to involve oxidative stress and other mechanisms triggered by hyperglycemia, which results in nerve damage and indirectly impairs sudomotor function.[28] The sweat glands are innervated by postganglionic, unmyelinated C-fibers belonging to the sympathetic nervous system, rendering them susceptible to injury as diabetes progresses. With an elongation of diabetes duration, the decline in sudomotor function becomes increasingly evident. In the linear mixed-effects model, the regression coefficient for HbA1c was −0.125 ($P < 0.05$), indicating that each 1% increase in HbA1c was associated with a decrease of 0.125 units in the slope. Similarly, the regression coefficient for fasting blood glucose was −0.135 ($P < 0.05$), suggesting that each 1% increase in fasting blood glucose was associated with a reduction of 0.135 units in the slope.

Techniques for evaluating sudomotor function include the Sudoscan and Neuropad patches, both of which are widely used in clinical settings. A study revealed that out of 31 subjects with IGT, 30 had abnormal sweat secretion according to Sudoscan test results.[29] Similar results were observed in a Chinese cohort with diabetes risk, where 78% of IGT individuals had abnormal Sudoscan.[29] Data from 212 high-risk diabetic Indian patients revealed Sudoscan abnormalities in 70% of IGT individuals and 46.53% of normoglycemia participants.[30] Zick et al reported a significant correlation between the two methods (Neuropad and Sudoscan), confirming Neuropad's ability to detect diabetic neuropathy.[31–34]

Our study revealed that sudomotor dysfunction was present not only in the prediabetes group (49.47%) but also in the normal glucose tolerance group (49.01%) and the newly diagnosed diabetes group (53.85%) (Table 1). Although a gradual worsening trend in sudomotor dysfunction was noted from the normal glucose tolerance group to the prediabetes group and further to the newly diagnosed diabetes group, no statistically significant differences were observed among these groups.

Eriksson et al reported no significant differences in peripheral nerve function between individuals with IGT and those with normal glucose tolerance tests (GTTs). Additionally, no notable variations were observed in median autonomic function measurements among groups with different glycemic statuses.[35] Our findings demonstrated a progressive deterioration in sudomotor function correlating with elevated glucose levels. Notably, a statistically significant association was observed between pre-existing diabetes mellitus and prolonged Neuropad color transition time ($P < 0.05$), consistent with established findings from comprehensive neuropathy assessments reported in previous studies.[36]

The present study consistently demonstrated that a history of diabetes mellitus exhibited the most robust correlation with impaired sudomotor function. Although various factors can affect sudomotor function, resulting in occasional abnormalities even in normoglycemia individuals, there was a notable elevation in impaired sudomotor function among those with a history of diabetes. We have currently developed 5 multifactor models (Table 2 and Table 4) with the aim of examining whether adjusting for certain factors alters the relationship between blood glucose levels and sweating dysfunction. Among the 5 models, BMI was added in Model 2 and eGFR was added Model 3. The results revealed that the relationship between blood glucose levels and sweating dysfunction still had statistical significance. From Cohen's f2, it was revealed that this association program has little change. This suggested that prolonged glucose dysregulation progressively and significantly compromised sudomotor function over time.

Furthermore, our results highlighted that, in addition to the duration of diabetes, other factors significantly influenced sudomotor function, including age, BMI, albumin, alcohol consumption history, and eGFR. Previous studies have shown that factors such as age,[37] ethnicity,[38] and body weight[39] significantly impact sudomotor function, which aligns with our results. Aging diminishes autonomic function, reducing the ability to control sweat glands and, hence, sudomotor function.[40] The decline in autonomic function that occurs with aging can impair the ability to regulate sweat gland function, as evidenced in elderly individuals who often exhibit decreased sudomotor function. This reduction may be attributed to factors such as diminished aerobic capacity and a decreased capacity for thermoregulatory adaptation.[41,42] As the result of our research, the regression coefficient for age (β = −0.030, $P = 0.048$; Table 3) highlighted a significant negative association with the slope of color change. Previous studies have demonstrated that BMI is significantly associated with early diabetic neuropathy.[43] The result of our research showed that the coefficient for BMI (β = 0.166, $P < 0.001$; Table 3) indicates a significant positive association with the slope of color change and a significant negative association with incomplete color change (β = −0.092, $P = 0.010$; Table 5). In obese patients, the basal metabolic rate is typically elevated. This increased metabolic rate leads to greater heat production within the body, necessitating enhanced heat dissipation through sweat evaporation, which can result in excessive sweating. Additionally, the activity of the sympathetic nervous system is often heightened in obese individuals. Since the sympathetic nervous system regulates sweat gland secretion, its overactivation may lead to excessive sweat gland activity, further contributing to hyperhidrosis. Albumin, an indicator of nutritional status, is critical for maintaining plasma colloid osmotic pressure and fluid balance, with low levels potentially reflecting autonomic damage and affecting sweat secretion.[44] It was found that the coefficient for albumin (β = 0.169, $P = 0.008$; Table 3) indicates a significant positive association with the slope of color change. A decrease in eGFR, which signifies compromised renal function, can result in the accumulation of metabolites, thereby influencing autonomic responses and impairing sudomotor performance.[45] It was showed that the coefficient for eGFR (β = 0.032, $P = 0.015$; Table 3) indicates a significant positive association with the slope of color change. Alcohol accelerates blood flow, stimulating sweat gland secretion. It was revealed that the coefficient for alcohol consumption history (β = 0.762, $P = 0.006$; Table 3) indicates a significant positive association with the slope of color change and a significant negative association with incomplete color change (β = −0.611, $P = 0.014$; Table 5). These findings emphasized the importance of evaluating sudomotor function in conjunction with glycemic control, especially in older individuals, those with abnormal BMI, poor nutritional status, impaired renal function, or a history of frequent alcohol consumption. This present study employed straightforward semi-quantitative and quantitative methodologies, along with simple techniques, to assess alterations in sudomotor function across continuous blood glucose profiles. Our findings suggest that incorporating Neuropad into routine metabolic assessments could help identify individuals at risk of autonomic neuropathy earlier in the glycemic spectrum, potentially guiding early interventions.

Neuropad is a non-invasive diagnostic tool designed for the assessment of sudomotor function, distinguished by its user-friendly operation and minimal reliance on complex equipment or specialized technical expertise. This device enables the early detection of sudomotor dysfunction, and its cost-effectiveness supports its widespread adoption in both clinical and community-based settings, as well as its utility in long-term monitoring and repeated evaluations. While Neuropad demonstrates relatively high diagnostic sensitivity for sudomotor function, its specificity is comparatively lower and may be influenced by subjective interpretation. The development of quantitative Neuropad addresses the limitations of subjective variability inherent in qualitative assessments, thereby establishing a robust foundation for the early screening of sweat secretion abnormalities.[46]

Our study is subject to several limitations, primarily due to its single-center nature and relatively small sample size, which may introduce biases in selection. Furthermore, the characteristics of our cohort precluded the conduct of an OGTT. The lack of OGTT data may lead to inaccuracies in classifying individuals with elevated postprandial blood glucose levels, potentially resulting in their misclassification into the normoglycemia group. Such misclassification could undermine the accuracy of differentiating among the normoglycemia, prediabetes, and newly diagnosed diabetes groups, particularly by overestimating the prevalence of abnormal sudomotor function among those incorrectly categorized as normoglycemic. In China, elevated postprandial blood glucose levels are relatively common, likely due to the high carbohydrate content characteristic of the traditional Chinese diet and the impaired early-phase insulin secretion frequently observed in the initial stages of diabetes.[47] Simultaneously, the absence of diabetes duration in our study represents a limitation, as it is a crucial factor influencing the progression of neuropathy. We plan to incorporate this indicator in future research, as a predictor, could refine our understanding of sudomotor dysfunction progression.

To validate the relationships between sudomotor function and metabolic indicators in a more diverse population, larger-scale, multicenter studies are required. It is worth noting that blood glucose levels exhibit high variability, leading to potential inconsistencies in both FGP and OGTT results. However, by incorporating HbA1c as a supplementary indicator, we aimed to enhance the sensitivity and specificity of our glucose metabolism assessment.

Conclusion

In conclusion, the results of this study demonstrate a significant impairment in sudomotor function among individuals with a history of diabetes. However, no statistically significant differences in sudomotor function were identified between individuals with prediabetes or newly diagnosed diabetes and those with normoglycemia. Key determinants influencing sudomotor function include age, BMI, serum albumin levels, alcohol consumption history, and eGFR. Future research should focus on implementing quantitative Neuropad assessment in large-scale, multicenter cohort studies involving populations with comprehensive fasting and postprandial blood glucose monitoring. This study will enable the evaluation of sudomotor function across different stages of diabetes progression and provide insights into its potential impact on the risk of future diabetic complications, such as diabetic foot ulceration.

Data Sharing Statement

All data relevant to the study are included in the article or uploaded as Supplementary Tables 1 and 2.

Patient Consent

The research had been registered in ClinicalTrials.gov (NCT05347420). Informed consent was obtained from all patients who voluntary participation in the experiment. Written informed consent was obtained from the patients for their information to be published in the manuscript.

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Disclosure

The authors report no conflicts of interest in this work.

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