

Diabetic Peripheral Neuropathy Associated with Cardiovascular Risk Factors and Glucagon-Like Peptide-I Concentrations Among Newly Diagnosed Patients with Type 2 Diabetes Mellitus

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Purpose: This study was aimed at the prevalence, cardiovascular risk factors of diabetic peripheral neuropathy (DPN), and the relationship between DPN and fasting glucagon-like peptide-1 (fGLP-1) concentrations in newly diagnosed patients with type 2 diabetes mellitus (nT2D).

Methods: A cross-sectional descriptive study was conducted from 2015 to 2020 with a population of 473 nT2D. Screening for DPN was based on the United Kingdom screening test. fGLP-1 was measured by enzyme-linked immunosorbent assay.

Results: The prevalence of DPN was 26.6%, in which mild grade was 17.3%, moderate grade was 8.2% and severe grade was 1.1% in total. Age (OR = 1.73, 95% CI 1.12–2.67, $p = 0.012$), smoking (OR = 1.64, 95% CI 1.03–2.62, $p = 0.037$), poor control HbA1c (OR = 2.66, 95% CI 1.23–5.76, $p = 0.01$), 24-h urinary albumin (24hUA) (OR = 2.49, 95% CI 1.26–4.94, $p = 0.007$), and diabetic retinopathy (OR = 3.17, 95% CI 1.46–6.89, $p = 0.002$) significantly increased the risk for DPN. In multivariate logistic regression analysis, hypertension (OR = 2.96, 95% CI 1.16–7.55, $p = 0.023$), triglyceride (OR = 1.50, 95% CI 1.11–2.03, $p = 0.009$), albumin (OR = 0.85, 95% CI 0.75–0.95, $p = 0.005$), and fGLP-1 (OR = 0.79, 95% CI 0.67–0.93, $p = 0.005$) correlated with DPN. The fGLP-1 concentrations were reduced significantly in DPN ($p < 0.001$). In particular, male patients with DPN had a significantly lower fGLP-1 levels than those without DPN ($p < 0.001$).

Conclusion: The prevalence of DPN among nT2D was 26.6%. Age, smoking, hypertension, HbA1c control, triglyceride, albumin, 24hUA, diabetic retinopathy were the associated risk factors of DPN, and fGLP-1 was negatively correlated with DPN (OR = 0.79, 95% CI 0.67–0.93, $p = 0.005$).

Keywords: newly diagnosed type 2 diabetes mellitus, diabetic peripheral neuropathy, cardiovascular risk factors, glucagon-like peptide-1 concentrations

Introduction

Diabetic peripheral neuropathy (DPN) is the most common complication of diabetes in general and occurs early.^{1–3} Diabetic neuropathy is a type of nerve damage all over the body and can alter autonomic motor, and sensory functions.⁴ DPN is the most common form of diabetic neuropathy, affecting the outer nerves of the limbs. It directly leads to changes in sensory function, abnormal feelings, and progressive numbness, and increases the risk of foot ulceration, amputation, cognitive dysfunction, and economic burden.^{5,6} Previous studies show that the prevalence of DPN

among patients with type 2 diabetes accounts for 2.0–78.8%, depending on the country, duration of diabetes, and examination methods.^{1,7–9} Nerve damage not only leads to loss of feeling that allows injuries to go unnoticed and expandable but also causes serious infections and possible amputations. The risk of amputation in diabetes patients may be more than 25 times greater than that of the non-diabetic population.¹⁰

The main mechanisms involved in peripheral nerve damage in type 2 diabetes are hyperglycemia, dyslipidemia, and insulin resistance. Firstly, hyperglycemia leads to mitochondrial dysfunction, endoplasmic reticulum stress, promotion of reactive oxygen generation, stimulation the sorbitol accumulation, and advanced glycation end products.^{8,11,12} Secondly, dyslipidemia increases free fatty acid-induced lipotoxicity, reactive oxidative stress, inflammation, cytokine, and chemokine production.^{12,13} Thirdly, insulin resistance develops peripheral neuropathy via reactive oxidative stress and inflammation.^{14,15}

Recently, studies have demonstrated that GLP-1 plays in the mechanism of DPN. GLP-1 may have direct nutritional activities on the nervous system, increase neurite outgrowth of adult sensory neurons in vitro like nerve growth factor,^{16,17} and play a role as a neuroprotective agent.^{18,19} Besides, GLP-1 may defend against *pyridoxine-induced sensory neuropathy*, which shows that GLP-1 could be a potential treatment in diabetic neuropathies.²⁰ Furthermore, GLP-1 has been proved to have benefits in microvascular complication diabetes - one mechanism leading to DNP, such as decreasing endothelium dysfunction, which is an early marker of atherosclerosis, arterial endothelial wall injury, and decrease peripheral nerve nutrition.^{21,22}

In Vietnam, the prevalence of diabetes is increasing rapidly (accounted for 5.0 to 6% of the total population). Chronic complications of diabetes are growing complex and burdening the healthcare system. DPN appears early at the time of diagnosing diabetes, causes difficulties in treatment, increases the rate of foot complications, amputation, and reduces the quality of life of patients. There is very little documentation about the DPN in nT2D in Viet Nam, and the correlation between plasma GLP-1 concentrations and DPN has not been elucidated. We carried out this study to estimate the prevalence, cardiovascular risk factors of DPN, and the association between DPN with GLP-1 concentrations among newly diagnosed patients with type 2 diabetes in Viet Nam.

Materials and Methods

Study Population and Design

A cross-sectional descriptive study was implemented in 473 Vietnamese patients with nT2D in the National Endocrinology Hospital (Hanoi, Vietnam) from January 2015 to December 2020.

Regarding type 2 diabetes, the diagnosis was based on the American Diabetes Association guideline (2019)²³ for the first time and patients did not relate to any antihyperglycemic treatments (such as biguanides, sulfonylureas, glitazones, incretin therapy, alpha-glucosidase inhibitor, sodium-glucose cotransporter-2 inhibitors, insulin therapy, etc). We excluded patients with conditions that affected GLP-1 concentrations (such as gastrointestinal surgery, bleeding ulcerative colitis, enteritis), and patients with severe heart failure, hemodynamic diseases (such as hemolytic anemia, aplastic anemia, moderate-to-severe anemia), systemic diseases (scleroderma, systemic lupus erythematosus), and severe diabetic conditions (hyperglycemic crises such as hyperosmolarity and diabetic ketoacidosis, hypoglycemia), amputation. Peripheral neuropathy was due to other conditions such as infections (HIV, tuberculosis, severe other infections), autoimmune diseases, inherited disorders, tumors, bone marrow disorders, end-stage renal disease, liver disease, hypothyroidism.

Clinical and Biochemical Assessments

General information of all patients was collected according to a uniform record. The patients were asked about age; gender; history of drug use, other comorbidities; smoking (tobacco); drinking (beer or wine); anthropometric measurements (height, weight, waist and hip circumference, waist-hip ratio, blood pressure, and pulse). Thorough clinical examination for symptoms of DPN at feet, legs, hands, and arms such as numbness, the reduction of ability to feel pain or temperature changes, tingling or burning sensation, sharp pains or cramps, increased sensitivity to touch, foot problems (ulcers, infections, and bone and joint pain)^{13,24} were performed.

Fasting blood samples were collected from 6:30 to 7:00 the next morning (the patients were asked to fast for at least 8 hours). Fasting plasma glucose (FPG) concentration was quantified by using a hexokinase assay (Beckman AU680, USA). Measurements of HbA1c were carried out by the high-performance liquid chromatography method (Adams A1C, Japan). Total cholesterol, triglyceride, LDL-C, HDL-C, albumin, aspartate and alanine aminotransferase, creatinine, electrolytes, and hsCRP were measured

quantitatively by the enzyme colorimetric method (Beckman AU680, USA). Blood insulin and C-peptide concentrations were measured by electrode chemiluminescence (COBAS E411, USA). Quantification of albumin, 24-hour urine was measured by auto-analyzed and immunoturbidimetric method (Beckman AU680, USA). White blood cell was counted by K-4500, Japan. Beta-cell function (HOMA-B) and insulin sensitivity (HOMA-S) and insulin resistance (HOMA-IR) were calculated from the automatic calculator available from <https://www.dtu.ox.ac.uk/homacalculator/> (Diabetes Trial Unit, University of Oxford, United Kingdom).

The criteria used in our study were as follows: for hypertension: systolic blood pressure (SBD) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg at least 2–3 visits with 2–3 measurements per visit; for glucose control grade: good-normal FPG < 7.0 mmol/L, poor control: FPG ≥ 7.0 mmol/L; for HbA1c control grades: good-normal control: HbA1c $< 6.5\%$, poor control: HbA1c $\geq 6.5\%$; for lipid disorders: if patients have at least one of the disorders namely high total cholesterol, high triglycerides, high LDL-C, and low HDL-C; for diabetic retinopathy: based on ophthalmoscopy, with proliferative or pre-proliferative retinopathies being diagnosed by an ophthalmologist.

Quantification of GLP-1 Levels by Enzyme-Linked Immunosorbent Assay (ELISA)

Fasting blood samples were collected from patients for fGLP-1 analysis at the same time as for other biochemical assessments. Collecting tubes were added dipeptidyl peptidase-4 inhibitor (DPP-IV Inhibitor, K579, BioVision, USA) before adding blood to avoid inactivation of GLP-1 by DPP-4. Then, these samples were centrifuged at 3000 rpm for 15 minutes to get the plasma. Finally, the plasma was analyzed with commercially available kits (Human ELISA GLP-1 kits, IBL, Japan, #27784) according to the manufacturer's protocol by ELISA apparatus (ThermoFisher Scientific, USA). Color changes were checked at a wavelength of 450 nm. The intra-assay and inter-assay coefficients of variation were less than 10% in enzyme immunoassays.

Screening for Peripheral Neuropathy

Screening for DPN was performed based on the United Kingdom screening test including symptom score and grade.²⁵

Symptoms: 1) Abnormal sensations felt: burning, numbness or tingling: 2 points; fatigue, aching or cramping: 1 point. 2) Site of discomfort: feet or soles: 2 points; calves: 1 point; elsewhere: 0 points. 3) Time of worst symptoms: night only: 2 points; both day and night: 1 point; day only/do not know: 0 points. 4) Alleviating factor: walking around: 2 points; standing: 1 point; sitting, lying, or no relief: 0 points. 5) Night-time awakening: Yes: 1 point; No: 0 points.

Grade: 0–2 points: (Normal) No peripheral neuropathy
3–4 points: Mild peripheral neuropathy
5–6 points: Moderate peripheral neuropathy
7–9 points: Severe peripheral neuropathy

Ethical Statement

All patients were provided written informed consents and agreed to participate in this study. The protocol was approved by the Institutional Review Board of Vietnam Military Medical University, Vietnam (Reference No 1996/2014/IRB-VMMU). The study was also conducted using good clinical practice following the Declaration of Helsinki.

Statistical Analysis

All variables were checked for normality with Kolmogorov-Smirnov test if sample size > 50 or Shapiro-Wilk test if $n < 50$. Continuous variables (such as age, BMI, HbA1c, total cholesterol, HDL-C, LDL-C, fGLP-1, etc) were expressed as mean \pm standard deviation for normal distribution variables or median (interquartile range, Q1-Q3) for skewed distribution variables. Differences between groups were examined with either Student's *t*-test or Mann-Whitney test. Categorical variables (such as hypertension, gender, DPN, smoking, drinking, etc) were expressed as percentage. The chi-square test for association was used to determine if there was a relationship between two categorical variables. The relationship between fGLP-1 concentrations and DPN was estimated using the Mann-Whitney test. Multivariate logistic regression analyses were chosen upon evaluation of the effects of fGLP-1 concentrations and other factors and DPN. Two-tailed *P*-values < 0.05 were set as statistically significant.

Data were analyzed with the SPSS version 26 (64-bit edition) for Windows (SPSS Inc, Chicago, IL).

Results

Demographic and Biomedical Findings

Age, fasting insulin levels, HDL-C, sodium ion, and HOMA-B in women were significantly higher than those in men. Male patients had higher waist and hip circumference, waist-to-hip

ratio, smoking, drinking, fasting blood glucose, HbA1c, aspartate aminotransferase, creatinine than those in women. There was no significant difference in both SBP, C-peptide, albumin, total cholesterol, triglyceride, LDL-C, alanine aminotransferase, fGLP-1, hsCRP, white blood cells, potassium ion, 24hUA, HOMA-S, HOMA-IR between male and female patients. Regarding the characteristics of diabetes, albeit those patients were firstly diagnosed with type 2 diabetes, their FPG, HbA1c, and HOMA-IR indices values were high, but BMI, HOMA-S, and HOMA-B indices values were low (Table 1).

Prevalence of Peripheral Neuropathy in Newly Diagnosed Patients with Type 2 Diabetes

In this study, the prevalence of DPN was 26.6% (in which, male patients made up 52.3% and female patients made up 47.7%). Regarding the severity of DPN, the percentage for mild DPN, moderate DPN, and severe DPN were 17.3%, 8.2%, and 1.1%, respectively, in total. There was no statistically significant association between gender and DPN ($p = 0.966$) (Table 2).

Table 1 The Demographic and Biomedical Characteristics of the Study Population

Variables, Unit	Men (n = 247)	Women (n = 226)	Overall (n = 473)
Age, years	52.00 (44.00–59.00)**	55.00 (50.00–62.00)**	54.00 (47.00–60.00)
BMI, kg/m ²	22.40 (20.80–24.24)	22.00 (20.11–24.20)	22.12 (20.31–24.21)
Waist circumference, cm	84.84 ± 8.00**	81.16 ± 8.45**	83.30 ± 8.35
Hip circumference, cm	93.00 (89.00–97.00) ⁺	90.00 (86.00–95.00) ⁺	92.00 (87.00–96.50)
Waist–hip ratio	0.91 (0.88–0.94)**	0.89 (0.86–0.93)**	0.90 (0.87–0.94)
Smoking	103 (47.1)**	1 (0.4)**	104 (22.0)
Drinking	162 (65.6)**	5 (2.2)**	167 (35.3)
SBP, mmHg	123.00 (120.00–140.00)	120.00 (114.50–140.00)	120.00 (120.00–140.00)
DBP, mmHg	80.00 (70.00–80.00) ⁺	80.00 (70.00–80.00) ⁺	80.00 (70.00–80.00)
FPG, mmol/L	9.90 (7.50–11.70) ⁺	9.85 (7.47–14.3) ⁺	10.70 (7.80–15.25)
HbA1c, %	11.80 (8.10–15.60) ⁺	8.91 (7.08–11.40) ⁺	9.50 (7.20–11.40)
C-peptide, nmol/L	0.74 (0.48–1.01)	0.76 (0.54–1.20)	0.75 (0.50–1.15)
Insulin, pmol/L	61.44 (38.05–95.50) ⁺	70.86 (45.60–106.77) ⁺	65.64 (41.64–104.83)
Albumin, g/L	41.15 (38.55–44.00)	41.00 (39.00–44.00)	41.10 (39.00–44.00)
Triglycerides, mmol/L	2.16 (1.44–3.65)	2.00 (1.36–3.28)	2.09 (1.40–3.40)
Total cholesterol, mmol/L	5.3 (4.36–6.16)	5.3 (4.51–6.20)	5.30 (4.41–6.17)
HDL-C, mmol/L	1.17 (0.99–1.43) ⁺	1.24 (1.07–1.50) ⁺	1.19 (1.02–1.48)
LDL-C, mmol/L	3.07 (2.45–4.08)	3.12 (2.40–4.02)	3.10 (2.43–4.05)
Lipid disorders, positive	211 (85.8)	182 (80.8)	393 (83.3)
Alanine transferase, U/L	27.00 (21.00–38.00)	26.00 (20.00–35.00)	27.00 (21.00–36.00)
Aspartate transferase, U/L	34.00 (24.00–52.00)**	29.00 (20.75–44.00)**	31.00 (22.00–49.00)
Creatinine, μmol/L	84.00 (75.00–92.00)**	69.00 (62.00–76.00)**	76.00 (67.00–86.00)
fGLP-1, pmol/L	6.25 (4.46–9.71)	6.49 (5.20–9.00)	6.37 (4.81–9.13)
hsCRP, mg/L	2.10 (1.01–5.22)	2.04 (1.01–4.56)	2.10 (1.01–4.79)
Potassium ion, mmol/L	3.90 (3.70–4.10)	3.80 (3.70–4.00)	3.90 (3.70–4.00)
Sodium ion, mmol/L	137.00 (135.00–139.00)**	138.00 (136.00–140.00)**	137.00 (136.00–139.00)
White blood cells (G/L)	7.88 (6.52–9.50)	7.50 (6.40–9.10)	7.72 (6.50–9.27)
24hUA, mg	3.98 (0.00–13.09)	3.04 (0.00–8.48)	3.61 (0.00–11.50)
24hUA, (≥30 mg)	21 (9.1)	16 (7.3)	37 (8.2)
HOMA-S (%)	43.40 (28.25–62.03)	42.90 (26.50–66.00)	43.20 (27.15–63.70)
HOMA-B (%)	32.35 (16.80–62.10) ⁺	42.40 (23.90–78.00) ⁺	36.20 (20.20–69.00)
HOMA-IR	2.30 (1.61–3.58)	2.33 (1.54–3.77)	2.31 (1.57–3.70)
Diabetic retinopathy	15 (6.6)	13 (6.2)	28 (6.4)

Notes: Data were expressed as mean±SD or median and interquartile range (Q1–Q3); * $P < 0.05$; ** $P < 0.001$ (between male and female group).

Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; fGLP-1, fasting glucagon-like peptide-1; hs-CRP, high-sensitivity C-reactive protein; 24hUA, 24-h urinary albumin; HOMA-S, insulin sensitivity; HOMA-B, beta-cell function; HOMA-IR insulin resistance.

Table 2 The Prevalence and Grade of Diabetic Peripheral Neuropathy in the Newly Diagnosed Patients with Type 2 Diabetes Mellitus

Variables		Men (n = 247)	Women (n = 226)	Overall (n = 473)
Peripheral Diabetic Neuropathy	Positive	66 (14.0)	60 (12.6)	126 (26.6)
	Negative	181 (38.3)	166 (35.1)	347 (73.4)
p*-Value		p = 0.966		
Grade	Mild	44 (9.3)	38 (8.0)	82 (17.3)
	Moderate	18 (3.8)	21 (4.4)	39 (8.2)
	Severe	4 (0.8)	1 (0.3)	5 (1.1)
	p*-Value		p = 0.534	

Note: *Chi-square tests; p-value (between men and women).

Cardiovascular Risk Factors of Peripheral Neuropathy in Newly Diagnosed Patients with Type 2 Diabetes

The prevalence of DPN appeared statistically significantly higher in patients aged ≥ 60 (34.5%); smoking (34.6%), poor HbA1c control (28.6%), present 24hUA (45.9%) and present diabetic retinopathy (50%). Age, smoking, poor control HbA1c; present 24hUA, present diabetic retinopathy increased the risk of DPN (OR = 1.73, 95% CI 1.12–2.67, p = 0.012; OR = 1.64, 95% CI 1.03–2.62, p = 0.037; OR = 2.66, 95% CI 1.23–5.76, p = 0.01; OR = 2.49, 95% CI 1.26–4.94, p = 0.007, and OR = 3.17, 95% CI 1.46–6.89, p = 0.002, respectively. The rate of DPN was not statistically significant compared with the gender, drinking, hypertension, BMI,

Table 3 The Relationship Between Cardiovascular Risk Factors and Diabetic Peripheral Neuropathy in the Newly Diagnosed Patients with Type 2 Diabetes Mellitus

Variables, Unit		Peripheral Diabetic Neuropathy		
		Positive	Negative	p*, OR, 95% CI
Age, years	<60 (n = 334)	78 (24.4)	256 (76.6)	p=0.012 OR=1.73 (1.12–2.67)
	≥ 60 (n = 139)	48 (34.5)	91 (65.5)	
Smoking	Active (n = 104)	36 (34.6)	68 (65.4)	p=0.037 OR=1.64 (1.03–2.62)
	None (n = 369)	90 (24.4)	279 (75.6)	
Drinking	Active (n = 167)	47 (28.1)	120 (71.9)	p=0.584
	None (n = 306)	79 (25.8)	227 (74.2)	
Hypertension	Positive (n = 141)	44 (31.2)	97 (68.8)	p=0.143
	Negative (n = 332)	82 (24.7)	250 (75.3)	
BMI, kg/m ²	<23 (n = 278)	72 (25.9)	206 (74.1)	p=0.664
	≥ 23 (n = 195)	54 (27.7)	141 (72.3)	
Lipid disorders	Positive (n = 393)	110 (28.0)	283 (72.0)	p=0.156
	Negative (n = 79)	16 (20.3)	83 (79.7)	
Glucose control	Good-normal (n = 71)	19 (26.8)	52 (73.2)	p=0.98
	Poor (n = 402)	107 (26.6)	295 (73.4)	
HbA1c control	Good-normal (n = 61)	8 (13.1)	53 (86.9)	p=0.01 OR=2.66 (1.23–5.76)
	Poor (n = 412)	118 (28.6)	294 (71.4)	
24hUA, mg	≥ 30 (n = 37)	17 (45.9)	20 (54.1)	p=0.007 OR=2.49 (1.26–4.94)
	<30 (n = 413)	105 (25.4)	308 (74.6)	
Diabetic retinopathy	Positive (n = 28)	14 (50.0)	14 (50.0)	p=0.002 OR=3.17 (1.46–6.89)
	Negative (n = 409)	98 (24.0)	311 (76.0)	

Note: *Chi-square tests.

Abbreviations: BMI, body mass index; 24hUA, 24-h urinary albumin; OR, odds ratio; CI, confidence interval.

lipid disorders and fasting glucose control in univariate analysis ($p > 0.05$) (Table 3).

Fasting GLP-I Concentrations Correlation to Diabetic Peripheral Neuropathy in Newly Diagnosed Patients with Type 2 Diabetes

A Mann–Whitney U -test showed that there was a statistically significant difference in concentration of fGLP-1 level between different DPN groups ($Z = -3.554$; $p < 0.001$). There was a statistically significant difference in fGLP-1 between male patients with and without DPN ($Z = -4.103$; $p < 0.001$). The median fGLP-1 concentration for patients with DPN was 5.27 pmol/L compared to 6.76 pmol/L in patients without DPN. Interestingly, while in the male group, the median fGLP-1 for present DPN was 4.11 pmol/L compared to 6.91 pmol/L in the non-DPN group, there was no statistically significant difference in fGLP-1 among female patients with and without DPN ($Z = -0.951$; $p = 0.342$) (Table 4).

The multivariate logistic regression analysis showed that the following factors had correlation to DPN in nT2D: hypertension (OR = 2.96, 95% CI 1.16–7.55, $p = 0.023$), HbA1c (OR = 1.22, 95% CI 1.01–1.47, $p = 0.042$), triglyceride (OR = 1.50, 95% CI 1.11–2.03, $p = 0.009$), albumin (OR = 0.85, 95% CI 0.75–0.95,

$p = 0.005$), and fGLP-1 (OR = 0.79, 95% CI 0.67–0.93, $p = 0.005$) (Table 5).

Discussion

The Prevalence of Peripheral Diabetic Neuropathy and Risk Factors

In our study, the prevalence of DPN in nT2D was 26.6%. Regarding the severity of DPN, the percentage for mild DPN, moderate DPN, and severe DPN was 17.3%, 8.2%, and 1.1%, respectively, in total. There was no statistically significant association between gender and DPN ($p = 0.966$). Previous studies showed that the prevalence of DPN was different among adults with diabetes depending on the nation, age, duration of diabetes, glucose control, and type 1 versus type 2 diabetes from 9.6% to 69% in Latin and American countries^{1,26,27} from 30.1% to 58% in Asian countries.^{28,29} Thus, the prevalence of DPN in our study was lower than that in other Asian countries due to several reasons. Firstly, participants in our study were nT2D, while other studies enrolled adult patients with long-duration of diabetes and, perhaps, with a relatively high prevalence of microvascular complications. Secondly, there were differences in methods between studies that were used to screen for DPN. We identified the presence of DPN based on clinical examination (the United Kingdom screening test) and other studies used to 10-g monofilament testing or neurothesiometer testing or electromyography.²⁸ Furthermore, the differences in anthropometric characteristics, social and cultural environment of Vietnamese type 2 diabetes compared to other countries such as low BMI (non-obese individuals diabetes), low waist and hip circumference, highly physical activity, or healthy lifestyles, low-fat diet. They were suggested that these factors could delay the onset of chronic complications and metabolic disorders in Vietnamese patients with type 2 diabetes.^{30,31}

Studies further demonstrated that risk factors for cardiovascular were predictors of the development of DPN in type 1 and type 2 diabetes patients.^{32,33}

In our study, the risk of developing DPN in patients aged ≥ 60 was higher than that in patients with age < 60 years (OR = 1.73, $p = 0.012$). Elderly patients with type 2 diabetes had a higher rate of complications including macro- and micro-vascular disease than young patients. Age was an independent risk factor for the DPN and associated with neurological dysfunction in both major nerve and minor nerve.^{34,35} Besides, previous studies and

Table 4 The Relationship Between Fasting GLP-I Concentrations and Diabetic Peripheral Neuropathy in the Newly Diagnosed Patients with Type 2 Diabetes Mellitus

	Diabetic Peripheral Neuropathy	
	Positive	Negative
Mean rank (n)		
Male	28.24 (27)	52.90 (63)
Female	37.22 (29)	42.36 (51)
Overall	66.41 (56)	94.88 (114)
Median fGLP-I (pmol/l) (n)		
Male	4.11 (27)	6.91 (63)
Female	6.37 (29)	6.64 (51)
Overall	5.27 (56)	6.76 (114)
Test Statistics**		
Male	$Z = -4.103$; $p < 0.001$, $n = 90$	
Female	$Z = -0.951$; $p = 0.342$, $n = 80$	
Overall	$Z = -3.554$; $p < 0.001$, $n = 170$	

Note: **Mann–Whitney U -tests.

Abbreviation: fGLP-I, fasting glucagon-like peptide-I.

Table 5 The Multivariate Logistic Regression Analysis Associated Other Factors with Diabetic Peripheral Neuropathy in the Newly Diagnosed Patients with Type 2 Diabetes Mellitus

Determinants, Unit	B	p	OR	95% CI
Hypertension (0 = negative, 1 = positive)	1.084	0.023	2.96	1.16–7.55
HbA1c, %	0.196	0.042	1.22	1.01–1.47
Triglyceride, mmol/L	0.404	0.009	1.50	1.11–2.03
Albumin, g/L	−0.166	0.005	0.85	0.75–0.95
fGLP-1, pmol/L	−0.235	0.005	0.79	0.67–0.93
HOMA-B, %	0.006	0.407	1.01	0.99–1.02
Urea, mmol/L	−0.177	0.267	0.84	0.61–1.15
Gender (1 = male, 2 = female)	0.585	0.185	1.79	0.76–4.26
Potassium ion, mmol/L	0.484	0.408	1.62	0.52–5.11
HDL-C, mmol/L	0.794	0.110	2.21	0.84–5.86
LDL-C, mmol/L	−0.108	0.578	0.90	0.61–1.31
White blood cells, G/L	−0.068	0.430	0.93	0.79–1.11
BMI (0 = BMI < 23, 1 = BMI ≥ 23 (kg/m ²))	0.410	0.362	1.51	0.62–3.64
Glucose control (0 = good–normal, 1 = poor)	−1.100	0.140	0.33	0.08–1.43

Abbreviations: fGLP-1, fasting glucagon-like peptide-1; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HOMA-B, beta-cell function; BMI, body mass index; OR, odds ratio; CI, confidence interval.

our study suggested that smoking was the most common risk factor for the development of vascular complications including DPN in type 2 diabetes.^{36,37}

Poor HbA1c control increased the risk of DPN in both univariate analysis and multivariate logistic regression analysis in nT2D. Chronic hyperglycemia elevated inflammatory factors that lead to peripheral nerves injuries such as tumor necrosis factor-alpha, interleukin-6,8, monocyte chemoattractant protein-1, transforming growth factor β , and C-reactive protein, and infiltration of cytokines into the vascular tissue and thus reduces peripheral neuropathy nutrition.^{38,39}

In our study, other microvascular complications included 24hUA ≥ 30 mg (8.2%), and diabetic retinopathy (6.4%), and these complications were significantly associated with the development of DPN. Recently, studies showed that positive family history, illiteracy, hypertension, higher HbA1c level, and DPN were associated with elevation of cardiovascular diseases events and caused of morbidity and mortality in diabetic patients.^{2,40,41} Diabetic nephropathy is closely related to the expansion of DPN in type 2 diabetes. Urinary albumin excretion rate can be used as predicting DPN process.^{42–44} Changes in urine albumin-to-creatinine ratio ($\geq 30\%$) increase the risk for new-onset DPN in type 2 diabetes (OR = 3.059, 95% CI 1.012–9.249).⁴⁵ Furthermore, diabetic retinopathy, especially severe diabetic retinopathy is correlated with DPN; and DPN was a factor like a tell-tale sign of diabetic retinopathy; thus, it is necessary to examine more

intensive ophthalmic disease.⁴ All microvascular complications of diabetes arose early, and they were related to each other via complex pathological mechanisms,^{3,41} therefore, it is essential to early detect and manage these complications as soon as possible, which can prevent their development and improve quality of life for type 2 diabetes patients.

The Relation Between Diabetic Peripheral Neuropathy and fGLP-1 Concentrations

Our study outlined the correlation between fGLP-1 concentrations and DPN in nT2D. A Mann–Whitney *U*-test showed that there was a statistically significant difference in fGLP-1 level between the patients with and without DPN. GLP-1 decreased significantly in patients with DPN in male patients and in overall.

Previous studies have reported that GLP-1 secretion was reduced in both fasting and postprandial patients with type 2 diabetes,^{46–48} which resulted in impaired insulin secretion, a decrease in beta-cell function, and an increase in insulin resistance.^{49,50} These effects caused hyperglycemia, oxidative stress, enhancing the synthesis of inflammatory cytokines, tumor necrosis factor (TNF)- α and MCP-1, and microvascular complications.^{21,51,52} GLP-1 influenced DPN via the indirect mechanisms of microvascular damage in type 2 diabetes. Receptor for advanced glycation end-products mRNA transcription was inhibited by GLP-1, leading to reduced reactive oxygen species production and decrease in vascular cell

adhesion molecule-1 expression. Thus, GLP-1 concentrations contributed to preventing the arterial wall from inflammatory response, atherosclerosis, oxidative stress, and increase endothelium relaxations.²² Besides, GLP-1 inhibited the formation of foam macrophages, prevented the inflammatory response to the artery, which was closely related to negative feedback of CD36 and acetyl-coenzyme-A, acetyltransferase-1, and modulates adhesion molecules, such as interleukin-10, CD136, and CD204.⁵³ GLP-1 reduced endothelial dysfunction, inflammatory response via the consequence of the decrease in nitrotyrosine, 8-iso prostaglandin F₂ α , sICAM-1, and interleukin-6,⁵⁴ which is important to cause neuropathy in type 2 diabetes.^{9,55}

Interestingly, in our study, while there was a significant difference between patients with DPN and without DPN in fGLP-1 in male patients, this trend was not seen in female patients. One explanation for this difference between men and women was tobacco use. Tobacco use contributes to the macro- and microvascular complications of type 2 diabetes mellitus. GLP-1 was evidenced to addressing comorbid tobacco use disorder in diabetes with smoking.³⁷ GLP-1 or analogs reduced the effect of alcohol to trigger the mesolimbic dopamine system, decreased alcohol intake, and ability self-administration.^{56,57} In our study, there were very few women who were drinking (2.2%) or smoking (0.4%) and smoking associated with an increased risk of DPN (OR = 1.64, 95% CI 1.03–2.62, $p = 0.037$). Thus, GLP-1 levels were significantly decreased only in men with DPN, but not in women.

In this study, the multivariate logistic regression analysis showed that the following factors had a significant correlation to DPN in firstly diagnosed type 2 diabetes: hypertension, HbA1c, triglyceride, albumin, and fGLP-1. Particularly, high HbA1c, high triglyceride, low albumin levels, and low fGLP-1 were risk factors for DPN. Previous studies evidenced that decreased levels of serum albumin, elevated triglyceride, and hypertension correlated with progression of DPN.^{58–60}

There were some limitations of the study. Our study was conducted on a relatively small sample size. Besides, we had not been able to use electromyography for early diagnosis of peripheral nerve conduction disturbances in patients with type 2 diabetes who had an asymptomatic peripheral neuropathy.

Conclusion

In conclusion, the prevalence of DPN among nT2D was screened by the United Kingdom screening test was 26.6%. Age, smoking, hypertension, HbA1c control, triglyceride, albumin, 24hUA, diabetic retinopathy were the associated

risk factors of DPN. In patients with DPN, GLP-1 concentrations were reduced significantly, and a decrease in GLP-1 was a risk factor for DPN.

Abbreviations

DPN, diabetic peripheral neuropathy; fGLP-1, fasting glucagon-like peptide-1; nT2D, newly diagnosed type 2 diabetes mellitus; DPP4, dipeptidyl peptidase-IV; ELISA, enzyme-linked immunosorbent assay; BMI, body mass index; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; FPG, fasting plasma glucose; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; 24hUA, 24-h urinary albumin; HOMA, homeostasis model assessment; HOMA-S, insulin sensitivity; HOMA-B, beta-cell function; HOMA-IR insulin resistance; OR, odds ratio; CI, confidence interval.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no potential conflicts of interest in this work.

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