ORIGINAL RESEARCH

Correlation Between Growth Differentiation Factor-15 and Peripheral Neuropathy in Patients with Type 2 Diabetes Mellitus

Yue Li [1,2,]*, Yuhui Wang[2,3,]*, Yonghong Cao[1,2], Xinxiu Zhang[1,2], Wu Dai[1,2], Yiran Zhao[1,2], Lei Zhang[1,2], Xiaofang Han[1,2]

[1]Department of Endocrinology, Hefei Hospital Affiliated to Anhui Medical University, Hefei, People's Republic of China; [2]The Fifth Clinical College of Anhui Medical University, Hefei, People's Republic of China; [3]Department of Cardiology, Hefei Hospital Affiliated to Anhui Medical University, Hefei, People's Republic of China

*These authors contributed equally to this work

Correspondence: Xiaofang Han, Email hxfanghf@sina.com

Purpose: To inquire into the relationship between diabetic peripheral neuropathy (DPN) and serum levels of growth differentiation factor-15 (GDF-15) in individuals with type 2 diabetes mellitus (T2DM).

Patients and Methods: Out of 162 T2DM patients classified according to the diagnostic criteria of DPN, 75 were allocated to the non-DPN group and 87 to the DPN group. In turn, based on serum GDF-15 quartiles, all patients were additionally divided (GDF-15 low to high) into group A (40 cases), group B (41 cases), group C (41 cases), and group D (40 cases). General data and laboratory indexes of patients were collected, and enzyme-linked immunosorbent assay (ELISA) was used to determine serum GDF-15 levels.

Results: Compared to the non-DPN group, in the DPN group GDF-15 levels were noticeably greater ($P < 0.001$). Using serum GDF-15 as a grouping variable, DPN prevalence and body mass index were gradually increased, motor and sensory nerve latencies were gradually lengthened, and amplitude (Amp) and nerve conduction velocity (NCV) were gradually decreased with increasing GDF-15 levels ($P < 0.05$). Linear regression modeling revealed that GDF-15 levels correlated positively with the latencies of sensory and motor nerves, and negatively with their corresponding NCV ($P < 0.05$). Binary logistic regression results indicated GDF-15 as an independent predictor for DPN ($P < 0.05$), whereas restricted cubic spline analysis indicated a dose-response, nonlinear relationship between GDF-15 and DPN.

Conclusion: Serum GDF-15 level strongly correlates with DPN, and may represent an independent predictor and a biological marker for the disease.

Keywords: growth differentiation factor 15, diabetic neuropathy, nerve conduction study, type 2 diabetes mellitus

Introduction

The most common chronic complication of diabetes mellitus (DM) is diabetic peripheral neuropathy (DPN).[1] The prevalence of DPN in adults with diabetes in the United States is estimated to be 28%, and a meta-analysis indicated that DPN occurs in up to 90% of patients with diabetes of >20 years' duration.[2,3] DPN imposes a substantial economic burden and diminishes quality of life for individuals with diabetes. In the United States, the projected expenses associated with DPN ranged from $3000 to $4000 annually per patient.[4] It is estimated that 43% of DPN patients experience anxiety, depression, and sleep disorders,[5] and previous studies have reported an average loss of 5.5 working days per month due to pain.[6] Additionally, DPN-induced loss of protective sensation increases the risk of foot ulcers and lower limb amputations. Approximately 25% of DM patients suffer from a foot ulcer throughout their lifespan,[7] whereas approximately 14%–24% will require limb amputation.[8] Therefore, early detection and identification of potential predictors for DPN is necessary.

A constituent of the transforming growth factor-β (TGF-β) family, growth differentiation factor-15 (GDF-15) is extensively expressed throughout the peripheral and central nervous systems.[9] It was found that damage to Schwann cells can directly cause upregulation of GDF-15 expression.[9] As a marker of oxidative stress, endothelial dysfunction, atherosclerosis, and inflammation, GDF-15 participates actively in type 2 diabetes mellitus (T2DM) and its complications.[10,11] Peripheral nerve injury caused by multiple pathways, including metabolic disorders and inflammation, is the primary mechanism of DPN development.[12] Accordingly, we hypothesize that elevated GDF-15 may be related to the pathogenesis of DPN.

Since reliable biomarkers and targets for predicting DPN are currently insufficient, we conducted this study to investigate the relationship between GDF-15 and DPN.

Material and Methods

Study Participants

We enrolled 162 consecutive T2DM patients who were admitted to the Second People's Hospital of Hefei City from August 2022 to June 2023 and met the inclusion and exclusion criteria. According to the diagnostic criteria of DPN, two groups of patients, ie the DPN group (n = 87) and the non-DPN group (n = 75), were established.

Inclusion criteria: (1) diagnosis based on the diagnostic criteria established by the World Health Organization (WHO) in 1999; (2) completion of electromyography (EMG). Exclusion criteria: (1) acute complications of diabetes; (2) gestational diabetes; (3) severe diseases and conditions, such as tumors and infections (C-reactive protein > 10 mg/L), heart failure (NYHA classification > II), liver failure (Prothrombin activity < 40%, Total bilirubin > 170 μmol/L), renal failure (estimated glomerular filtration rate < 30 mL/min per 1.73 m^2 by the CKD-EPI formula), etc.; (4) diagnosed and/ or treated mental illness; (5) peripheral neurological disorders caused by other conditions, such as Parkinson's disease, herniated lumbar discs, Guillain-Barré syndrome, etc.

Data Collection

The patients' baseline data and laboratory findings were registered: (1) The demographics, medical history, and body measurement data, including age (years), sex, height (m), weight (kg), duration of DM (from now on referred to as duration, years), metformin medication, and hypertension status were collected through interviews. Body mass index (BMI, kg/m^2) was recorded through measurements by trained clinicians. (2) Collection and determination of peripheral blood specimens was performed after an 8-hour fasting period, from a sample of venous blood obtained in the early morning. After blood centrifugation, an immunoturbidimetric assay (ADVIA2400, Siemens, Germany) was used to determine triglyceride (TG, mmol/L), total cholesterol (TC, mmol/L), high-density lipoprotein (HDL, mmol/L), low-density lipoprotein (LDL, mmol/L), serum uric acid (UA, μmol/L), serum creatinine (Scr, μmol/L), and fasting blood glucose (FBG, mmol/L). Fasting insulin (INS, pmol/L) was measured with an automated chemiluminescence immunoassay (IMMULITE 2000, Siemens, Germany). Glycosylated hemoglobin A1c (HbA1c) was measured using a Trinity Biotech Premier Hb9210 kit (Trinity Biotech Plc., Ireland). Urine albumin creatine ratio (ACR) was measured using a urine-formed elements analyzer (AVE-764, AVE, China). (3) For GDF-15 determination, all blood samples were stored at −80°C before measurements. An enzyme-linked immunosorbent assay kit (Cusabio Biotechnology, China) was used to measure GDF-15 (pg/mL).

Electrophysiologic Testing

All enrolled subjects were tested using an electromyographic evoked potential apparatus (Neptune NDI-092; Haishen Suzhou Medical Instruments Co., Ltd., China). Motor nerves were selected from the median, ulnar, common peroneal, and tibial nerves; sensory nerves were chosen from the median, ulnar, and sural nerves. The latencies, amplitude (Amp), and nerve conduction velocity (NCV) of the motor and sensory nerves were recorded bilaterally in the study subjects. Given the complexity and specialized nature of this procedure, the assessment of electrophysiological parameters was assisted by two experienced electrophysiologists (Supplementary Appendix S1).

Definitions

(1) T2DM was defined based on the 1999 WHO diagnostic criteria (Supplementary Appendix S2).[13]

(2) DPN was determined using a tiered structure consisting of three levels of confirmed, clinical, or subclinical diagnostic criteria. The evaluation was primarily by clinical observations and nerve conduction test results (Supplementary Appendix S3).[14]

(3) Homeostasis model assessment of insulin resistance (HOMA-IR) index = FPG (mmol/L) × fasting insulin (μU/mL)/22.5 (Supplementary Appendix S4).

Statistical Analysis

SPSS, version 26.0 (IBM Company, Chicago, IL, USA), and R Studio, version 4.2.1 (R Foundation for Statistical Computing) were used to conduct the statistical analysis. Shapiro–Wilk test was used to test the normality of a variable. Normally distributed measures were expressed as mean ± standard deviation ($\bar{x} \pm$ s), Student's t-tests were used to compare two groups, and one-way analysis of variance (ANOVA) was used to compare several groups. Non-normally distributed measures were expressed as median and interquartile spacing [M (P25, P75)], and the Kruskal–Wallis H-test or the Mann–Whitney U-test was used to compare intergroup differences. Count data were presented as cases (percentage) [n (%)], and chi-squared tests were used to compare groups. We explored the correlation between GDF-15 and nerve conduction using linear regression modeling. The restricted cubic spline (RCS) method was performed to test for a nonlinear relationship between GDF-15 and DPN. Predictors for DPN were analyzed using multivariable binary logistic regression. To maintain the odds ratio (OR) values, beta values, and their 95% confidence intervals (CI) for GDF-15 at an appropriate scale, we reduced the value of GDF-15 to one percent of its original value when constructing linear regression and logistic regression models. Therefore, the results should be interpreted per 100 unit change. $P < 0.05$ indicated a statistically significant difference.

Results

Population Characteristics

On comparison of clinical data among patient groups, patients with DPN were significantly older and had higher duration, BMI, HbA1c, UA, ACR, and GDF-15 than those in the non-DPN group (Table 1). We compared also the clinical data based on serum GDF-15 as a grouping variable (Table 2). The results showed that there were remarkable differences in sex, prevalence of DPN, BMI, UA, Scr, and ACR between the four different groups. Overall, as the level of GDF-15 increased, the prevalence of DPN and BMI increased gradually (Table 2).

Table 1 Characteristics of the Study Population

	DPN group (n = 87)	Non-DPN group (n = 75)	t / z /X^2	p-value
Age (years)	62.94±11.55	58.09 ± 10.41	−2.789	0.006
Men, n (%)	53 (60.92)	43 (57.33)	0.215	0.643
Duration (years)	8 (5,13)	5 (2,10)	−2.509	0.012
Hypertension, n (%)	44 (50.57)	33 (44)	0.698	0.403
Metformin, n (%)	50 (57.47)	45 (60)	0.106	0.745
BMI (kg/m^2)	25.77 ± 4.05	24.22±2.33	−2.450	0.014
TC (mmol/L)	4.64±1.37	4.47±1.09	−0.862	0.390
TG (mmol/L)	1.50 (1.09, 2.38)	1.33 (0.98, 2.09)	−1.077	0.282
UA (μmol/L)	324.90 (266, 416)	283 (244, 332.9)	−2.867	0.004
FBG (mmol/L)	8 (6.76, 9.8)	7.30 (6.08, 8.8)	−1.905	0.057

(*Continued*)

Table 1 (Continued).

	DPN group (n = 87)	Non-DPN group (n = 75)	t / z /X^2	p-value
LDL (mmol/L)	2.35 (1.86, 3.04)	2.28 (1.83, 3.24)	−0.405	0.686
HDL (mmol/L)	1.18 (0.99, 1.44)	1.17 (1.02, 1.35)	−0.531	0.596
Scr (μmol/L)	64 (55, 75.5)	65 (51, 77)	−0.027	0.979
HbA1c (%)	8.80 (7.5, 10.9)	7.90 (7, 9.5)	−2.533	0.011
HOMA-IR	2.18 (1.08, 4.14)	2.07 (1.02, 3.21)	−0.7	0.484
ACR (mg/g)	40.04 (12.54, 107.2)	13.43 (6.84, 34.12)	−4.489	<0.001
GDF-15 (pg/mL)	612.31 (386.58,918.92)	366.23 (212.16,540.81)	−4.919	<0.001

Notes: Data are presented as mean ± SD, median (interquartile range), or number (percentage). Student's *t*-test and Mann–Whitney *U*-test were used for comparisons among two groups. Chi-squared test was used for between-group comparisons of count data.

Abbreviations: DPN, diabetic peripheral neuropathy; BMI, body mass index; TC, total cholesterol; TG, triglyceride; UA, serum uric acid; FBG, fasting blood glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; Scr, serum creatinine; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; ACR, urine albumin/creatinine ratio; GDF-15, growth differentiation factor-15.

Table 2 Characteristics of the Study Population Based on GDF-15 Levels

	Serum GDF-15 level				F/z/X^2	p-value
	(<25%) (Group A) (121.14–297.39 pg/mL)	(25%–50%) (Group B) (299.11–474.17 pg/mL)	(50%–75%) (Group C) (486.55–770.71 pg/mL)	(≥75%) (Group D) (775.34–2066.99 pg/mL)		
Age (years)	59.08±11.09	61.34±9.99	60.12±10.68	62.25±13.26	0.606	0.612
Men, n (%)	27 (67.5)	24 (58.54)	17 (41.46)	28 (70)	8.424	0.038
Duration (years)	8 (3.25, 10)	8 (3.5, 11.5)	7 (3.5, 13.5)	8 (4, 13)	0.288	0.962
Hypertension, n (%)	19 (47.50)	19 (46.34)	19 (46.34)	20 (50.00)	0.144	0.986
Metformin, n (%)	22 (55.00)	26 (63.41)	22 (53.66)	25 (62.50)	1.269	0.736
DPN, n (%)	13 (32.50)	18 (43.90)	23 (56.10)	33 (82.50)	22.253	<0.001
BMI (kg/m^2)	23.87±2.49	24.36±2.69	24.69±2.65	27.32±4.56	17.257	0.001
TC (mmol/L)	4.75±1.18	4.36±1.37	4.3±1.06	4.85±1.31	1.990	0.118
TG (mmol/L)	1.60 (1.04, 2.56)	1.35 (1.03, 2)	1.29 (0.99, 1.65)	1.55 (1.02, 3.67)	3.176	0.365
FBG (mmol/L)	7.78 (6.23, 8.75)	7.80 (5.91, 9.75)	7.40 (6.43, 9.59)	7.74 (6.29, 9.55)	0.339	0.952
LDL (mmol/L)	2.70±0.97	2.39±0.96	2.32±0.84	2.72±1.05	1.871	0.137
HDL (mmol/L)	1.22 (1.04, 1.40)	1.16 (1.03, 1.52)	1.19 (0.98, 1.39)	1.18 (0.96, 1.37)	0.783	0.854
UA (μmol/L)	299.45 (248.78, 332.98)	283.60 (254.40, 337.35)	276.00 (229.90, 340.30)	400.05 (274.23, 528.85)	20.878	<0.001
Scr (μmol/L)	63.75 (52.95, 76.33)	61.30 (50.65, 72.40)	60.00 (43.20, 72.50)	67.85 (60.00, 79.83)	8.016	0.046
ACR (mg/g)	21.83 (5.58, 43.81)	16.38 (6.83, 29.82)	20.46 (10.00, 42.97)	93.43 (18.27, 222.16)	23.247	<0.001
HOMA-IR	2.15 (1.09, 3.51)	1.70 (0.79, 3.01)	2.23 (1.05, 3.29)	2.34 (1.10, 4.37)	2.666	0.446
HbA1c (%)	8.25 (7.5, 10.63)	8.30 (6.85, 10.45)	8.40 (6.75, 10.8)	8.85 (7.55, 11.63)	3.760	0.289

Notes: Data are presented as mean ± SD, median (interquartile range), or number (percentage). One-way ANOVA and the Kruskal–Wallis *H*-test were used to compare samples from three or more groups. Chi-squared test was used for among-group comparisons of count data.

Abbreviations: GDF-15, growth differentiation factor-15; DPN, diabetic peripheral neuropathy; BMI, body mass index; TC, total cholesterol; TG, triglyceride; FBG, fasting blood glucose; LDL, low-density lipoprotein; HDL, high-density lipoprotein; UA, serum uric acid; Scr, serum creatinine; ACR, urine albumin/creatinine ratio; HOMA-IR, homeostasis model assessment of insulin resistance; HbA1c, glycosylated hemoglobin.

Correlation Analysis of Nerve Conduction and GDF-15

We next compared electromyography data from T2DM patients with different GDF-15 levels. The results showed differences in motor and sensory nerves between groups with different GDF-15 levels (P < 0.05). We noted that electromyography activity varied with GDF-15 levels, with increasing GDF-15 levels correlating with prolonged motor and sensory nerve latencies and decreased Amp and NCV (Table 3).

Table 3 Characterization of Nerve Conduction in Patients with Different GDF-15 Levels

		GDF-15 levels				p-value
		(<25%) (Group A) (121.14–297.39 pg/mL)	(25%–50%) (Group B) (299.11–474.17 pg/mL)	(50%–75%) (Group C) (486.55–770.71 pg/mL)	(≥75%) (Group D) (775.34–2066.99 pg/mL)	
Motor	Latency (ms)	2.83 (2.47, 3.35)	3.09 (2.81, 3.72)	3.36 (2.97, 3.74)	3.46 (3.14, 4.03)	<0.001
	Amp (mV)	8.61 (7.11, 10.14)	8.38 (6.33, 9.95)	7.88 (6.11, 9.56)	7.30 (5.77, 8.24)	0.018
	NCV (m/s)	52.45±3.77	51.99±3.50	50.10±3.83	49.60±4.52	0.002
Sensory	Latency (ms)	2.36 (2.20, 2.58)	2.55 (2.29, 2.73)	2.62 (2.34, 3.42)	2.65 (2.32, 3.54)	0.001
	Amp (μV)	14.87 (10.40, 18.65)	12.68 (10.01, 15.11)	11.14 (9.18, 14.27)	9.96 (6.76, 14.68)	0.001
	NCV (m/s)	58.44±4.38	57.23±5.37	56.22±4.73	54.73±5.37	0.009

Notes: Data are presented as mean ± SD, median (interquartile range), or number (percentage). One-way ANOVA and the Kruskal–Wallis H-test were used to compare samples from three or more groups.
Abbreviations: GDF-15, growth differentiation factor-15; Amp, amplitude; NCV, nerve conduction velocity.

Table 4 Multivariable Linear Regression Analysis of Nerve Conduction and GDF-15

Independent Variable	Dependent Variable	B	95% CI	p-value
GDF-15	Motor latencies (ms)	0.06	0.03, 0.09	<0.001
	Motor Amp (mV)	−0.14	−0.25, −0.03	0.012
	Motor NCV (m/s)	−0.29	−0.45, −0.12	0.001
	Sensory latencies (ms)	0.02	0.01, 0.03	0.004
	Sensory Amp (μV)	−0.23	−0.49, 0.04	0.090
	Sensory NCV (m/s)	−0.31	−0.48, −0.13	0.001

Notes: Linear regression models were used to explore the correlation between GDF-15 and nerve conduction properties.
Abbreviations: GDF-15, growth differentiation factor-15; Amp, amplitude; NCV, nerve conduction velocity.

Multivariable Linear Regression

A multiple linear regression analysis, which included variables with P < 0.05 in the single-factor logistic regression, and variance inflation factor (VIF) <5 was next conducted. The results demonstrated that GDF-15 correlated positively with the latency of sensory and motor nerves, and negatively with their NCV (Table 4 and Supplementary Tables 1–6).

Table 5 Logistic Regression Analysis of DPN Predictors

Variable	Univariate Analysis			VIF	Multivariate Analysis		
	OR	95% CI	p-value		OR	95% CI	p-value
GDF-15 (100 pg/mL)	1.30	1.16, 1.47	<0.001	1.12	1.24	1.09, 1.43	0.002
Age (years)	1.04	1.01, 1.07	0.007	1.44	1.03	0.99, 1.07	0.147
Male	1.16	0.62, 2.18	0.643	1.85			
Duration (years)	1.07	1.01, 1.13	0.016	1.25	1.03	0.97, 1.11	0.304
BMI (kg/m^2)	1.16	1.05, 1.30	0.006	1.49	1.03	0.9, 1.19	0.667

(*Continued*)

Table 5 (Continued).

Variable	Univariate Analysis			VIF	Multivariate Analysis		
	OR	95% CI	p-value		OR	95% CI	p-value
Hypertension	1.30	0.70, 2.43	0.404	1.40			
Metformin	0.90	0.48, 1.69	0.745	1.13			
TG (mmol/L)	1.15	0.98, 1.47	0.267	1.19			
TC (mmol/L)	1.12	0.87, 1.45	0.388	5.61			
HDL (mmol/L)	1.37	0.72, 2.96	0.364	1.92			
LDL (mmol/L)	1.05	0.76, 1.45	0.767	4.79			
Scr (μmol/L)	1.00	0.99, 1.01	0.882	2.28			
UA (μmol/L)	1.01	1.00, 1.01	0.002	1.55	1.00	1.00, 1.01	0.383
HbA1c (%)	1.22	1.07, 1.41	0.006	1.18	1.19	1.00, 1.44	0.061
HOMA-IR	1.00	0.98, 1.02	0.742	1.07			
FBG (mmol/L)	1.12	0.99, 1.28	0.093	1.17			
ACR (mg/g)	1.01	1.01, 1.02	0.001	1.40	1.01	1.00, 1.02	0.029

Notes: Logistic regression models were used to explore independent predictors for DPN.
Abbreviations: GDF-15, growth differentiation factor-15; BMI, body mass index; TG, triglyceride; TC, total choles-terol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Scr, serum creatinine; UA, serum uric acid; HbA1c, glycosylated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; FBG, fasting blood glucose; ACR, urine albumin/creatinine ratio.

Multivariable Logistic Regression

A multivariate binary logistic regression analysis, which included variables with P < 0.05 in the single-factor logistic regression, and VIF <5 was next conducted. The results indicated a strong correlation between GDF-15 and an elevated risk of DPN. Specifically, the likelihood of developing DPN rose by ~24% with each 100 pg/mL increment in GDF-15 levels (OR = 1.24, 95% confidence interval (CI): 1.09–1.43, P = 0.002) (Table 5).

Nonlinear Relationship Between GDF-15 and DPN

The RCS suggested that when GDF-15 is below 914.28 pg/mL, the occurrence of DPN increases remarkably as the level of GDF-15 increases (OR = 1.34, 95% 1.12~1.64, P = 0.002). In turn, a saturation effect is seen when GDF-15 exceeds 914.28 pg/mL, determining a nonlinear correlation between GDF-15 and DPN in our study subjects (Figure 1 and Supplementary Table 7).

Discussion

Approximately 50% of individuals with diabetes are projected to acquire diabetic peripheral neuropathy (DPN) over time, making the identification of biomarkers for early-stage DPN crucial.[15] The purpose of this study was to examine the link between GDF-15 and DPN by revealing the correlation between GDF-15 levels and nerve conduction parameters and DPN risk.

GDF-15 is a stress-responsive chemokine member of the transforming growth factor-β (TGF-β) superfamily. Elevated GDF-15 expression is associated with metabolic diseases, inflammation, cancer, and cardiovascular disease. Numerous studies have confirmed that GDF-15 is significantly correlated with the incidence of diabetes and is a high-risk biomarker for this condition.[16,17] In addition, research has showed that GDF-15 levels have a tendency to rise when microvascular injury worsens, and are positively linked to complications of macrovascular disease.[18,19] In our study, significant differences in BMI, UA, Scr, and ACR were found among patients with different GDF-15 levels. More importantly, a high level of GDF-15 was a predictor for DPN independent of traditional predictors such as age, BMI, duration, UA, HbA1c, and ACR (OR: 1.24, 95% CI: 1.09~1.43, P = 0.002).

The present study revealed a significantly higher BMI in the highest GDF-15 group (group D) compared to the lowest GDF-15 group (group A) (r = 0.197, P = 0.017), a finding consistent with Lee et al.[20] However, contradictory results emerged in previous research, which found that elevated levels of GDF-15 caused macrophage M2 polarization and promoted an improved inflammatory state and weight loss.[21] Notably, studies by Vila and Ho et al found no correlation
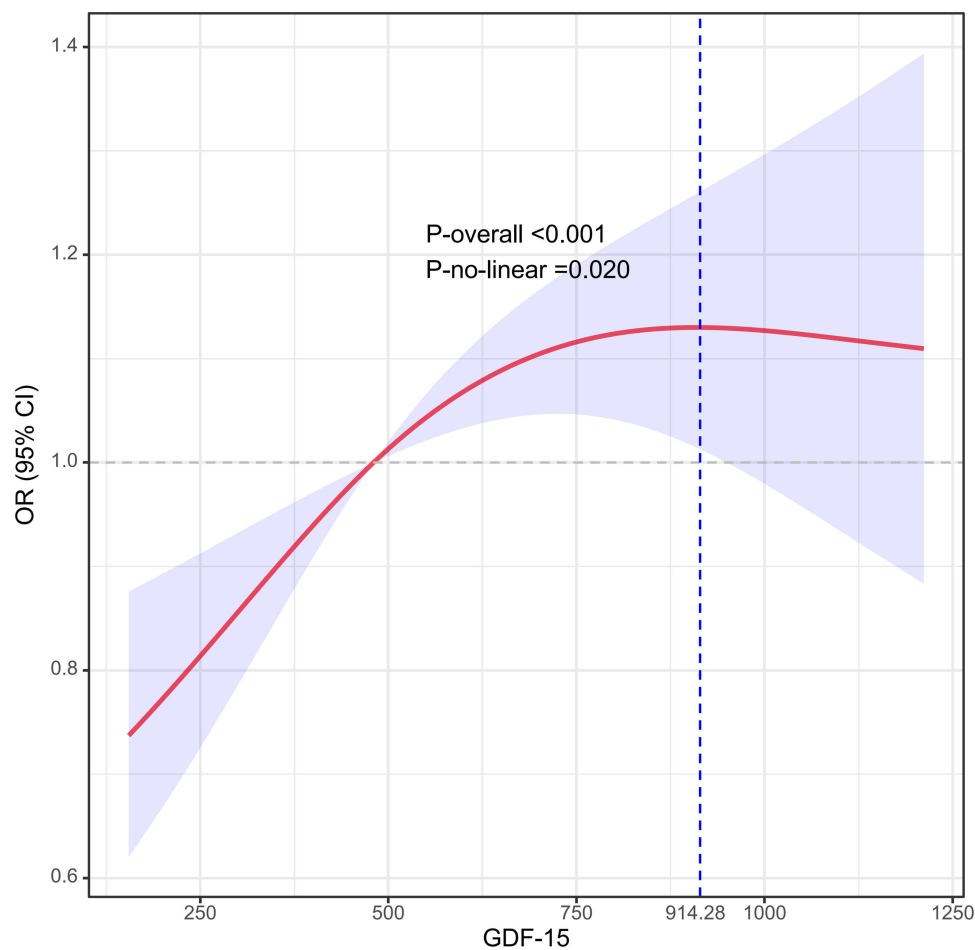
Figure 1 Correlation between GDF-15 and DPN. Odds ratios (OR) are shown as solid lines, and 95% confidence intervals (CI) are shown as purple areas. The dashed line corresponds to the turning point.

between GDF-15 and BMI.[22,23] In turn, a controlled study concluded that T2DM patients taking metformin had 40% higher GDF-15 levels than those who did not take this medication.[24] In contrast, in the present study no relationship was found between oral metformin and GDF-15 level. This discrepancy may be related to patient selection, study design, and/ or drug use. Another study reported that metformin prevented weight gain in wild-type mice fed a high fat diet. The authors hypothesized that metformin induces intestinal secretion of GDF-15 into the bloodstream, which activates the hindbrain and the nucleus accumbens via the GFRAL pathway, thereby affecting feeding behavior and reducing body weight.[25]

The complex pathophysiological mechanisms of DPN are thought to arise in the context of diabetes. As a common vascular factor, high glucose levels are a significant predictor for DM and its complications.[26] Indicators of dysglycemia, including chronic hyperglycemia (HbA1c) and time in range, have been shown in this and other studies to be predictors for DPN.[27] Additionally, the progression of DPN is linked to oxidative stress, mitochondrial dysfunction, inflammatory response, and lipid metabolism disorders.[28–31] Serum GDF-15 has been shown to predict tibial motor neuropathy and ulnar and median sensory neuropathy in patients with DM, suggesting that there is a significant correlation between elevated levels of GDF-15 and DPN.[32] Consistent with this, in this work we discovered that GDF-15 levels were markedly elevated in patients with T2DM without comorbid DPN, whereas the occurrence of DPN gradually increased with GDF-15. In this respect, a dose-response correlation between GDF-15 and DPN was found by RCS analysis. When GDF-15 was below 914.28 pg/mL, the risk of DPN prevalence increased with increasing GDF-15 levels (OR = 1.34, 95% 1.12~1.64, P = 0.002). We also found that GDF-15 levels showed a positive linear correlation with the latency of sensory and motor nerves and a negative linear correlation with NCV. This was consistent with the study of Weng et al,[32]

suggesting that DPN-related nerve damage was aggravated by increased GDF-15 levels. Therefore, elevated circulating GDF-15 levels may be a potential predictor for DPN.

Several possible mechanisms may explain the relationship between GDF-15 and DPN. Insulin resistance is considered a common factor in the pathogenesis of T2DM and DPN. Studies have shown that GDF-15 is a reliable indicator of insulin resistance, regardless of other factors.[33] On the one hand, increasing GDF-15 levels during stress improves insulin resistance through the PPAR β/δ- Adenosine 5- monophosphate (AMP)- activated protein kinase (AMPK) pathway.[34] On the other hand, overexpression of GDF-15 increases glucose uptake and promotes glucose-induced insulin secretion by upregulating the major glucose transporter and downregulating metallothionein-1 (MT-1) expression.[35] In addition, GDF-15 protects pancreatic islet β cells function by activating the PI3K-Akt-eNOS signaling pathway and attenuating the expression of NF-κB, JNK, and cysteinyl aspartate-specific proteinase-3 (Caspase-3), and by exerting anti-apoptotic properties.[36–38]

Studies have confirmed that DPN is characterized by low-grade chronic subclinical inflammation.[31] High glucose levels trigger increased release of pro-inflammatory factors and active production of reactive oxygen species, which induce apoptosis of neurons and Schwann cells in peripheral nerves, resulting in neurological and vascular changes.[30] Data suggest that Schwann cells directly release GDF-15 upon cell injury.[39] GDF-15, being an anti-inflammatory protein, hinders the activation of macrophages and has a beneficial impact on chronic inflammatory conditions like T2DM.[10]

Study Limitations

There are certain constraints in the current investigation. First, this is a cross-sectional study, which cannot confirm a causal relationship between GDF-15 and the development of DPN. Hence, sampling size should be further enlarged to conduct a prospective study in the future. Second, the specific mechanism(s) underlying the association between GDF-15 and DPN need to be identified. Third, the degree of abnormality of the nerves examined was not accounted for in this study, so it was not possible to explore lesion differences between sensory and motor or upper and lower limb nerves. Fourth, this study included a relatively limited number of participants and did not include a control group with normal blood glucose. The bias brought by the small-sample study was unavoidable, and there were some markers or indicators (such as FBG, HbA1c, HOMA-IR, etc). whose serum levels were theoretically associated with GDF-15 but did not show significance.

Conclusion

In summary, high levels of GDF-15 are an independent predictor for DPN. As the GDF-15 level increased, the latency period of sensory and motor nerves of DM patients was prolonged. The concomitant decrease in NCV indicates a close correlation between GDF-15 expression and diabetic peripheral nerve injury. Since this correlation is highly significant for assessing the pathophysiology of DPN and the severity of the disease, future studies should focus on the mechanisms and pathways involved, to aid convenient screening for DPN in primary hospitals. Furthermore, because of its role in enhancing insulin sensitivity and reducing body weight, GDF-15 offers possible avenues for developing insulin sensitizers and weight loss drugs.

Abbreviations

ANOVA, Analysis of variance; BMI, Body mass index; CI, Confidence intervals; DM, Diabetes mellitus; DPN, Diabetic peripheral neuropathy; FBG, Fasting blood glucose; HDL, High-density lipoprotein; LDL, Low-density lipoprotein; NCV, Nerve conduction velocity; OR, Odds ratios; RCS, Restricted cubic spline; ROS, Reactive oxygen species; TC, Total cholesterol; TIR, Time in range; UA, Uric acid; WHO, World Health Organization; AMPK, Adenosine 5'- monophosphate (AMP)- activated protein kinase.

Ethics Approval and Informed Consent

The study conforms to the principles of the Helsinki Declaration, and it was approved by the hospital's Medical Ethics Committee (No. 2023-keyan-108). Each patient signed an informed permission form. Blood samples were obtained from the remaining samples of routine admission tests, ensuring that there was no additional risk to the patients.

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Disclosure

All authors have declared no conflicts of interest and have consented to the publication of the data described in this manuscript.

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