Are Hyperlipidemia and Lipid-Lowering Drugs Risk Factors for Diabetic Peripheral Neuropathy?

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Abstract

Aims

Previous studies showed conflicting relationship between hyperlipidemia, lipid-lowering therapy and diabetic peripheral neuropathy (DPN). As most of these works emerges from the Western and Australian countries, our study aims to investigate whether hyperlipidemia or lipid-lowering drugs is associated with the risk of DPN in Taiwanese patients with type 2 diabetes (T2D).

Methods

A cross-sectional, hospital-based observation study in adults with T2D was conducted from January to October 2013. DPN was screened using the Michigan Neuropathy Screening Instrument. Diagnosis of hyperlipidemia was based on serum levels of lipid profiles. Patients taking lipid-lowering drugs were identified at enrollment.

Results

2,448 participants were enrolled, 524 (21.4%) of whom had DPN. Patients with DPN had lower plasma total cholesterol (TC; 185.6 ± 38.6 mg/dL vs 193.4 ± 42.3 mg/dL, $P < 0.001$) and low-density lipoprotein cholesterol levels (LDL-C; 114.6 ± 32.7 mg/dL vs 119 ± 30.8 mg/dL, $P = 0.019$). Multivariate analysis demonstrated that neither hyperlipidemia nor lipid-lowering drugs was associated with a risk of DPN. Subgroup analysis revealed that high TC, LDL-C, and statin or fibrate use were not associated with DPN occurrence.

Conclusion

Our results suggests that neither hyperlipidemia nor lipid-lowering medication was associated with DPN in adults with T2D. DPN is a multifactorial disease, and our findings indicate that lipid metabolism may play a minor role in its pathogenesis.

Introduction

Diabetic peripheral neuropathy (DPN) is the prevailing chronic complication in patients with type 1 (T1D) and type 2 diabetes (T2D). The lifetime prevalence of DPN can reach as high as 50% in adults with diabetes ¹, and it contributes to numerous disabling morbidities, such as diabetic foot ulceration and consequent lower limb amputation ². The most common type of DPN is distal symmetric polyneuropathy (DSP), which accounts for approximately 75% of all DPN cases ¹.

Because there is no known disease-modifying therapy for DPN other than serum glucose control, risk factor reduction in vulnerable populations is essential to limit future cases of DPN. The incidence of DPN in patients with T1D has the potential to be reduced by up to 60–70% with appropriate glycemic control measures^{3,4}; in contrast, preventing DPN by treating hyperglycemia in T2D yields only a 5–7% reduction in DPN incidence^{5,6}. Despite strict glucose control, more than 40% of diabetic patients are eventually diagnosed with peripheral neuropathy, suggesting that hyperglycemia is not the sole instigator of DPN⁶. The risk factors reported in previous studies include hyperglycemia, elevated glycated hemoglobin levels (HbA1c), increased duration of diabetes, insulin resistance, metabolic syndrome, hypertension, smoking, alcohol abuse, and abdominal obesity^{1,7}. Dyslipidemia may be another risk factor for DPN. Studies have found that high plasma triglycerides (TGs) and low high-density lipoprotein cholesterol (HDL-C) levels were associated with DPN in patients with diabetes^{8–10}. Unlike the well-established correlation between high TG and low HDL-C levels, the correlation is variable between DPN and other serum lipid components, such as total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) levels. Some studies have found a positive correlation between elevated serum TC levels and DPN^{11,12}, while others report that low LDL-C and TC levels are also risk factors for DPN^{13,14}. Furthermore, conflicting data have been reported on the impacts of dyslipidemia treatment on DPN. Two Danish studies found that treatment with either statin or fibrate was associated with a lower incidence of DPN^{15,16}. However, one nationwide study in the United States demonstrated that the prevalence of peripheral neuropathy was significantly higher among statin-users compared with non-users¹⁷. At the present time, there is insufficient evidence to advocate the association between lipid-lowering drugs and DPN in Asian population. The objective of the present study is to determine whether lipid-lowering drugs or hyperlipidemia is associated with an increased risk of DPN among Han Taiwanese adults with T2D.

Methods

Study Design and Participants

This was a retrospective, cross-sectional observational study. Patients with prevalent or newly diagnosed T2D over 20 years of age between January 2013 and October 2013 were eligible for inclusion. Each of the participants was diagnosed by endocrinologists in the outpatient units at a Taiwanese tertiary medical center, which serves approximately 6,500 outpatients and 1,500 inpatients every day. All eligible patients were enrolled in our diabetes care network, hence detailed demographic and clinical recordings were regularly documented. The diagnoses of T2D were based on the criteria of American Diabetes Association (ADA). Individuals who were diagnosed with T1D or gestational diabetes, and whose plasma lipid measurements were not available were excluded. Before drawn for analysis, patients' information was anonymized by computer system, and the researchers were blinded to these data. The study was approved by the Institutional Review Board of Taichung Veterans General Hospital (CG18082B-1). Because of the retrospective and anonymous nature of this study, the need for informed consent was waived by Taichung Veterans General Hospital Institutional Review Board. All methods were performed in accordance with the relevant guidelines and regulations.

Anthropometric measurements

Upon entry into this study, a case-management nurse performed anthropometric measurements to all participants. The anthropometric measurements included height, weight, waist circumference, and body mass index (BMI). Resting systolic and diastolic blood pressure were measured in the right arm when the patient was in a sitting position. For the details on the anthropometric measurements, please refer to our published studies^{18–22}. Besides, the care-management nurse was also responsible for recording all of the eligible patients' previous or current disease status, duration of diabetes, hypoglycemic medication use, plasma lipid profiles, lipid-lowering drugs (including statins and fibrates) prescription and lifestyle habits, including smoking or alcohol drinking.

Biochemical data

Laboratory examinations were administered during endocrinology outpatient visits. In the morning after an overnight fasting period, blood samples were obtained from the antecubital vein. Fasting plasma glucose (using standard enzymatic methods), HbA1c (using high-performance liquid chromatography), and plasma lipid profiles (using standard enzymatic methods), including TC, HDL-C, LDL-C, and TG, were measured and recorded. To identify the individuals with hyperlipidemia, we adopted the following cut-off points: TG: > 200 mg/dL, TC: > 200 mg/dL, and LDL-C: > 130 mg/dL, according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III²³.

Using the six-variable Modification of Diet in Renal Disease Eq. 2⁴, estimated glomerular filtration rate (eGFR) was estimated as:

$$186 \times \text{Serum creatinine}^{-1.154} \times \text{Age}^{-0.203} \times (0.742 \text{ if female})$$

For the patients who had received lipid-lowering drugs, their baseline lipid levels were defined as the mean plasma lipid values (including TC, HDL-C, LDL-C and TG) in the 5 years prior to drug prescription. For the individuals who had never received lipid-lowering drugs, the baseline lipid profiles were circumscribed as the 5-year mean plasma lipid levels prior to study enrollment, from 2008 to 2012. Meanwhile, the follow-up lipid levels were measured in both lipid-lowering drug users and non-users. In the former group, the follow-up lipid values were defined as the mean lipid values in the 5 years after medication prescription. In the latter group, the mean lipid values within the 5 years after study entry, from 2013 to 2017, were regarded as their follow-up lipid values.

Diagnosis of hyperlipidemia and comorbidities

Diagnosis of hyperlipidemia depended on their plasma lipid profiles recorded when they were enrolled in our study. Individuals who had either hypercholesterolemia (TC > 200 mg/dL), hyper-LDL-C (LDL-C > 130 mg/dL), or hypertriglyceridemia (TG > 200 mg/dL) were divided into the hyperlipidemic group. If the participants did not have hyperlipidemia, they were regarded as normolipidemic. Patients were

categorized into three groups on the basis of their lipidemic profiles and usage of lipid-lowering drugs. Patients who were normolipidemic and had never received lipid-lowering drugs were marked as the NL-N group. Those who administered lipid-lowering drugs were divided further depending on the hyperlipidemia diagnoses into two groups, test group 1 (normolipidemic patients receiving lipid-lowering drugs [NL-D]) and test group 2 (hyperlipidemic patients taking lipid-lowering drugs [HL-D]).

Any of the following outpatient or inpatient claims recorded from 2010 to 2012 were considered as comorbidities. These comorbidities, which were also identified using ICD-9-CM codes, included cardiovascular disease (CVD; ICD-9-CM 390–438), ischemic heart disease (ICD-9-CM 410–414), and liver disease (ICD-9-CM 571–573). Both ischemic heart disease and cardiovascular disease were classified as co-morbid heart disease in our study.

Assessment of diabetic peripheral neuropathy

All of the enrolled patients received assessment of DPN by the same trained and certificated care-management nurse to minimize the inter-rater reliability. DPN was evaluated based on the second component of Michigan Neuropathy Screening Instrument (MNSI). Based on the latest position statement of DPN by the American Diabetes Association (ADA), the MNSI was recommended as a validated instrument to identify the neuropathy end points for researches and clinical trials²⁵. The MNSI was widely used in abundant clinical studies of patients with T2D^{5,8,15,26}, including our published works^{18–22}. Physical appearance of feet, ulceration, ankle deep tendon reflexes, and the perception of light touch (using Semmes-Weinstein 5.07 10-g monofilament) and distal vibration (using 128-Hz tuning fork) were investigated. As previous validated studies in adults²⁷, individuals whose MNSI examination (MNSIE) score more than two were assigned to the DPN group. Based on the current diagnostic criteria for DPN, those patients in the DPN group were supposed to be categorized as possible or probable DPN²⁸.

Statistical Methods

Descriptive statistics were presented as the mean values $\pm$ standard deviation (SD) and as the numbers with percentages. We used Fisher's exact test or chi-squared test to analyze categorical variables, while the analyses of continuous variables were conducted using ANOVA tests.

Multivariate logistic regression analyses were carried out to explore the effect of each identified independent variable on DPN. The multivariate regression models included all the confounders and the variables that had shown a significant correlation, and the adjusted odds ratios (OR) with 95% confidence interval (CI) were calculated between the comparison groups. The statistical significance level chosen was P value less than 0.05 ($P < 0.05$), and all tests were two-sided. All the data were analyzed using statistical package SAS version 9.4 for Windows.

Results

Clinical and demographic characteristics

The sample's clinical and demographic characteristics are summarized in Table 1. A total of 2,448 patients were included in our study, 524 (21.4%) of whom were in the DPN group. The mean age of participants was 64.0 ± 12.9 years at the time of the investigation. 1409 (57.6%) of the sample were male and 1039 (42.4%) were female. The mean duration of diabetes was 10.3 ± 8.4 years, and the mean serum HbA1c level was $7.4 \pm 1.4\%$ (57 ± 15.3 mmol/mol). The majority of patients (96.2%) had received at least one form of pharmacological treatment for diabetes.

Table 1
Clinical and sociodemographic characteristics of the study

Variable	Total (n = 2448)		Without neuropathy (n = 1,924)		With neuropathy (n = 524)		P value
	N	%	N	%	N	%	
Sociodemographic factors							
Age, years	64.0 ± 12.9		62.1 ± 12.4		71.1 ± 12.4		< 0.001
≥ 65	1149	46.9	777	40.4	372	71.0	< 0.001
Male Gender	1409	57.6	1090	56.7	319	60.9	0.083
BMI, kg/m ²	25.7 ± 4.1		25.8 ± 4.1		25.4 ± 4.1		0.071
Waist circumference, cm	90.9 ± 10.5		90.4 ± 10.4		92.6 ± 10.4		0.030
SBP ≥ 130 mmHg or DBP ≥ 85 mmHg	1389	57.4	1075	56.5	314	39.4	0.095
Smoker	236	9.6	201	10.4	35	6.7	0.010
Alcohol drinker	86	3.5	66	3.4	20	3.8	0.666
Diabetes-related factors							
Fasting plasma glucose, mg/dL	143.2 ± 46.3		143.4 ± 45.9		142.6 ± 48		0.745
HbA1c, % (mmol/mol)	7.4 ± 1.4		7.4 ± 1.4		7.5 ± 1.5		0.589
Duration of diabetes, years	10.3 ± 8.4		9.3 ± 7.9		13.9 ± 9.4		< 0.001
Type of diabetes treatment							< 0.001
No medication	77	3.8	59	3.7	18	4.0	
OHA only	1430	69.8	1163	72.6	267	59.9	
Insulin only	156	7.6	100	6.2	56	12.6	
Insulin + OHA	385	18.8	280	17.5	105	23.5	

Data are expressed as mean ± SD for continuous variables and frequency (%) for categorical variables. Differences in continuous variables by ANOVA; differences in categorical variables by Fisher's exact or chi-squared test.

BMI, body mass index; kg, kilograms; cm, centimeters; HbA1c, glycated hemoglobin; OHA, oral hypoglycemic agent; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; IHD, ischemic heart disease.

Variable	Total (n = 2448)		Without neuropathy (n = 1,924)		With neuropathy (n = 524)		P value
	N	%	N	%	N	%	
Lipid-lowering drugs							0.148
No medication	396	16.2	298	15.5	98	18.7	
statin only	1654	67.6	1305	67.8	349	66.6	
fibrate only	63	2.6	47	2.4	16	3.1	
statin + fibrate	335	13.7	274	14.2	61	11.6	
Biochemical factors							
Baseline TC, mg/dL	191.7 ± 41.6		193.4 ± 42.3		185.6 ± 38.6		< 0.001
≥ 200	878	36.3	709	37.3	169	32.5	0.042
Baseline TG, mg/dL	199.7 ± 228.6		198.6 ± 223.1		204.5 ± 252.5		0.795
≥ 200	207	30.0	168	29.8	39	31.0	0.796
Baseline HDL-C, mg/dL	50.3 ± 13.2		50.3 ± 12.9		50.2 ± 14.1		0.833
Female < 50; male < 40	749	31.5	582	31.2	167	32.7	0.508
Baseline LDL-C, mg/dL	118.0 ± 31.3		119 ± 30.8		114.6 ± 32.7		0.019
≥ 130	524	31.5	423	32.7	101	27.5	0.060
Follow-up TC, mg/dL	161.0 ± 28.3		162.4 ± 28.1		155.7 ± 28.2		< 0.001
≥ 200	187	7.8	154	8.2	33	6.5	0.212
Follow-up TG, mg/dL	151.1 ± 118.6		153.2 ± 123.4		143.1 ± 97.6		0.147
≥ 200	240	17.9	189	17.7	51	18.5	0.767
Follow-up HDL-C, mg/dL	50.2 ± 12.6		50.4 ± 12.5		49.8 ± 13.2		0.344
Female < 50; male < 40	742	31.1	587	31.2	155	30.6	0.804
Follow-up LDL-C, mg/dL	93.7 ± 23.7		94.8 ± 23.7		89.7 ± 23.1		< 0.001

Data are expressed as mean ± SD for continuous variables and frequency (%) for categorical variables. Differences in continuous variables by ANOVA; differences in categorical variables by Fisher's exact or chi-squared test.

BMI, body mass index; kg, kilograms; cm, centimeters; HbA1c, glycated hemoglobin; OHA, oral hypoglycemic agent; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; IHD, ischemic heart disease.

Variable	Total (n = 2448)		Without neuropathy (n = 1,924)		With neuropathy (n = 524)		P value
	N	%	N	%	N	%	
≥ 130	150	6.3	125	6.7	25	4.9	0.154
eGFR	77.9 $\pm$ 30.9		81.5 $\pm$ 29.8		65.1 $\pm$ 31.6		< 0.001
< 60 ml/min/1.73m ²	603	27.8	388	22.8	215	45.7	< 0.001
Comorbidities							
Heart disease (CVD or IHD)	482	19.7	297	15.4	185	35.3	< 0.001
Liver disease	48	2.0	36	1.9	12	2.3	0.540
Data are expressed as mean $\pm$ SD for continuous variables and frequency (%) for categorical variables. Differences in continuous variables by ANOVA; differences in categorical variables by Fisher's exact or chi-squared test.							
BMI, body mass index; kg, kilograms; cm, centimeters; HbA1c, glycated hemoglobin; OHA, oral hypoglycemic agent; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate; CVD, cardiovascular disease; IHD, ischemic heart disease.							

The patients with DPN were significantly older than the patients without DPN (71.1 $\pm$ 12.4 years vs 62.1 $\pm$ 12.4 years, $P < 0.001$). Compared to those without DPN, patients with DPN tended to have a larger waist circumference (92.6 $\pm$ 10.4 cm vs 90.4 $\pm$ 10.4 cm, $P = 0.030$), were more likely to smoke ($P = 0.010$), and had a longer duration of diabetes (13.9 $\pm$ 9.4 years vs 9.3 $\pm$ 7.9 years, $P < 0.001$), fewer prescriptions for oral hypoglycemic medication, more insulin prescriptions, lower eGFR levels (65.1 $\pm$ 31.6 vs 81.5 $\pm$ 29.8 mL/min/1.73m², $P < 0.001$), and higher rates of co-morbid heart disease (35.3% vs 15.4%, $P < 0.001$). No differences were found between DPN patients and controls with respect to gender, BMI, history of alcohol consumption, systolic and diastolic blood pressure, fasting plasma glucose, HbA1c levels, number of lipid-lowering drug prescriptions, and co-morbid liver disease.

In respect to the plasma lipid levels, the patients with DPN had not only lower baseline and follow-up TC values (baseline: 185.6 $\pm$ 38.6 vs 193.4 $\pm$ 42.3 mg/dL, $P < 0.001$; follow-up: 155.7 $\pm$ 28.2 vs 162.4 $\pm$ 28.1 mg/dL, $P < 0.001$), but also lower baseline and follow-up LDL-C levels (baseline: 114.6 $\pm$ 32.7 vs 119 $\pm$ 30.8 mg/dL, $P = 0.019$; follow-up: 89.7 $\pm$ 23.1 vs 94.8 $\pm$ 23.7 mg/dL, $P < 0.001$). No differences were found in plasma HDL-C or TGs levels.

Comparison of DPN risks between NL-N, NL-D, and HL-D

As mentioned, the 2,448 patients were allocated to one of three groups—NL-N, NL-D, or HL-D—depending on the lipidemic and prescription status of lipid-lowering drugs. The NL-N group comprised 396 patients (16.2%), 98 of whom had DPN; the NL-D group comprised 946 patients (38.6%), 213 of whom had DPN;

and the HL-D group comprised 1106 individuals (45.2%), 213 of whom had DPN. To determine whether hyperlipidemia or lipid-lowering drugs were associated with DPN, multivariate logistic regression analysis was performed, revealing no differences in the risk of DPN between the NL-N and NL-D group (OR: 1.10; 95%CI: 0.58–2.09; Table 2). These results indicate that in patients without hyperlipidemia, intake of lipid-lowering medication did not impact the risk of DPN. Furthermore, the risk of DPN in the HL-D group did not significantly differ from those in the NL-N or NL-D group, suggesting that neither hyperlipidemia nor lipid-lowering drugs significantly influenced the risk of DPN in patients with T2D.

Table 2

Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) for DPN, according to lipidemic status and lipid-lowering drug use condition

Variables	Adjusted OR ^a	95% CI	P-value
Sub-analysis			
NL-N	1.00	—	—
NL-D	1.10	0.58–2.09	0.771
HL-D	0.89	0.45–1.76	0.734
Sub-analysis			
NL-D	1.00	—	—
NL-N	0.91	0.48–1.72	0.771
HL-D	0.81	0.49–1.34	0.410
NL-N, normolipidemic non-lipid-lowering drug users; NL-D, normolipidemic lipid-lowering drug users; HL-D, hyperlipidemic lipid-lowering drug users.			
^a Adjusted for age, sex, waist, smoking, duration of diabetes, type of diabetes treatment, eGFR, heart disease.			

Differential impacts of LDL-C or TC on DPN in NL-N, NL-D, and HL-D

Significantly lower baseline and follow-up LDL-C and TC were found in the DPN population in our study. To explore whether plasma LDL-C or TC concentrations differentially affected risk of DPN, the HL group was subcategorized into two groups on the basis of plasma LDL-C and TC values. Patients with high plasma LDL-C levels (> 130 mg/dL) were allocated to the HLDL group, whereas those with low levels (< 130 mg/dL) were assigned to the NLDL group. Meanwhile, individuals with high plasma TC (> 200 mg/dL) and normal plasma TC (< 200 mg/dL) levels were assigned to the HTC and NTC group, respectively.

Multivariate logistic regression analysis was performed to determine whether baseline plasma LDL-C or TC levels were independently correlated with DPN. Relative to the NTC-N group, no significant differences were found with regard to DPN in either the NTC-D or HTC-D group (Table 3). The corresponding adjusted

ORs of DPN were 1.09 (95% CI: 0.58–2.05, $P = 0.781$) and 0.85 (95% CI: 0.42–1.74, $P = 0.661$), respectively. Similarly, no differences in DPN risk were found between the NLDL-N, NLDL-D (OR: 1.42, 95%CI: 0.72–2.8; $P = 0.308$), and HLDL-D (OR: 1.37, 95% CI: 0.61–3.07; $P = 0.447$) groups.

Table 3

Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) for DPN, according to classification of lipid profiles

Variables	Adjusted OR ^a	95% CI	P-value
Sub-analysis – Baseline TC			
Baseline NTC-N	1.00	—	—
Baseline NTC-D	1.09	0.58–2.05	0.781
Baseline HTC-D	0.85	0.42–1.74	0.661
Sub-analysis – Baseline LDL-C			
Baseline NLDL-N	1.00	—	—
Baseline NLDL-D	1.42	0.72–2.8	0.308
Baseline HLDL-D	1.37	0.61–3.07	0.447
Sub-analysis – Follow-up TC			
Follow-up NTC-N	1.00	—	—
Follow-up NTC-D	1.10	0.59–2.05	0.770
Follow-up HTC-D	0.72	0.2–2.62	0.617
Sub-analysis – Follow-up LDLC			
Follow-up NLDL-N	1.00	—	—
Follow-up NLDL-D	1.09	0.58–2.03	0.790
Follow-up HLDL-D	0.75	0.2–2.79	0.668
NTC-N, normocholesterolemic non-lipid-lowering drug users; NTC-D, normocholesterolemic lipid-lowering drug users; HTC-D, hypercholesterolemic lipid-lowering drug users; NLDL-N, normal LDL-C non-lipid-lowering drug users; NLDL-D: normal LDL-C lipid-lowering drug users; HLDL-D: hyper-LDL-C lipid-lowering drug users.			
^a Adjusted for age, sex, waist, smoking, duration of diabetes, type of diabetes treatment, eGFR, heart disease.			

Regarding follow-up plasma TC and LDL-C levels, similar results were found. Multivariate analysis revealed no differences in the DPN risk between the NTC-N, NTC-D (OR: 1.10, 95% CI: 0.59–2.05), and HTC-D (OR: 0.72, 95% CI: 0.2–2.62) group. Lastly, compared with the NLDL-N group, neither the NLDL-D nor HLDL-D group showed significant differences in the risk of DPN, with corresponding adjusted ORs of

1.09 (95% CI: 0.58–2.03) and 0.75 (95% CI: 0.2–2.79), respectively. These results suggest that plasma LDL-C and TC levels were not associated with DPN in our study.

Differential impacts of statin or fibrate on DPN in NL-N, NL-D, and HL-D

Finally, to determine whether different classes of lipid-lowering drugs had diverse effects on the risk of DPN, we categorized the patients who received medication intervention into two subgroups: the statin (S) and the fibrate (F) group. The results of the multivariate logistic regression analysis are shown in Table 4.

Table 4
Adjusted odd ratios (ORs) and 95% confidence intervals (CIs) for DPN, according to different classes of lipid-lowering drugs use

Variables	Adjusted OR ^a	95% CI	P-value
Sub-analysis – Statin			
NL-N	1.00	—	—
NL-S	1.09	0.59–2.03	0.776
HL-S	0.89	0.46–1.71	0.720
Sub-analysis – Fibrate			
NL-N	1.00	—	—
NL-F	0.73	0.33–1.61	0.431
HL-F	0.50	0.16–1.6	0.245
NL-N, normolipidemic non-lipid-lowering drug users; NL-S, normolipidemic statin users; HL-S, hyperlipidemic statin users; NL-F, normolipidemic fibrate users; HL-F, hyperlipidemic fibrate users			
^a Adjusted for age, sex, waist, smoking, duration of diabetes, type of diabetes treatment, eGFR, heart disease.			

First, relative to the NL-N group, no significant differences in the risk of DPN were found in the NL-S and HL-S groups. The corresponding adjusted ORs were 1.09 (95% CI: 0.59–2.03) and 0.89 (95% CI: 0.46–1.71) in the NL-S and HL-S group, respectively. As concerns fibrate use, no group was significantly associated with DPN. Our results suggest that neither statin nor fibrate are significant risk factors for DPN.

Discussion

To the best of our knowledge, this is the first large-scale cross-sectional study aimed at investigating the contribution of hyperlipidemia and lipid-lowering drugs to the development of DPN in T2D adults in Taiwan. Our study demonstrated that neither hyperlipidemia nor lipid-lowering drugs was associated with an increased risk of developing DPN. This finding remained consistent in patients with either

hypercholesterolemia, hyper-LDL-C, or who received statin or fibrate treatment. Moreover, patients with DPN in our study tended to have lower serum TC and LDL-C levels than those without DPN.

Compared with previous studies, our study consisted of more T2D patients who were under lipid-lowering drugs²⁹. 81.3 percent of our patients received statin alone or in combination with fibrate. There were 946 patients who was normolipidemic but still received lipid-lowering drugs, mostly statin. The possible explanation was that statin was regarded as a cornerstone of prevention of atherosclerotic disease in patients with T2D. Based on the guideline of blood cholesterol management from American College of Cardiology/American Heart Association (ACC/AHA) in 2013, statin is recommended in diabetic patients whose serum LDL levels are between 70 to 189 mg/dL³⁰. This recommendation is mainly aimed to reduce the atherosclerotic cardiovascular risk in patients with diabetes. Therefore, in our study, many patients might still receive statin even they did not have hyperlipidemia. However, the aforementioned subgroup analysis showed that there was no difference in the risk of DPN between the normolipidemic patients who received lipid-lowering drugs or not. This finding implicated that statin was proven to have benefits in risk reduction in macrovascular complications, but when it comes to microvascular complications, this effect might be obscure.

Preclinical studies have described diverse pathophysiological mechanisms, resulting from increased intracellular glucose level, elevated serum free fatty acids, oxidized or glycated lipoproteins, in the development and progression of DPN^{7,31,32}. Despite the molecular evidence implicating hyperlipidemia in the etiopathogenesis of DPN, clinical research yields conflicting results on the correlation between hyperlipidemia and DPN. The Utah Diabetic Neuropathy study, which enrolled 218 T2D patients who either had no symptoms of neuropathy or had symptoms for fewer than 5 years, showed that hypertriglyceridemia (defined as plasma TG ≥ 150 mg/dL) was associated with an increased risk of DPN, especially small fiber neuropathy³³. Another study performed magnetic resonance neurography on 100 patients with T2D and found that low plasma TC and LDL-C levels significantly contributed to the severity of diabetic neuropathic lesions¹³. These findings aligned with some of ours, namely, that we also found that participants with DPN had significantly lower baseline and follow-up TC and LDL-C levels than those without DPN. A plausible explanation may be that lower cholesterol levels lead to an insufficient cholesterol supply for neurite regeneration following diabetic neuropathic injury. A recent meta-analysis of 39 randomized controlled trials investigating the relationship between DPN and hyperlipidemia demonstrated that patients with DPN had higher TG and lower HDL-C levels relative to controls³⁴. No significant differences in TC and LDL-C levels were found between the DPN and control group. Subgroup analysis clarified that only the patients with both T1D and DPN had higher TG levels than patients in the control group, whereas serum TG levels in T2D did not differ from those of controls. This meta-analysis also illustrated that reduced serum TC and LDL-C levels may indicate a transition from an asymptomatic condition to a severe pain condition in patients with DPN.

Meanwhile, the evidence in support of DPN management by lowering serum lipid levels remains insufficient and controversial³². Previous observational studies supported that lipid-lowering drugs were

protective against DPN. In 2014, a Danish T2D cohort study of 15,679 prevalent statin users and 47,037 non-statin users found that prevalent statin users had a 35% risk reduction of developing DPN (hazard ratio: 0.66, $P < 0.0001$)¹⁶. In 2019, a Taiwanese study investigating the effects of statin on diabetic triopathy in T2D patients found a 15% reduced risk of new-onset DPN among statin users relative to non-statin users³⁵. However, a larger Danish T2D cohort study published in 2020 that enrolled 59,255 new statin users, 75,528 prevalent statin users, and 124,842 non-users found no evidence between statin therapy and risk of DPN. Moreover, they even showed a temporarily increased risk of DPN within the first year after statin initiation among new statin users (adjusted hazard ratio: 1.30, 95% CI: 1.12–1.53)³⁶. Our research also supported the lack of meaningful correlation between hyperlipidemia and increased risk of DPN after correcting for confounding factors (e.g., duration of diabetes). Furthermore, lipid-lowering drugs were neither a protective nor risk factor for DPN in our study. In the subgroup analysis focusing on the impacts of different lipid spectrum (including TC and LDL) and lipid-lowering drugs (including statin and fibrate) on the risk of DPN, our results remain consistent. Ultimately, our findings contradict the evidence in support of hyperlipidemia-related pathogenesis in DPN development.

The advantages of our research design are its large sample size, the use standardized and published data collection protocols, and the inclusion of detailed information with regard to confounding factors, laboratory data, and treatment of T2D and hyperlipidemia. Additionally, we adopted the MNSI, a validated clinical screening tool of DPN that is sensitive, specific, non-invasive, and easily administered by a single trained professional.

Our study also had several limitations. Firstly, statin and fibrate were the only lipid-lowering drugs studied; new generation lipid-lowering drugs were not included, such as ezetimibe or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Secondly, the diagnosis of DPN was not corroborated by other laboratory techniques, such as nerve conduction studies, corneal confocal microscopy, laser Doppler flare imaging, sudomotor axon reflex assessment, quantitative sensory testing, and skin biopsy. Although the latest ADA position statement of DPN did not rigorously require electrophysiological examination for DPN screening, it is a requisite for diagnosis of confirmed DPN^{25,28}. Based on the current diagnostic criteria for DPN, an abnormal nerve conduction study and neuropathic symptoms and/or signs are essential to diagnose confirmed DPN. Clinical symptoms and signs without electrophysiological evidence only contribute to the diagnosis of possible or probable DPN³⁷. Without electrophysiological corroboration, we instead used the MNSI to identify the patients who had possible or probable DPN. Besides, although some patients with DPN might demonstrated overt neurological symptoms, up to 50 percentage of DPN may be asymptomatic. In order to broadly assess the cases with incidental or subclinical DPN in a less-invasive procedure and to prevent further neuropathic injuries, we adopted the second portion of the MNSI for DPN investigation. Lastly, given the ethnic homogeneity of our sample, the results may not be representative of all diabetic patients.

Conclusion

Our study demonstrated that neither hyperlipidemia nor lipid-lowering pharmacological intervention was associated with an increased risk of DPN in patients with T2D. Although preclinical studies suggest that hyperlipidemia may be involved in the pathogenesis of DPN, this hypothesis was not supported by our data. DPN is a complex and multifactorial microvasculopathy attributed to diverse mechanisms. Our results suggest that hyperlipidemia may not be a prominent contributor to microvasculopathies, including DPN. Further longitudinal studies are warranted to test the causality of hyperlipidemia and DPN. Our study also found a pattern of lower TC and LDL-C levels in T2D patients with DPN. Future research efforts are needed to investigate whether low TC or LDL-C levels are independent risk factors for DPN.

List Of Abbreviations

NL-N: normolipidemic non-lipid-lowering drug users.

NL-D: normolipidemic lipid-lowering drug users.

HL-D: hyperlipidemic lipid-lowering drug users.

NTC-N: normocholesterolemic non-lipid-lowering drug users.

NTC-D: normocholesterolemic lipid-lowering drug users.

HTC-D: hypercholesterolemic lipid-lowering drug users.

NLDL-N: normal LDL-C non-lipid-lowering drug users.

NLDL-D: normal LDL-C lipid-lowering drug users.

HLDL-D: hyper-LDL-C lipid-lowering drug users.

NL-S: normolipidemic statin users.

HL-S: hyperlipidemic statin users.

NL-F: normolipidemic fibrate users.

HL-F, hyperlipidemic fibrate users.

Declarations

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Author Contributions

K-C Chang: draft manuscript preparation and revising. Y-W Pai: advisor on writing, manuscript editing. Y-W Pai, I-T Lee, M-H Chang: study design, analysis and interpretation of results. C-H Lin: data analysis and statistical computation. All authors reviewed the results and approved the final version of the manuscript.

Competing Interests Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

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