Original Article

Prevalence of Peripheral Neuropathy in Thai Patients with Type 2 Diabetes and Associated Risk Factors

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Objective: To determine the prevalence and associated factors of peripheral neuropathy among patients with type 2 diabetes mellitus (T2DM) in Thailand.

Materials and Methods: The authors performed a nationwide cross-sectional study of patients with T2DM based on the report of the Medical Research Network of the Consortium of the Thai Medical Schools. The present study evaluated quality of care among T2DM patients from the Ministry of Public Health and Bangkok Metropolitan Administration Hospital between 2014 and 2015. Prevalence rates and 95% confidence interval (CI) were calculated, and univariate and multivariate analyses were performed to determine the correlation between diabetic peripheral neuropathy (DPN) and medications. Other potential underlying factors including history of hypertension, peripheral arterial diseases, renal insufficiency, wound appearance, and amputation were also evaluated.

Results: Data from 65,904 T2DM patients was evaluated, 1,808 (2.7%) of whom had DPN. On multivariable analysis adjusted for patient characteristics and relevant complications, the risk of neuropathy was significantly greater in insulin users (adjusted odds ratio [AOR] 1.318; 95% CI 1.161 to 1.496), as well as in calcium channel blocker users (AOR 1.186; 95% CI 1.056 to 1.333). Moreover, regression analysis showed that age (AOR 1.025; 95% CI 1.02 to 1.031), smoking habit (AOR 1.297; 95% CI 1.008 to 1.669), renal insufficiency (AOR 1.735; 95% CI 1.523 to 1.977), dyslipidemia (AOR 1.311; 95% CI 1.145 to 1.502), diabetic retinopathy (AOR 2.936; 95% CI 2.527 to 3.410), and peripheral arterial diseases (AOR 21.456; 95% CI 16.37 to 28.123) were associated with DPN.

Conclusion: Peripheral neuropathy can occur in T2DM patients showing microvascular symptoms and in those who receive certain hypoglycemic and antihypertensive agents. Early evaluation and effective treatments are essential to prevent progressive neuropathy.

Keywords: Diabetes, Neuropathy, Prevalence, Insulin, Complications

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Type 2 diabetes mellitus (T2DM) is a progressive condition that is responsible for 6% of all deaths caused by non-communicable diseases worldwide(1). Its prevalence among adults has increased globally from 246 million in 2006 to 425 million in 2017(2). Thailand has witnessed a rapid rise in incidences of T2DM that is evidently related to shifting in sociodemographic, economic, and lifestyle-related factors. A previous cohort study found that the incidence of T2DM in the Thai population was 177 per 10,000 between 2005 and 2013(3). The rise in the Thai diabetic population has led to a greater need for effective health management, included screening for diabetes in high-risk populations and the promotion of complication-reducing lifestyles(4).

Diabetic peripheral neuropathy (DPN) is a common occurring chronic microvascular

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complication affecting patients' quality of life and finances, as well as those of their families. DPN can lead to significant infections, foot ulcerations, and eventually lower limb amputation, and is classified into two main types based on symptoms, 1) sensorimotor neuropathy involving pain, paranesthesia, and sensory loss, and 2) autonomic neuropathy that causes pupillomotor, cardiovascular[5], urogenital, and gastrointestinal function impairment as well as thermoregulatory system dysfunction[6]. Autonomic neuropathy has been demonstrated to increase morbidity and mortality rates owing to cardiovascular involvement[5]. Moreover, DPN is associated with various ocular disorders such as diabetic retinopathy, anterior ischemic optic neuropathy, and diabetic papillopathy[7].

Polypharmacy is common in older adults, especially those who have been diagnosed with hypertension or diabetes[8]. In fact, multiple medications may increase the risk of diabetic complications in adults older than 70 years[9]. Numerous medications are reportedly associated with peripheral neuropathy. Furthermore, drug-induced peripheral neuropathy generally occurs weeks to months after commencing therapy, and can be permanent or only partially reversible[10].

In Thailand, there are few studies describing the prevalence of DPN in patients with T2DM or factors associated with its development. Information regarding the relationship between medication and peripheral neuropathy in the Thai population is also limited. Therefore, in the present study, the authors aimed to determine the prevalence of DPN in T2DM patients treated at the Thai government hospitals and to identify the significant risk factors for this condition. The authors also aimed to determine the correlation between medications received by patients with T2DM and the incidence of DPN. The outcomes of the present study ought to help improving the capacity of healthcare workers to prevent and treat microvascular diseases.

Materials and Methods

Ethics statement

All patients were recruited from the Outpatient Department. Informed consents were given by all patients before enrollment. The present study was approved by the Institutional Review Board, Royal Thai Army Department, Bangkok, Thailand (approval number; S039h/60_Exp) in accordance with the Declaration of Helsinki, the Council for International Organizations of Medical Science, and the International Council for Harmonisation "Good Clinical Practice" guidelines. Patient medical information were recorded by well-trained research nurses and collected into a case record form.

Study design and participants

The authors conducted a nationwide cross-sectional study composed of a secondary analysis on type 2 diabetes and hypertension (the DM/HT dataset) developed by the Medical Research Foundation (MRF). An assessment of the quality of care of patients diagnosed with T2DM and hypertension at the Ministry of Public Health (MoPH) and Bangkok Metropolitan Administration Hospitals in Thailand between 2014 and 2015 was performed by the Medical Research Network of the Consortium of the Thai Medical Schools (MedResNet). The inclusion criteria of the survey comprised T2DM patients aged 35 years or older who received regular medical care in the targeted hospitals for at least 12 months[11].

The objective of the present survey was to evaluate the status of care among patients with diabetes visiting public hospitals of the MoPH and was supported by the Thai National Health Security Office (NHSO).

Data collection

Data from 65,904 patients with T2DM were obtained from the MedResNet. Stratified two-stage cluster sampling was applied for patients registered at the Bangkok Metropolitan Administration hospitals and patients from the hospitals administered by the MoPH were stratified using single-stage cluster sampling.

The American Diabetic Association (ADA) criteria were used to diagnose T2DM (haemoglobin A1c [HbA1c] of 7% or greater, fasting plasma glucose of 126 mg per dL or more, a two-hour plasma glucose of 200 mg per dL or more during an oral glucose tolerance test, or random plasma glucose of 200 mg per dL or more). Patient characteristics including average age, sex, smoking status, body mass index (BMI, less than 25 versus 25 kg per m^2 or more), low-density lipoprotein (LDL), and cholesterol level (of less than 100 versus 100 mg per dL or above) were extracted from case records. The waist circumference was measured at the level of the iliac crest and determined following standard clinical guideline for men (more than 90 cm) and women (more than 80 cm).

Peripheral neuropathy was defined as International Classification of Diseases Tenth

Table 1. Characteristics of the study population

	Without neuropathy (n=64,096) n (%)	Neuropathy (n=1,808) n (%)	p-value
Sex			
Male	20,383 (97.3)	565 (2.7)	0.614
Female	43,693 (97.2)	1,243 (2.8)	
Age (year); mean±SD			
Total	61.2±11.0	64.4 ±10.8	<0.001
Male	61.35±11.0	64.2±10.4	<0.001
Female	61.13±11.0	64.3±10.5	<0.001
Body mass index (kg/m^2)			
<25	30,690 (97.1)	915 (2.9)	0.016
≥25	31,494 (97.4)	835 (2.6)	
Glycated haemoglobin			
<7%	18,305 (97.5)	475 (2.5)	0.032
≥7%	32,445 (97.2)	951 (2.8)	
Waist circumference (cm)			
<90 in men/<80 in women	14,039 (97.5)	367 (2.5)	0.215
≥90 in men/≥80 in women	33,567 (97.3)	948 (2.7)	
LDL cholesterol level (mg/dL)			
<100	24,951 (97.2)	708 (2.8)	0.451
≥100	31,253 (97.3)	853 (2.7)	
Smoking history			
Smoker	2,720 (96.9)	86 (3.1)	0.329
Non-smoker	57,882 (97.2)	1,640 (2.8)	
History of hypertension			
Yes	14,685 (97.9)	320 (2.1)	<0.001
No	49,411 (97.1)	1,488 (2.9)	
Diabetic retinopathy			
Yes	4,010 (92.1)	343 (7.9)	<0.001
No	60,086 (97.6)	1,465 (2.4)	
Dyslipidaemia			
Yes	45,515 (97.0)	1,409 (3.0)	<0.001
No	18,581 (97.1)	399 (2.1)	
Peripheral arterial disease			
Yes	212 (59.2)	146 (40.8)	<0.001
No	63,884 (97.5)	1,662 (2.5)	
Renal insufficiency			
Yes	10,597 (94.8)	582 (5.2)	<0.001
No	53,499 (97.8)	1,226 (2.2)	

SD=standard deviation; LDL=low-density lipoprotein

Statistical significance was determined using the chi-square test except for the mean age between groups, which was determined using an independent t-test

Revision (ICD10) codes E11.40. Potential factors related to DPN including hypertension status, retinopathy, nephropathy, dyslipidemia status, peripheral arterial diseases (PAD), renal insufficiency, and pharmacological treatment were also recorded. Diabetic retinopathy was diagnosed by ophthalmologists and identified by ICD10 codes H36.0x. Renal insufficiency was identified by ICD10 codes N18.9[11]. Drugs were categorized as hypoglycemic agents (i.e., insulin and non-insulin medications), antihypertensive drugs, and lipid-lowering agents. The authors also examined the appearance of wounds and whether amputations were performed in diabetic patients with and without neuropathy.

Statistical analysis

Descriptive statistics were reported as means and standard deviations for continuous variables and as frequencies (percentages) for categorical variables. The prevalence and 95% confidence interval (CI) were also determined. The chi-squared was applied to identify factors associated with the development of DPN. Multivariable logistic regression models were performed to explore the association between DPN outcomes and potentially related factors (e.g., medications for vascular or non-vascular complications). The IBM SPSS Statistics software, version 23 (IBM Corp., Armonk, NY, USA) was used for data analyses. A p-value of less than 0.05 was considered statistically significant.

Results

Data from 65,904 patients with T2DM were retrieved. The patient's characteristics in the present study were as followed, mean age 61.3±11 years, BMI 25.6±5 kg per m^2, waist circumference 88.4±11 cm, LDL cholesterol level 108.9±38 mg per dL, and HbA1c 7.9±2%. There were 1,808 patients with peripheral neuropathy (565 men and 1,243 women). Data of relevant characteristics such as smoking history, presence of hypertension, retinopathy, PAD, dyslipidemia, and renal insufficiency are presented in Table 1. The medications and other agents administered to the patients are listed in Table 2.

Multivariable analysis adjusted by age, BMI, HbA1c, smoking history, and relevant complications indicated a significantly higher risk of DPN in insulin users (adjusted odds ratio [AOR] 1.318, 95% CI 1.161 to 1.496) and in those receiving calcium channel blockers (CCBs) (AOR 1.186, 95% CI 1.056 to 1.333) (Table 3). Additionally, average age (AOR 1.027, 95% CI 1.02 to 1.031) and smoking history (AOR 1.297, 95% CI 1.008 to 1.669) were also significantly associated with DPN. Other microvascular complications such as PAD, renal

Table 2. Use of antihypertensive, antilipidemic and hypoglycaemic agents

	Without neuropathy (n=64,096) n (%)	Neuropathy (n=1,808) n (%)	p-value
Diuretics			
No	51,519 (97.4)	1,373 (2.6)	
Yes	12,577 (96.7)	435 (3.3)	<0.001
ACEIs			
No	36,224 (97.3)	996 (2.7)	
Yes	27,872 (97.3)	812 (2.8)	0.228
Angiotensin receptor blockers			
No	54,268 (97.3)	1,481 (2.7)	
Yes	9,828 (96.8)	327 (3.2)	0.001
Adrenergic receptor blockers			
No	51,217 (97.3)	1,397 (2.7)	
Yes	12,879 (96.9)	411 (3.1)	0.006
Calcium channel blockers			
No	39,862 (97.4)	1,066 (2.6)	
Yes	24,234 (97.0)	742 (3.0)	0.005
Vasodilators			
No	61,827 (97.3)	1,716 (2.7)	
Yes	2,269 (96.1)	92 (3.9)	<0.001
Centrally acting antihypertensive drugs			
No	63,527 (97.3)	1,788 (2.7)	
Yes	569 (96.6)	20 (3.4)	<0.33
Fibrates			
No	56,091 (97.3)	1,584 (2.7)	
Yes	8,005 (97.3)	224 (2.7)	0.899
Niacins			
No	64,018 (97.3)	1,806 (2.7)	
Yes	78 (97.5)	2 (2.5)	0.894
Statins			
No	25,228 (97.5)	646 (2.5)	
Yes	38,868 (97.1)	1,162 (2.9)	0.002
Biguanides			
No	17,975 (96.7)	619 (3.3)	<0.001
Yes	46,121 (97.5)	1,189 (2.5)	
Sulfonylurea			
No	23,302 (97.0)	728 (3.0)	0.001
Yes	40,794 (97.4)	1,080 (2.6)	
Thiazolidinedione			
No	58,189 (97.3)	1,615 (2.7)	
Yes	5,907 (96.8)	193 (3.2)	0.035
α-glucosidase inhibitors			
No	63,718 (97.3)		
Yes	378 (96.2)	15 (3.08)	0.191
DPP-IV inhibitors			
No	63,478 (97.3)	1,788 (2.7)	
Yes	618 (96.9)	20 (3.1)	0.543
GLP-1 analogue			
No	64,068 (97.3)	1,807 (2.7)	
Yes	28 (96.6)	1 (3.4)	0.816
Insulin			
No	49,945 (97.7)	1,193 (2.3)	
Yes	14,151 (95.8)	615 (4.2)	<0.001

ACEIs=angiotensin-converting enzyme inhibitors; GLP-1=glucagon-like peptide-1; DPP-IV=dipeptidyl peptidase-IV

Statistical significance was determined using the chi-square test

insufficiency, diabetic retinopathy, and dyslipidemia were also found to be significantly associated with an increased risk of DPN ($p<0.05$) (Table 3). DPN was also significantly associated with foot wounds and lower limb amputations in patients with T2DM ($p<0.001$) (Table 4).

Discussion

Many lower- and middle-income countries, including Thailand, have experienced rapid economic, social, and healthcare shifts over the past 10 years. Such changes are potentially responsible for decreased the rates of infectious diseases, but also for the increased incidences of non-communicable disorders such as hypertension, obesity, and T2DM[12]. In the present study, analysis of data from the MoPH and Bangkok Metropolitan Administration hospitals across the country revealed a significantly higher prevalence of DPN in patients admitted to the Bangkok metropolitan registered hospitals (data not shown). Interestingly, a previous study of the Thai population by Aekplakorn et al in 2009 reported a higher prevalence of diabetes in urban areas than in rural regions[13], which points to the effect of socioeconomic changes in the former locales on the incidence rate of metabolic diseases.

DPN is a major complication of chronic diabetes that may limit active daily living in afflicted patients because of ulcers or amputation. The incidence rate of T2DM patients with neuropathy determined via MedResNet data analysis was consistent with previous findings by Bansal et al[14], who also found

Table 3. Univariate and multivariate analysis of factors associated with diabetic peripheral neuropathy

	Crude odds ratio	95% CI	p-value	Adjusted odds ratio	95% CI	p-value
Age (mean±SD, 61.3±11 years)	1.03	1.00 to 1.03	<0.001	1.03	1.02 to 1.03	<0.001
BMI (kg/m^2)						
<25	1.13	1.02 to 1.24	0.016			
≥25	1					
HbA1c						
≤7	1.13	1.01 to 1.27	0.032			
>7	1					
Smoking history						
Yes	1.12	0.90 to 1.39	0.329	1.30	1.01 to 1.67	0.043
No	1			1		
Renal insufficiency						
Yes	2.40	2.17 to 2.65	<0.001	1.74	1.52 to 1.98	<0.001
No	1			1		
Hypertension						
Yes	1.38	1.22 to 1.56	<0.001			
No	1					
Dyslipidaemia						
Yes	1.44	1.29 to 1.61	<0.001	1.31	1.15 to 1.50	<0.001
No	1			1		
Peripheral arterial diseases						
Yes	26.47	21.32 to 32.87	<0.001	21.46	16.37 to 28.12	<0.001
No	1			1		
Diabetic retinopathy						
Yes	3.51	3.11 to 3.36	<0.001	2.94	2.53 to 3.41	<0.001
No	1			1		
Diuretics						
Yes	1.29	1.16 to 1.45	<0.001			
No	1					
Calcium channel blockers						
Yes	1.15	1.04 to 1.26	0.005	1.19	1.06 to 1.33	0.004
No	1			1		
Vasodilators						
Yes	1.46	1.18 to 1.81	<0.001			
No	1					
Adrenergic receptor blockers						
Yes	1.17	1.05 to 1.31	0.006			
No	1					
ARBs						
Yes	1.22	1.08 to 1.38	0.001			
No	1					
Statins						
Yes	1.17	1.06 to 1.29	0.002			
No	1					
Thiazolidinedione						
Yes	1.18	1.01 to 1.37	0.035			
No	1					
Insulin						
Yes	1.82	1.65 to 2.01	<0.001	1.32	1.16 to 1.47	<0.001
No	1			1		

SD=standard deviation; CI=confidence interval; HbA1c=glycated haemoglobin; ARBs=angiotensin II receptor blockers

Data was adjusted for body mass index, HbA1C, hypertension, diuretics, vasodilators, adrenergic receptor blockers, ARBs, statins, and thiazolidinedione

Table 4. Lower limb complications

	Without neuropathy (n=64,096) n (%)	Neuropathy (n=1,808) n (%)	p-value
Toe amputation			
Yes	50 (0.1)	18 (1.0)	<0.001
No	64,046 (99.9)	1,790 (99.0)	
Foot amputation			
Yes	5 (0.0)	2 (0.1)	N/A
No	64,091 (100)	1,806 (99.9)	
Below knee amputation			
Yes	5 (0.0)	4 (0.2)	N/A
No	64,091 (100)	1,804 (99.8)	
Above knee amputation			
Yes	1 (0.0)	0 (0.0)	N/A
No	64,095 (100)	1,808 (100)	
Wound appearance			
Yes	1,532 (2.4)	180 (10.0)	<0.001
No	62,564 (97.6)	1,628 (90.0)	

N/A=not applicable

Statistical significance was determined using the chi-squared test

no difference in DPN prevalence between male and female patients with diabetes. In both sexes, PAD, retinopathy, and renal insufficiency were found to be strongly associated with DPN. In fact, the presence of peripheral vascular diseases was shown to cause ischemia, gangrene, and impaired wound healing that resulted in amputations[15]. The present study showed that DPN in patients with T2DM is a contributing risk factor to lower extremity amputations. Moreover, poor glucose control, a longer duration of affliction with diabetes[16], infected ulcers, and kidney disease[17] also significantly exacerbated the risk of major amputation. Implementing guidelines for foot care as well as early screening for amputation risk factors must be considered for all patients with chronic diabetes, although data do suggest that the rate of major amputations in diabetic patients has been decreasing in many countries[17,18].

Older age, smoking, dyslipidemia, and receiving insulin or CCBs were also found to be significantly associated with an increased risk of DPN in the present study. Previous investigations showed that increasing age is a well-known risk factor for DPN[19,20] and T2DM[3]. Individuals aged 55 years and older were reported to have a higher risk of being diagnosed with T2DM than those under 55 years[4].

Smoking was also demonstrated to increase the risk of neuropathy in patients with diabetes[21]. Moreover, diabetic patients who smoked had elevated HbA1c[22], required higher insulin dosage[23], and experienced insulin resistance[24]. It was previously shown that smoking increased oxidative stress and systemic inflammation[25], and could also induce microvascular complications such as neuropathy, retinopathy, and nephropathy via mechanisms involving hypoxemia and microvascular insufficiency[26]. The authors, therefore, included smoking in the present multivariate analysis even though it was not a significant factor on univariate analysis.

Medication-induced peripheral neuropathies are uncommon but are important to consider, and proper prevention and treatment methods are required to lower the prevalence of these symptoms. In fact, numerous agents including chemotherapeutics, statins, hydralazine, and amiodarone were shown to induce peripheral neuropathy[10,27]. In the present study, insulin use was strongly associated with DPN. The present data suggested a relatively higher prevalence of DPN among T2DM patients uncontrolled with oral hypoglycemic agents. A previous study found that such oral hypoglycemic agents, insulin treatment, and retinopathy were factors associated with DPN[28], which was consistent with the present study findings. Additionally, the authors found that the use of CCBs was also significantly associated with DPN. Previous studies showed that progressive myopathy, myalgias, arthralgias, and weakness[29] can occur in patients receiving continuous amlodipine therapy. Such maladies can be exacerbated by combining CCBs with statins[30].

Myopathy and peripheral neuropathy are common in patients receiving statins. The incidence of neuropathy was higher in patients receiving statin treatment for longer than two years than in non-statin users[31]. However, the present study multivariate model did not reveal a relationship between statin treatment and DPN, which might be owing to the effect of adjusting the data for different parameters.

The present work employed a cross-sectional study, and as such, the results could show only associated factors of DPN. The authors analyzed the data from between 2014 and 2015 Thailand DM/HT study of the NHSO from the MedResNet central data management system. In the present study, the authors were aware of missing data from the observation study. Although the data represented a relatively large sample size of the study population, some crucial data regarding medications were missing. As it is a nationwide (real life situation) study, the

associations between factors and outcomes were able to be exhibited[32]. The limitations of the present study include the data collection using retrospective medical reviews that contain incomplete data records containing some unverified medical diagnoses. In addition, the study population did not include the participants from university hospitals causing a significant underestimation of DPN complications[11].

Conclusion

The authors found DPN to be highly prevalent, especially in T2DM patients with PAD, retinopathy, and renal insufficiency. The uses of insulin or certain antihypertensive agent were found to correlate with DPN, especially in chronic T2DM. Moreover, smoking significantly increased the risk of microvascular complications causing ulcerations and amputations. Therefore, proper diagnosis and effective foot care education is required. The high rates of DPN in T2DM patients in Thailand can be reduced if early detection and prevention are implemented. Screening of high-risk patients and appropriate treatment of DPN in afflicted T2DM patients should be mandatory.

What is already known on this topic?

DPN is a common adverse effect of diabetes that severely impairs patients' quality of life. Interestingly, the combinations of medications taken by older adults for age-related diseases have been implicated in neuropathy. However, the role of such medications, as well as risk factors for DPN in the Thai diabetic population in general, have not been thoroughly explored.

What this study adds?

After evaluating data from 65,904 T2DM patients, including 1,808 (2.7%) with DPN, this study showed that the risk of neuropathy was significantly higher in insulin and CCB users than in non-users. Moreover, older age, smoking, renal insufficiency, dyslipidemia, diabetic retinopathy, and peripheral arterial diseases were all significantly associated with DPN. The outcomes of this study should help improving the capacity of healthcare workers to prevent and treat microvascular diseases.

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Conflicts of interest

The authors declare no conflict of interest.

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