• Clinical Research •

Risk factors of developing non-arteric ischemic optic neuropathy in patients with type 2 diabetes mellitus: a single-center retrospective cohort study

Parinee Kemchoknatee[1], *Duanghathai Tangon*[2], *Thansit Srisombut*[1,2]

[1]Department of Ophthalmology, Rangsit University, Rajavithi Hospital, Thung Phaya Thai, Ratchathewi, Bangkok 10400, Thailand

[2]Faculty of Medicine, Rajavithi Hospital, Rangsit University, Thung Phaya Thai, Ratchathewi, Bangkok 10400, Thailand

Correspondence to: Parinee Kemchoknatee. Department of Ophthalmology, Rangsit University, Rajavithi Hospital, 2, Phaya Thai Rd, Thung Phaya Thai, Ratchathewi, Bangkok 10400, Thailand. parinee.eye52@gmail.com

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Abstract

● **AIM:** To determine the risk factors and time to non-arteric ischemic optic neuropathy (NAION) occurrence among Thai type 2 diabetes mellitus (T2DM) patients.

● **METHODS:** A retrospective review of 266 newly diagnosed T2DM cases at Rajavithi Hospital between 2007 and 2016 was conducted to determine time to occurrence of NAION and evaluate associated risk factors.

● **RESULTS:** Hypertension and dyslipidemia were the most common pre-existing vascular diseases and there was a significant male predominance in the NAION group. The mean age of the NAION group was significantly higher than that of the group without NAION. A higher proportion of subjects in the NAION group had hypertension, dyslipidemia, high diastolic blood pressure, smokers, and had a small cup-to-disc ratio (CDR). Higher levels of triglycerides and low-density lipoprotein-cholesterol in the group with NAION. Fifty-five patients among 266 participants (20.68%) developed NAION during a mean follow-up time of 81.26±25.04mo. In a multivariable logistic regression analysis, dyslipidemia (OR=8.36, 95%CI, 3.447–20.273, *P*<0.001), high low density lipoprotein levels (OR=1.017, 95%CI, 1.004–1.029, *P*=0.009), and small CDR (OR=11.92, 95%CI, 4.477–31.741, *P*<0.001) were significant risk factors for NAION development. Smoking was the strongest predictive risk (OR=12.843, 95%CI, 3.959–41.659, *P*<0.001). Vascular complications of T2DM and aspirin were not associated with NAION.

● **CONCLUSION:** T2DM patients with dyslipidemia or a small CDR should be carefully followed up as they are at increased risk of developing NAION.

● **KEYWORDS:** non-arteric ischemic optic neuropathy; systemic vascular disease; type 2 diabetes mellitus; hypertension; dyslipidemia

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INTRODUCTION

Non-arteric ischemic optic neuropathy (NAION) is one of the most common causes of optic neuropathy in people over the age of 50y. It is believed that poor perfusion of the short posterior ciliary artery results in optic nerve swelling which can eventually lead to ischemia of the optic nerve. Patients with NAION typically present with painless visual loss, swelling disc with or without splinter hemorrhage, or optic nerve-related visual field defect[1-2].

Common vascular diseases such as type 2 diabetes mellitus (T2DM), hypertension, and dyslipidemia are acknowledged as risk factors of NAION in both western and Asian populations[1,3-6]. According to Medicare data, people in western countries in the age range 68–95y with diabetes mellitus (DM) have a 40% higher risk of developing NAION[7]; however, the influence of laboratory test data and some systemic vascular diseases were not taken into account when measuring time to development of NAION. In addition, their results might be difficult to generalize to younger age groups and Asian populations. Regarding the impact of DM on ischemic optic neuropathy, Hayreh and Zimmerman[8] proposed that there was a significantly longer duration of disc swelling in patients with DM than in non-diabetics, although it seemed that there were some differences in clinical characteristics or prognosis between DM and the disease nature. In Thai populations, there is a paucity of data regarding the associated risk factors for NAION among T2DM.

The purposes of the present study were to determine risk factors affecting NAION occurrence, and to evaluate time to occurrence of NAION among Thai T2DM patients.

PARTICIPANTS AND METHODS

Ethical Approval The study was approved by Rajavithi Hospital Research Ethics Committee, EC number 190/2565. All the patients provided written informed consent before data were collected. Principles outlined in the Declaration of Helsinki was followed.

Methods and Data Collection Between January 1, 2007 and December 31, 2016, we conducted a retrospective study of newly-diagnosed T2DM patients. All electrical medical records of the 2718 patients with new diagnosis of T2DM in the Department of Ophthalmology and Internal Medicine during that period were enrolled in this study, and followed for the occurrence of NAION. NAION diagnosis was based on established criteria in the literature[9], which include acute painless optic neuropathy with evidence of relative afferent pupillary defect (RAPD), swelling disc appearance or crowded disc within one month, or optic nerve-related visual field defect. Our experienced neuro-ophthalmologist made all diagnoses and carefully identified atypical features for further investigation.

Inclusion criteria for our cohort study were as follows: 1) first diagnosed T2DM patients aged ≥18y, diagnosed by Internist at our center, in accordance with the diagnostic criteria described in recent international guidelines[10], with a follow-up time more than 5y. The exclusion criteria were patients with: 1) other optic neuropathies affecting optic disc edema or visual acuity, such as optic neuritis, or traumatic, infectious, or compressive optic neuropathies; 2) incomplete medical data; 3) no data on initial ophthalmic assessment; 4) unreliable diagnostic dates.

Data Collection Demographic details were recorded, with baseline characteristics of T2DM such as pre-existing systemic vascular diseases diagnosed based on the recent international consensus, including hypertension, dyslipidemia, ischemic heart disease, and cerebrovascular disease[10-12]. History of smoking was also recorded, and ophthalmic characteristics of NAION based on the aforementioned criteria[9]. Date of diagnosis of T2DM and NAION recorded in electronic database were retrospectively reviewed for time to NAION occurrence. Biochemistry data were retrospectively reviewed, including serum of fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), triglyceride, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), and total cholesterol (TC). Mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) of each patient were noted, ophthalmic data including best corrected visual acuity (BCVA) using distant visual acuity chart was converted to logarithmic of the minimal angle of resolution (logMAR) for statistical proposes, cup-to-disc ratio (CDR), RAPD, and fundus examination for diagnosis of disc drusen, with additional cases diagnosed using OCT. Visual field was tested by Humphrey Field Analyzer HFA II 750 (Carl Zeiss Meditec Inc, Dublin, CA, USA) employing a 30-2 threshold program with the Swedish Interactive Threshold Algorithm (SITA) Fast strategy. Color vision was evaluated using Ishihara color plates. The BCVA for the two groups was acquired at the initial visit for the group without T2DM and at the time of NAION diagnosis for the group with T2DM. Current or previous treatments were retrospectively reviewed, such as anti-hypertensives, anti-hyperglycemia and lipid lowering medications, and aspirin.

Statistical Analysis Continuous variables were expressed as mean and standard deviation (SD) for normally distributed data, and as median and interquartile range (IQR) for non-normally distributed data. Categorical variables were expressed as percentages, and Students' *t* test or Mann-Whitney *U* test were employed for analyzing normally or non-normally distributed continuous data. We used Chi-square or Fisher exact test for comparisons of two groups of categorical data. Univariable and multivariable logistic regression analysis were employed for evaluating risk factors for NAION occurrence. All covariates were analyzed in a univariable analysis, selected based on previous studies in the literature and clinical significance. Potential risk factors considered significant at a P value <0.2 in univariable analysis were included in multivariable analysis. In cases of simultaneous, sequential or recurrent NAION, only the first affected eye was included in binary logistic analysis. Statistical significance was set at a P<0.05. All statistical analyses were performed using SPSS version 25 (SPSS, Inc, Chicago, II, USA).

RESULTS

Of the 2718 patients with new diagnosis of T2DM who were enrolled in our study, 2452 were excluded due to not fulfilling our inclusion criteria as follows: 1307 had a follow-up time of less than 5y; a further 45 had incomplete medical records; 1087 had an uncertain date of diagnosis of either NAION or T2DM or both; 9 had a duration of onset of greater than 30d; and 4 had pale disc morphology at initial ophthalmic assessment. In our cohort, 15 patients presented with sequential NAION, while there were no cases of concurrent or recurrent NAION.

Baseline Demographic and Visual Characteristics Among T2DM Patients A total of 266 patients with T2DM were therefore recruited into the present study (Table 1). The mean age of the whole cohort was 50.56±11.50y. There was a significant difference between patient age in the two groups (P=0.02), with old age (≥50y) being significantly more common in the T2DM with NAION group (P=0.02), in which a male predominance was also noted (50.9%, P=0.044).

Table 1 Baseline characteristics of T2DM patients with and without NAION at diagnosis *n* (%)

Characteristic, *n* (%)	Total (*n*=266)	T2DM with NAION (*n*=55)	T2DM without NAION (*n*=211)	*P*
Male	104 (39.1)	28 (50.9)	76 (36.0)	0.044[c]
Mean age, y (SD)	50.56 (11.50)	53.76 (10.77)	49.72 (11.57)	0.02[c]
Age ≥50y	162 (60.9)	41 (74.5)	121 (57.3)	0.02[c]
Comorbid disease				
T2DM	266 (100)			
With vascular complication	101 (38)	20 (36.4)	81 (38.4)	0.783
Minor vascular	104 (39.1)	20 (36.4)	84 (39.8)	0.641
Diabetic retinopathy	99 (37.2)	17 (30.9)	82 (38.9)	0.277
Diabetic nephropathy	21 (7.9)	4 (7.3)	17 (8.1)	0.848
Diabetic neuropathy	16 (6)	2 (3.6)	14 (6.6)	0.405
Major vascular	25 (9.4)	5 (9.1)	20 (9.5)	0.93
Peripheral arterial disease	15 (5.6)	2 (3.6)	13 (6.2)	0.743
Coronary heart disease	19 (7.1)	4 (7.3)	15 (7.1)	>0.99
Hypertension	131 (49.2)	34 (61.8)	97 (46)	0.036[c]
Dyslipidemia	70 (26.3)	36 (65.5)	34 (16.1)	<0.001[c]
Ischemic heart disease	29 (10.9)	5 (9.1)	24 (11.4)	0.628
Cerebrovascular disease	31 (11.7)	5 (9.1)	26 (12.3)	0.506
Obstructive sleep apnea	1 (0.4)	0	1 (0.5)	0.607
Time to NAION, mo (SD)		48.78 (27.13)	-	
Mean follow-up time, mo (SD)	81.26 (25.04)	77.58 (23.97)	82.22 (25.28)	0.264
Current smoker	30 (11.3)	18 (32.7)	12 (5.7)	<0.001[c]
Laboratory data (SD)				
Mean HbA1c level (%)	7.98 (1.53)	8.24 (1.35)	7.91 (1.57)	0.157
Mean FBS (mg/dL)	176.20 (60.09)	190.15 (48.65)	172.51 (62.35)	0.053
Mean LDL (mg/dL)	112.49 (36.15)	134.65 (33.42)	106.71 (33.42)	<0.001[c]
Mean HDL (mg/dL)	50.00 (16.89)	51.05 (9.88)	50.44 (18.3)	0.738
Mean triglycerides (mg/dL)	159.54 (76.13)	183.14 (71.89)	153.36 (76.16)	0.01[c]
Mean SBP (mm Hg)	141.39 (16.83)	140.38 (21.01)	141.66 (15.61)	0.618
Mean DBP (mm Hg)	76.98 (11.46)	83.12 (15.20)	75.38 (9.69)	0.001[c]
Drug				
Antihyperglycemic	262 (98.5)	53 (96.4)	209 (99.1)	0.190[a]
Metformin	243 (91.4)	51 (92.7)	192 (91)	0.794[a]
Antihypertensive[b]	122 (93.1)	34 (100)	88 (90.7)	0.111
Lipid lowering[b]	67 (95.7)	34 (94.4)	33 (97.1)	>0.99[a]
Aspirin	123 (46.2)	31 (56.4)	92 (43.6)	0.091

T2DM: Diabetic mellitus type 2; NAION: Non-arteric anterior ischemic optic neuropathy; HbA1c: Glycated hemoglobin unit reported as %; FBS: Fasting blood sugar; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; SBP: Systolic blood pressure; DBP: Diastolic blood pressure. [a]Analysed using Fisher exact test; [b]Antihypertensive and lipid-lowering drugs were analysed only in patients with hypertension (131 patients) and dyslipidemia (70 patients); [c]*P*<0.05.

There were no significant differences between minor or major vascular complications of T2DM, ischemic heart disease, cerebrovascular disease, or obstructive sleep apnea (OSA) in the two groups (all *P*>0.05). With respect to comorbidity diseases in the entire cohort, the most common pre-existing disease was hypertension (49.2%), followed by dyslipidemia (26.3%). There was a higher proportion of hypertension, dyslipidemia, and current smokers in the NAION group (*P*=0.036, <0.001, and <0.001 respectively). Average time to development of NAION was 48.78±27.13mo. Regarding biochemistry data, there was no significant difference between serum of HbA1c and FBS in the two groups (*P*=0.157, 0.053 respectively), but mean serum levels of triglycerides and LDL were significantly higher in the NAION group (*P*=0.01 and *P*<0.001 respectively). The NAION group had a significantly higher DBP of 83.12±15.20 mm Hg (*P*=0.001). In our series, the most commonly-used anti-hyperglycemic medication was metformin (91.4%). There was no significant difference between

Table 2 Baseline visual characteristics of T2DM patients with and without NAION at diagnosis

Characteristic	Total (*n*=266)	T2DM with NAION (*n*=55)	T2DM without NAION (*n*=211)	*P*
BCVA, mean (SD)	1.51 (1.03)	1.51 (1.03)	0.69 (0.84)	<0.001
CDR ratio, mean (SD)	0.38 (0.05)	0.30 (0.03)	0.39 (0.03)	<0.001
Small CDR, *n* (%)	62 (23.3)	52 (94.5)	10 (4.7)	<0.001
Optic disc drusen	0	0	0	
Visual field dB, mean (SD)	-	-16.16 (0.93)	-	

T2DM: Diabetic mellitus type 2; NAION: Non-arteric anterior ischemic optic neuropathy; BCVA: Best corrected visual acuity; dB: Decibel; CDR: Cup-to-disc ratio. Small CDR defined as CDR≤0.3. BCVA in T2DM with NAION group was obtained at the time of NAION diagnosis, while in the without NAION group was acquired at the first follow-up visit.

the use of anti-hyperglycemic, anti-hypertensive or lipid lowering medications or aspirin in the two groups (all $P>0.05$). Table 2 shows that there were significant differences between baseline visual characteristics in terms of mean BCVA, mean CDR, and proportion of small CDR in the 2 groups (all $P<0.001$).

Risk Factors for Occurrence of NAION Among T2DM Patients Older age, male gender, hypertension, dyslipidemia, FBS, HbA1c, smoking, small CDR, hypertriglyceridemia, and high LDL levels significantly increased the odds ratio (OR) of developing NAION in univariable logistic analysis, as shown in Table 3 (all $P<0.2$). After adjusting all covariate factors in multivariable binary logistic analysis, 4 variables remained statistically significant: dyslipidemia increased the risk of developing NAION with an OR=8.360 (95%CI: 3.447–20.273, $P<0.001$); similarly, LDL was found to increase the likelihood of NAION, with OR=1.017 (95%CI: 1.004–1.029, $P=0.009$); having a small CDR increased the risk almost 12 times (OR=11.920, 95%CI: 4.477–31.741, $P<0.001$); and smoking was identified as the strongest risk factor of NAION with OR=12.843 (95%CI: 3.959–41.659, $P<0.001$). In this study, older age, male gender, hypertension, hypertriglyceridemia, and FBS lost statistical significance in multivariable analysis. Overall, the NAION occurrence among T2DM patients was 20.68% in the present study.

Table 3 Univariable and multivariable logistic regression model for the risk factor of developing NAION

Variable	Odds ratio	95%CI	*P*
Univariable			
Old age	2.176	1.12–4.237	0.022[a]
Gender (male)	1.842	1.012–3.352	0.046[a]
Hypertension	1.903	1.036–3.494	0.038[a]
Dyslipidemia	9.864	5.068–19.2	<0.001[a]
Smoker	8.068	3.588–18.141	<0.001[a]
Small CDR	8.733	4.501–16.944	<0.001[a]
FBS (per 1 mg/dL)	1.004	1.000–1.009	0.059
HbA1c (per 1%)	1.145	0.949–4.383	0.158
LDL (per 1 mg/dL)	1.021	1.012–1.030	<0.001[a]
Triglyceride (per 1 mg/dL)	1.005	1.001-1.008	0.012[a]
Multivariable			
Old age	0.780	0.236–2.575	0.683
Gender (Male)	1.649	0.713–3.814	0.242
Hypertension	1.258	0.460–3.439	0.655
Dyslipidemia	8.360	3.447–20.273	<0.001[a]
Smoke	12.843	3.959–41.659	<0.001[a]
Small CDR	11.920	4.477–31.741	<0.001[a]
FBS (per 1 mg/dL)	1.005	0.998–1.011	0.161
Triglyceride (per 1 mg/dL)	1.001	0.994–1.006	0.977
LDL (per 1 mg/dL)	1.017	1.004–1.029	0.009[a]

HbA1c: Glycosylated hemoglobin;FBS: Fasting blood sugar; LDL: Low-density lipoprotein; CDR: Cup-to-disc ratio; CI: Confidence interval. Small CDR defined as CDR≤0.3. [a]$P<0.05$.

DISCUSSION

The present study found that the most common co-existing vascular diseases in T2DM with NAION were dyslipidemia (65.5%) and hypertension (61.8%). In addition, increased LDL, smoking, and having a small CDR were identified as significant risk factors of developing NAION.

Currently, the association between T2DM and NAION is inconclusive. Previous studies have proposed that diabetes increases leukocytosis, leading to occlusion of capillaries, with the attendant oxidative stress eventually resulting in vascular endothelium damage[13]. Some researchers have found that T2DM patients are predisposed to hypercoagulability and have an increased risk of developing NAION[14]. Several studies have revealed that T2DM is a significant risk factor for NAION[4,15-16]. In western populations, Jacobson *et al*[4] found that T2DM increased the OR of developing NAION by 2 times. Similarly, Kim *et al*[16] observed that having T2DM carried a four-fold higher risk in Korean populations. Regarding the influence of T2DM and age of onset of NAION, Repka *et al*[17] revealed that the incidence of T2DM was higher in people in the age range 45–64y; however, there was no difference in those aged more than 65y. Conversely, Lee *et al*[7] observed that T2DM was found to entail an almost 40% increased risk of NAION in those aged 68–95y. Our previous article found that 61.3% of NAION patients with mean age of 55.8y had T2DM[18], and the present study observed no difference between age of onset and T2DM occurrence. Regarding the

association between T2DM and NAION development, Li *et al*[15] revealed that patients with T2DM in Asian population tended to develop sequential NAION; unfortunately, we could not test this hypothesis since our study aimed to evaluate risk factors for the first affected T2DM eye progressing to NAION. Interestingly, there was an almost significant difference between increased FBS levels in the two groups in the present study (P=0.053); however, the statistical significance was lost in multiple logistic analysis. This was in contrast to the results of a Chinese study which noted that a higher fasting sugar level rendered patients about 21% more prone to developing NAION (OR=1.218, P<0.001)[19], with the authors concluded that it was not T2DM itself, but rather poor glycemic control, that was an actual risk factor for NAION. However, NAION pathogenesis is multifactorial, involving compromise of the optic disc microcirculation and often associated with systemic vascular risk factors. Poor glycemic control is therefore among the factors that play a role, but not in isolation. Unlike thromboembolic events that present as severe acute interrupted blood supply, NAION is more subtle in severity reflecting a complex interplay of factors. In context of T2DM, OCT with retinal nerve fiber layer thickness may provide further insights into the pathogenesis of NAION. Recent studies have found that thinner temporal-quardrant peripapillary retinal nerve fiber layer (pRNFLT) in acute NAION eyes was associated with favorable visual outcomes[20].

In people aged under 50y, Deramo *et al*[21] revealed that a higher cholesterol level of ≥240 mg/dL was a significant risk factor for developing NAION. Similarly, in Korean populations, also proposed that hypercholesterolemia (a random cholesterol level of 240 mg/dL) was identified as a risk factor which increased the chance of developing NAION by 5 times (OR=5.2, P=0.001)[16]. In contrast, Chatziralli *et al*[22] observed that there was no association between HDL or LDL levels and NAION development, the authors further noting that hypertriglyceridemia almost doubled the risk of NAION. Our finding was in line with those of previous reports[16,21], in revealing that dyslipidemia and high LDL were potential risk factors of NAION in Thai populations. Our result was supported by the theory that dyslipidemia causes vascular endothelial dysfunction, produces atherosclerotic plaque which renders patients prone to developing hypertension, and increases the chances of vascular insufficiency, resulting in poor perfusion at the optic nerve[23].

Previous researchers have described the influence of smoking on NAION development in western populations[24]. Kim *et al*[16] also noted that smoking quadrupled the risk of NAION in Korean patients. Correspondingly, the present study found that there was a significantly higher proportion of smokers in the T2DM with NAION group, with an almost 13-fold higher OR. Smoking can affect small blood vessels in several processes by increasing blood viscosity due to increased concentrations of leukocytes or erythrocytes, decreasing oxygen concentration, or reducing HDL levels[25].

Small CDR has been observed to be a risk factor of NAION development[26]. In Asian populations, Kim *et al*[16] revealed that having small CDR was the strongest risk factor, increasing the chance of developing NAION approximately 17 times (P<0.001). The results of the present study were similar to those of previous reports in that we found that small CDR entailed an almost 12-fold increase in the risk of developing NAION. This finding is supported by the theory that swelling of optic nerves in the crowded optic disc eventually produces a vicious cycle of ischemic processes at the optic nerve[27].

The impact of gender on the risk of NAION development has differed among studies. Liu *et al*[5] conducted a Meta-analysis and revealed that being male resulted in an almost 70% higher risk of NAION. In our study, although a significant male predominance was observed in the progression to NAION group, the influence of gender in predicting NAION was lost in multivariable analysis. Our finding is supported by a study of Nuzzi *et al*[28] which showed that estrogen therapy in a rodent NAION model yielded no benefit. Interestingly, a large cohort study in menopausal women found that, after adjusting for confounding factors, hormone replacement therapy (HRT–estrogens) was significantly associated with an increased incidence of NAION, with longer periods of HRT correlating with a higher incidence of NAION[29]. However, the explanatory effect of estrogens on NAION pathogenesis is still unknown.

The relationship between hypertension and NAION development has varied among studies. Recently, in a large-scale Meta-analysis, Liu *et al*[5] reported that hypertension carried a 28% higher risk. Although previous research in the literature found that hypertension was a common pre-existing vascular disease in NAION patients[4,16]. Our result was in agreement with the finding of a Korean study in the sense that, while there was a significantly higher prevalence of hypertension, it was not identified as a potential risk factor[16].

In the present study, we observed no association between aspirin use and occurrence of NAION, which is consistent with evidences from a recent review[30]. Likewise, anti-hyperglycemic, anti-hypertensive, and lipid-lowering medications had no efficacy in preventing NAION occurrence. Regarding the benefits of anti-hyperglycemic medication in decreasing the risk of NAION, Tan *et al*[31] reported some neuroprotective effects of sulfonylurea in an animal model, and we propose that future studies with large samples of diabetic participants at various severity levels are warranted in order to assess the impact of anti-hyperglycemic drugs.

No associations were noted in our series between vascular complications (such as diabetic retinopathy or diabetic nephropathy) and NAION development. Our findings were in agreement with those reached by previous research, that there was no difference between DR in the two groups. A nationwide Taiwanese cohort study discovered that having end-stage renal disease entailed an approximately 3-fold increase in the risk of developing NAION[32]; however, the present study found no significant influence of diabetic nephropathy on NAION development. The small number of T2DM patients with diabetic nephropathy (only 21 cases in the whole cohort) may have diluted the power of analysis.

Some limitations of our research should be addressed. First, because of its retrospective nature, some potential factors may have been underdiagnosed or omitted, such as the use of phosphodiesterase-5 inhibitor. Second, as our hospital is a referral center, our participants may not accurately represent the overall T2DM population. Third, the benefit of aspirin therapy or anti-hyperglycemic, anti-hypertensive, or lipid-lowering medications could not be evaluated due to ethical concerns. However, this is the first study of Thai T2DM patients to report a NAION occurrence rate of 20.68%, with a mean time to NAION onset of 48.78mo. It also found that dyslipidemia, smoking, and small CDR were significant risk factors of NAION in T2DM patients.

In conclusion, the occurrence rate of NAION among T2DM was 20.68%, with a mean time to occurrence of 48mo. dyslipidemia, smoking, and small CDR were identified as the strongest risk factors of NAION development in T2DM patients. T2DM patients with small CDR or dyslipidemia should be carefully followed up, as they tend to have an increased risk of developing NAION.

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