Original Article

Risk Factors Associated with Diabetic Retinopathy and Thalassemia Prevalence Survey in Diabetes Mellitus Patients at Six Primary Care Units of Naresuan University Hospital: A Cross-Sectional Study

Tanate Chira-adisai MD[1], Rossukon Khotcharrat MD[1], Kanin Luangsawang MD[1]

[1] Department of Ophthalmology, Faculty of Medicine, Naresuan University, Phitsanulok, Thailand

Objective: To evaluate the risk factors and prevalence of diabetic retinopathy (DR) in both medical and socioeconomic aspects and find prevalence of thalassemia which associated hemoglobin A1c (HbA1c) measurement in diabetes mellitus (DM) patients at six primary care units (PCU) of Naresuan University Hospital (NUH).

Materials and Methods: A cross-sectional survey of DM patients participated in annual proactive DR screening program at six PCU of NUH between December 2016 and March 2017 was conducted. Medical data were retrieved from medical records at PCU. Patients were also interviewed to gather socioeconomic information. Fundus examination was done by indirect ophthalmoscope. Three milliliters of blood was collected from each patient on the same day for Hb analysis.

Results: Four hundred and eighty-eight DM patients participated in the present study. Mean age, duration of DM, fasting blood sugar (FBS) level, and HbA1c level were 61.2±9.8 years, 8 years (4 to 12), 124 mg/dL (108 to 151.5), and 7.1% (6.5 to 8.1), respectively. Prevalence of overall DR was 2.9% (14 patients) and proliferative DR was 0.2% (1 patient). Risk factors of DR were HbA1c at 7% or more [adjusted OR 4.7 (95% CI 1.4 to 13.5) and p=0.011] and emotional stress [adjusted OR 3.3 (95% CI 1.1 to 9.8) and p=0.033). Thalassemia screening found 116 patients had abnormal hemoglobin. Ninety-three patients were HbE trait, eight were HbE, ten were alpha-thalassemia trait, two were beta-thalassemia trait, one was HbH, one was alpha- and beta-thalassemia trait (α/β), and one was alpha-thalassemia trait and HbE trait (α/E), and all of them were thalassemia minor or intermedia. Only four patients from HbE trait group had DR. The mean HbA1c in all groups of patients with either normal or abnormal hemoglobin were not statistically significant different.

Conclusion: The present study showed that HbA1c and emotional stress might have played an important role in association with DR development. Thalassemia minor and intermedia seemed not to associate with HbA1c measurement.

Keywords: Diabetic retinopathy; Thalassemia; Primary care unit; Naresuan university; Risk factors

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Diabetes mellitus (DM) is commonly known as a group of metabolic disorders characterized by chronically high level of blood sugar. It can cause many complications throughout the organs of human body, for instance, ischemic heart disease, cerebrovascular disease, foot ulcers, and neuropathy. One of the most concerned complications and leading causes of blindness in working-age adults is diabetic retinopathy (DR). Prevalence of DR in patients with DM was high with a global overall at 34.6%[1] and responsible for 2.6% of blindness and 1.9% of moderate to severe visual impairment[2]. Three major risk factors for DR included diabetes duration, hemoglobin A1c (HbA1c), and blood pressure[3,4]. Thus, good control of DM and regular DR screening were two of the most important things to prevent the adverse events mentioned above[5].

To minimize the microvascular and neuropathic complications of diabetes, the American Diabetes Association (ADA) published the latest guideline in 2020[6] recommending keeping glycated hemoglobin (HbA1c) which is currently the primary measure guiding glucose management and a valuable marker of the risk of developing diabetic complications in non-pregnant adults at less than 7%. Glucose is bound to the N-terminal valine of the β chain hemoglobin and

Correspondence to:

Chira-adisai T.

Department of Ophthalmology, Faculty of Medicine, Naresuan University 99, Moo 9, Muang, Tha Pho, Phitsanulok 65000, Thailand

Phone: +66-81-8384422

Email: yoshiki911@hotmail.com

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HbA1c is the major portion of glycated hemoglobin[7]. Therefore, various studies found an error of HbA1c measurements in patients with β chain hemoglobin abnormalities[7,8]. In addition, the authors' literatures review found that Phitsanulok province, where Naresuan University Hospital (NUH) is responsible for, had the highest prevalence of hemoglobin E (HbE) among the Northern Provinces of Thailand at 25% in population that participated in prenatal diagnosis counseling program at Buddhachinaraj Hospital in 1991[9]. As HbE is a disease of β chain hemoglobin mutation, this might cause some discrepancies of HbA1c measurement in diabetic patients.

In the present study, the authors attempted to improve the routine annual proactive DR screening program at six primary care units (PCU) of NUH by not only collecting the data about DR and identifying the risk factors from the medical-related history but also socioeconomic history. The authors integrated a thalassemia screening to the present study program looking for any signs of incongruity between laboratory and clinical manifestations.

Materials and Methods

The present study was a cross-sectional survey with ethical approval from the Institutional Review Board of Naresuan University, Phitsanulok, Thailand (IRB No. 161/59) and conducted rigorously in accordance with the Declaration of Helsinki.

Sample size of the present study survey was calculated by the formula for estimation as followed:

$n = (Z\alpha/_2)^2 PQ / d^2$

$Z_{0.05/2}=1.96$, P=0.3889[9], Q=1–0.3889, d=0.05

n = 365.2

The inclusion criteria were:

1) All the patients diagnosed as DM whose age was 16 years or older and participated the DR screening program at the time of the present study survey.

Criteria for diagnosis of DM were[10]:

- Fasting blood sugar (FBS) of 126 m/dL or more, or
- Oral glucose tolerance test (OGTT) of 200 m/dL or more, or
- Random blood sugar (RBS) of 200 m/dL or more associated with diabetic symptoms, or
- HbA1C at 6.5% or higher

2) The patient must have been registered in the House Registration of six districts affiliated with NUH, which were Tha Pho, Tha Thong, Ngio Ngam, Wat Phrik, Sao Hin, and Wang Nam Khu.

3) The patient must have been informed about the study and given his or her consent to participate in the present study.

The exclusion criterion was with patients that had any ocular abnormalities in both eyes making the fundus examination un-processable.

Between December 2016 and March 2017, Department of Ophthalmology, Faculty of Medicine, Naresuan University proceeded the annual proactive DR screening program at six PCU in the districts mentioned above. At the PCU, one drop of tetracaine hydrochloride 0.5% (Tetracaine® ophthalmic solution, Alcon Laboratories (Thailand) Co Ltd, Bangkok, Thailand) followed by one drop of tropicamide 1% (Mydriacil® ophthalmic solution, Alcon Laboratories (Thailand) Co Ltd, Bangkok, Thailand) four times with five minutes interval between each drop were administered to each of the patients' eye to dilate the pupil for thorough fundus examination by ophthalmologists from the Department using indirect ophthalmoscope. The severity of DR was recorded using the international classification[11]. In the meantime, the medical data of all patients were collected from their medical records which were gender, age, duration of DM, FBS, HbA1c, blood pressure for hypertension at systolic blood pressure of 140 mmHg or higher or diastolic blood pressure of 90 mmHg or higher[12], low density lipoprotein (LDL; hypercholesterolemia, LDL of 100 or more)[13], triglyceride (TG; hypertriglyceridemia, TG of 200 or more)[13], foot ulcer, albumin-creatinine ratio (proteinuria, albumin-creatinine of 30 mg/g)[13], history of smoking and alcohol consumption, and substance abuse. After fundus examination, 3 mL of blood sample was drawn from right or left cubital vein of all patients and contained in ethylenediaminetetraacetic acid (EDTA) tube then transferred to thalassemia laboratory at NUH on the same day. Hemoglobin typing was analyzed by VARIANT II® Hemoglobin Testing System (Bio-Rad Laboratories Co. Ltd., Bangkok, Thailand) with high performance liquid chromatography (HPLC), and polymerase chain reaction (PCR) for alpha thalassemia was done by CFX96® Real Time System (Bio-Rad Laboratories Co. Ltd., Bangkok, Thailand) with real time PCR technique.

Finally, a questionnaire about socio-economy was conducted to collect the data about marital status, educational level, income, debt, treatment compliance, exercise, stress, health education, and private health insurance.

Primary outcome of the present study was to find

Table 1. Demographic data

Age (years); mean±SD (range)	61.2±9.8 (31 to 87)
Sex (male:female)	138:350
Type of diabetes mellitus (II/I)	479:9
Duration of diabetes mellitus (years); median (P_{25}, P_{75})	8 (4, 12)
Diabetic retinopathy (eyes/patients*); n (%)	
No DR	956 (98.0)/474 (97.1)
Mild NPDR	12 (8.0)/8 (1.6)
Moderate NPDR	5 (0.5)/4 (0.8)
Severe NPDR	1 (0.1)/1 (0.2)
PDR	2 (0.2)/1 (0.2)
Diabetic macular edema (eyes)	1 (0.1%)
Fasting blood sugar (mg/dL); median (P_{25}, P_{75}) (range)	124 (108, 151.5) (49 to 383)
Hemoglobin A1C (%); median (P_{25}, P_{75}) (range)	7.1 (6.5, 8.1) (4.5 to 14.6)
Hemoglobin typing (normal/abnormal)	372:116

DR=diabetic retinopathy; NPDR=nonproliferative diabetic retinopathy; PDR=proliferative diabetic retinopathy

* Considered from the more severe eye of patient

risk factors associated with DR in patients at six PCU of NUH, and secondary outcomes were prevalence of DR, thalassemia, and association between hemoglobinopathies and HbA1c in the present study group of patients

Pearson's chi-square or Fisher's exact test was used analyze categorical variables. Mann-Whitney U test or Kruskal-Wallis H test was used to analyze continuous independent variables. Multiple logistic regression was used to identify potential risk factors of DR and Spearman's rank correlation coefficient was used to find a correlation between variables. The continuous data were shown in mean ± standard deviation (SD) if they were normally distributed and in median (P_{25}, P_{75}) if they were not. A p-value of less than 0.05 was considered statistically significant

Results

Demographic data

Four hundred and eighty-eight diabetic patients were enrolled to the present study. Nine of them were diagnosed with DM type 1 and the rest with type 2. Twenty eyes had DR. One eye had diabetic macular edema. Mean FBS and mean HbA1c were 134±45 mg/dL and 7.5±1.6%, respectively.

Fourteen patients (2.9%, 20 eyes) had DR, which could be classified as eight (1.6%) mild non-proliferative diabetic retinopathy (NPDR), four (0.8%) moderate NPDR, one (0.2%) severe NPDR, and one (0.2%) PDR, consecutively (Table 1).

Table 2. Relationship of diabetic retinopathy and medical factors

	DR (n=14); n (%)	No DR (n=474); n (%)	p-value
Sex			0.980
Male	4 (2.9)	134 (97.1)	
Female	10 (2.9)	340 (97.1)	
Age (years)			0.292
30 to 49	0 (0.0)	56 (100)	
50 to 69	12 (3.6)	324 (96.4)	
70 or more	2 (2.1)	94 (97.9)	
Duration of DM (years)			0.039*
Less than 10	6 (2.2)	273 (97.8)	
10 to 19	4 (2.4)	160 (97.6)	
20 or more	4 (8.9)	41 (91.1)	
Fasting blood sugar (mg/dL)[T]			0.001*
Less than 160	7 (1.7)	395 (98.3)	
160 or more	7 (8.1)	79 (91.9)	
Hemoglobin A1c (%)			0.002*
Less than 7	5 (1.4)	345 (68.6)	
7 or more	9 (6.5)	128 (93.5)	
Hypertension			0.833
No	4 (2.6)	418 (97.4)	
Yes	10 (3.0)	236 (97.0)	
Hypercholesterolemia			0.726
No	4 (3.3)	116 (96.7)	
Yes	10 (2.7)	385 (97.3)	
Hypertriglyceridemia			0.275
No	6 (4.1)	139 (95.9)	
Yes	8 (2.3)	335 (97.7)	
Foot ulcer			0.583
No	14 (2.9)	464 (97.1)	
Yes	0 (0.0)	10 (100)	
Proteinuria			0.688
No	11 (2.7)	392 (97.3)	
Yes	3 (3.5)	82 (96.5)	
Hemoglobinopathy			0.669
No	10 (2.7)	362 (97.3)	
Yes	4 (3.4)	112 (96.6)	
Smoking			0.315
No	14 (3.6)	442 (96.9)	
Yes	0 (0.0)	32 (100)	
Alcohol consumption			0.749
No	13 (2.9)	428 (97.1)	
Yes	1 (2.1)	46 (97.9)	
Substance abuse			0.699
No	14 (2.9)	469 (97.1)	
Yes	0 (0.0)	5 (100)	

DM=diabetes mellitus; DR=diabetic retinopathy; SBP=systolic blood pressure; DBP=diastolic blood pressure; LDL=low-density lipoprotein; TG=triglyceride

* Statistically significant, Pearson's chi-square or Fisher's exact test;
[T] Statistically significant from this cut-point

Table 3. Relationship of diabetic retinopathy and socioeconomic factors

	DR (n=14); n (%)	No DR (n=474); n (%)	p-value
Marital status			0.810
Single	1 (5.0)	19 (95.0)	
Married	11 (3.1)	341 (96.9)	
Separated	0 (0.0)	10 (100)	
Divorced	1 (4.0)	24 (96.0)	
Widowed	1 (1.2)	80 (98.8)	
Educational level			0.196
Less than primary school	2 (1.0)	198 (99.0)	
Primary or secondary school	11 (4.4)	240 (95.6)	
High school	1 (3.0)	32 (97.0)	
University or college	0 (0.0)	4 (100)	
Income (Baht)			0.693
Less than 5,000	9 (3.5)	246 (96.5)	
5,000 to 9,999	5 (2.9)	166 (97.1)	
10,000 to 19,999	0 (0.0)	41 (100)	
20,000 to 49,999	0 (0.0)	20 (100)	
50,000 to 99,999	0 (0.0)	1 (100)	
Debt			0.209
No	9 (3.9)	224 (96.1)	
Yes	5 (2.0)	250 (98)	
Compliance with treatment			0.475
Never miss any visit	12 (2.8)	410 (97.2)	
Miss some visit	1 (1.9)	53 (98.1)	
Miss more than half of visits	1 (8.3)	11 (91.7)	
Exercise			0.332
At least once a week	12 (3.3)	352 (96.7)	
Never	2 (1.6)	122 (98.4)	
Stress (self-report)			0.026*
No	7 (1.9)	366 (98.1)	
Yes	7 (6.1)	108 (93.9)	
Health education by			0.916
Physician	0 (0.0)	13 (100)	
Primary care unit	8 (3.4)	224 (96.6)	
Village health volunteer	6 (2.5)	230 (97.5)	
Media	0 (0.0)	4 (100)	
No	0 (0.0)	3 (100)	
Private health insurance			0.398
Yes	12 (3.2)	360 (96.8)	
No	2 (1.7)	114 (98.3)	

DR=diabetic retinopathy

* Statistically significant, Pearson's chi-square or Fisher's exact test

Table 4. Multiple logistic regression of potential relating factors of diabetic retinopathy

	Adjusted OR (95% CI)	p-value
Duration of DM 20 years or more	1.7 (0.6 to 5)	0.355
FBS 160 mg/dL or more	0.4 (0.1 to 1.5)	0.183
HbA1c 7% or more	4.7 (1.4 to 13.5)	0.011*
Stress	3.3 (1.1 to 9.8)	0.033*

DM=diabetes mellitus; FBS=fasting blood glucose; HbA1c=hemoglobin A1c; OR=odds ratio; CI=confident interval

* Statistically significant

Primary outcome: risk factors associated with DR

Considering both medical (Table 2) and socioeconomic factors (Table 3), the results showed that longer duration of DM, FBS at or greater than 160 mg%, HbA1c at or greater than 7%, and emotional stress were statistically significant associated with DR (p=0.039, 0.001, and 0.002, respectively). These four factors were then analyzed again with multiple logistic regression and it was found that only high level of HbA1c [adjusted OR 4.7 (95% CI 1.4 to 13.5) and p=0.011] and emotional stress [adjusted OR 3.3 (95% CI 1.1 to 9.8) and p=0.033] were truly associated with DR (Table 4).

Secondary outcome: screening for thalassemia

Hemoglobinopathies were found in 116 (23.8%) patients and alpha-1 PCR positive in 12 (2.5%) patients (Table 5) with most of patients were HbE trait in 93 (19.1%) patients. The other variances are shown in Table 6 without statistically significant difference between DR and No DR groups.

Statistically significant difference of HbA1c level was not found among normal Hb and all Hb variances groups (p=0.160) and there was statistically significant positive correction between HbA1C level and FBS level of the same Hb variance except in β trait, HbH, α/β, and α/E groups, which could not be calculated because of low number of patients in these groups (Table 7).

Discussion

The prevalence of DM patients with DR in the present study was 2.9%. The prevalence was lower than the study from authors' annual DR screening program between 2013 and 2015, which had been 8.3%, 10.2%, and 7.4%[14], respectively. Comparing to the global prevalence at 34.6%[1] and 24% to 31%[15-18] in Thailand, the number in the present studies were much lower. The possible reasons of this low prevalence might have been because of the small sample size, but in the other hand, the present study

Table 5. Hemoglobin typing

	DR (n=14); mean±SD	No DR (n=474); mean±SD	Total (n=488); mean±SD	p-value
HbA (%)	76.4±11.5	79±13.6	78.9±13.5	0.034*
HbA2 (%)	8.8±10.3	8.3±13	8.4±12.9	0.230
HbF (%)	0.6±0.4	0.6±0.7	0.6±0.7	0.913
α-1 PCR positive; n (%)	0 (0.0)	11 (2.3)	11 (2.3)	0.564
Abnormal Hb; n (%)	4 (28.6)	112 (23.6)	116 (23.8)	0.669

Hb=hemoglobin; PCR=polymerase chain reaction; DR=diabetic retinopathy; SD=standard deviation

* Statistically significant different between DR and no DR group (Mann-Whitney U test)

Table 6. Hemoglobin variances

	DR (n=14); n (%)	No DR (n=474); n (%)	Total (n=488); n (%)	p-value
HbE trait	4 (28.6)	89 (18.8)	93 (19.1)	
HbE	0 (0.0)	8 (1.7)	8 (1.6)	
α trait	0 (0.0)	10 (2.1)	10 (2.0)	
β trait	0 (0.0)	2 (0.4)	2 (0.4)	
HbH	0 (0.0)	1 (0.2)	1 (0.2)	
α/β	0 (0.0)	1 (0.2)	1 (0.2)	
α/E	0 (0.0)	1 (0.2)	1 (0.2)	
Total	4 (28.6)	112 (23.6)	116 (23.8)	0.985

Hb=hemoglobin; DR=diabetic retinopathy

Table 7. Hemoglobinopathy and HbA1c level correlation

	HbA1c (%); mean±SD	FBS (mg/dL); mean±SD	r	p-value
Normal typing (n=372)	7.5±1.6	135.4±45.6	0.6	<0.001ᵀ
HbE trait (n=93)	7.7±1.6	130.4±42.6	0.7	<0.001ᵀ
HbE (n=8)	7.9±2.4	140.4±62.3	0.7	0.047ᵀ
α trait (n=10)	7.5±1.4	133.5±40.4	0.9	0.002ᵀ
β trait (n=2)	9.3±2.6	144±22.6	N/A	N/A
HbH (n=1)	4.5	160	N/A	N/A
α/β (n=1)	5.7	168	N/A	N/A
α/E (n=1)	9.1	169	N/A	N/A

Hb=hemoglobin; FBS=fasting blood glucose; r=correlation coefficient; N/A=not applicable

ᵀ Statistically significant positive correlation between HbA1c and FBS level of the same Hb variance, Spearman's rank correlation coefficient

had a strong primary care team members who had been taking an exceptionally good care and educating the patients in their responsible areas. Thirdly, registered DM patients in the present study areas were around 1,500 but only 488 (32.5%) joined the present study program at PCUs during the time of survey, which meant more than half of the DM patients were missing or receiving their treatment elsewhere including NUH, and the authors did not collect the data of those patients. Finally, it was the policy to advise all the patients with DR in the present study screening program to receive their medical attention at NUH, which could be accessed conveniently for the patients in the area, so this might have explained the even low prevalence in the present study.

The associated risk factors with DR in the present study were HbA1c level at or greater than 7% and emotional stress. While high HbA1c level as a risk factor of DR was repeatedly mentioned many times in previous studies[3,4,19,20], direct relationship between emotional stress and DR had not been brought up much to the authors knowledge. Oxidative stress played its important role in DR development resulted from losing equilibrium of reactive oxygen species (ROS) in retinal cells[21], and chronic psychological stress also affected ROS and led to oxidative damage[22], so it might have been the reason the patients with emotional stress were more likely to develop DR, but this relationship needs further and better study.

The other two major risk factors of DR, were duration of DR of 20 years or longer and hypertension[3,4], which could not be found significantly associated with DR in the present study. Nine-point-one percent of patients diagnosed as DM for 20 years or longer in the present study compared to 51.2% in a systematic literature review[3] was far lesser; hence, the association of duration of DM and DR could be different between the studies. Patients with hypertension, with a BP of 140 over 90 mmHg or higher, was around 50% in both the present study and the reviewed, but the authors should probably look more deeply in hypertensive staging to find the real cut-point of BP that affected DR.

Variant Hb found in the present study seemed not to affect HbA1c level because all the patients were not transfusion dependent thalassemia (thalassemia minor and intermedia)[23], which did not cause

severe hemolysis. There was some interference of heterozygous variants with specific HbA1c methods[7,8], but fortunately, NUH uses D-10® (Bio-Rad Laboratories Co. Ltd., Bangkok, Thailand) with ion-exchange HPLC method to measure HbA1c level which had no interference reported.

However, there was some concern in patients with thalassemia major whose HbA1c results might have been falsely interpreted depending on red blood cell lifespan, transfusion, and the method used. In these cases, continuous glucose monitoring could be beneficial[24].

Several limitations could be recognized in the present study. Not all the registered DM patients in the present study area participated in the DR screening program. In the future, data from all accessible sources, for example, NUH, private clinic, and private hospital should be included to limit any missing data.

DR screening was done by 10 to 12 ophthalmologists so the finding might not have been totally correlated. However, this issue is unlikely to be constraining because the program itself is a routine annual activity of the Department, which every member must take part. Therefore, this had only a minor effect because all certified ophthalmologists could evaluate DR almost similarly.

The prevalence of thalassemia was expectedly low. Multicenter study in different regions of Thailand should be conducted to gain more information for analysis.

Conclusion

Regular DR screening is important for DM patients to prevent blindness and severe visual impairment. Effective PCU helps controlling the disease. HbA1c is the primary target to be focused and emotional stress might play an important role in association with DR development. HbA1c measurement seemed not to be associated with thalassemia minor and intermedia, which were not transfusion dependent and did not affect RBC lifespan. Therefore, in Thailand, where most thalassemia patients are in these groups of disease, thalassemia screening is probably not necessary in patients with DM.

What is already known on this topic?

Longer diabetic duration, high HbA1c level, and high blood pressure were important risk factors of DR.

Some variants of β chain hemoglobin interfered HbA1c measurement by some methods.

According to the survey in 1991, Phitsanulok had the highest prevalence of HbE, which was β chain hemoglobin mutation, among the northern provinces of Thailand at 25%.

What this study adds?

Emotional stress might have played an important role in developing of DR.

HbE trait had the highest prevalence among the patients in the present study at 19.1% and all the hemoglobin variants detected were not thalassemia major, which causes hemolysis and requires blood transfusion.

Although HbA1c measurement interference was reported in some patients with β chain hemoglobin mutations, the present study method at NUH, which is ion-exchange HPLC by D-10® (Bio-Rad Laboratories Co. Ltd., Bangkok, Thailand), was not affected.

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Conflicts of interest

The authors declare no conflict of interest.

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