FACTORS ASSOCIATED WITH DIABETIC RETINOPATHY AMONG TYPE 2 DIABETIC PATIENTS: A HOSPITAL BASED CASE-CONTROL STUDY

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Abstract. The objective of this study was to determine factors associated with diabetic retinopathy (DR) among type 2 diabetics in Thailand. We conducted a hospital based case-control study in Nakhon Nayok Province, between August 2008 and July 2010. The subjects were comprised of 230 cases (with DR) and 230 controls (without DR) who were gender and age matched. All subjects were interviewed and their medical records were reviewed. Seventy-five percent of subjects were married and 42% were aged 60-69 years. Fifty-five percent had a primary school education, 27% had no occupation and 67% had family income >10,000 Baht per month. On multiple logistic regression analysis, factors associated with DR were: having a fasting plasma glucose (FPG) of 141-160 mg/dl, 161-180 mg/dl and >180 mg/dl [OR = 7.23; 95% confidence interval CI: 2.80-18.72; OR = 4.33; 95% CI: 1.66-11.33, and OR = 3.76; 95% CI: 1.39-10.18], having a HbA1c >9% (OR = 2.26; 95% CI: 1.15-4.43), having a BMI ≥ 30 kg/m^2 (OR = 2.09; 95% CI: 1.04-4.19), and having hypertension (OR = 1.80; 95% CI: 1.19-2.71). Elevated blood sugar, blood pressure and body weight are all associated with DR. Further study is needed to determine if controlling these factors could reduce the prevalence of DR.

Keywords: diabetic retinopathy, type 2 diabetic patients, risk factors

INTRODUCTION

Diabetes mellitus (DM) is an important public health problem worldwide. The World Health Organization (2006) estimated there were 171 million people worldwide with DM in 2000 and predicted this number would increase to 366 million people by 2030. The Forth National Health Examination Survey in Thailand found the prevalence of DM to be 6.9%, 7.7% among females and 6.0% among males (Health Systems Research Institute, 2009). Thailand spends a great deal of money to treat DM and its complications, such as cardiovascular disease, renal failure, foot amputations and blindness (Nitiyanant, 2008). Greater than 75% of patients who have DM for more than 20 years will develop some form of diabetic retinopathy

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(DR) (Wild *et al*, 2004). Diabetics have 25 times the risk of blindness than non-diabetics (Guillermo *et al*, 2002). We studied the factors associated with DR among Thai diabetics.

MATERIALS AND METHODS

Study population and data collection techniques

We conducted a hospital based case-control study between August 2008 and July 2010 among diabetics attending diabetic clinics at five public hospitals in Nakhon Nayok Province, Thailand (HRH Princess Maha Chakri Sirindhorn Medical Center, Nakhon Nayok Hospital, Banna Hospital, Pakplee Hospital and Ongkharak Hospital). We divided subjects into 2 groups: those with DR and those without DR (controls) by stereoscopic fundus photographic examination conducted by ophthalmologists. The 2 study groups were age (±5 years) and gender matched and subjects were chosen randomly. Study subjects must have been willing to participate. Subjects gave written informed consent prior to participation in the study. The study was approved by the Ethics Committee for Research in Human Subjects of Mahidol University (Ref. No. MUPH 2010-083) and the Department of Disease Control (Ref No. 8/53-420).

All subjects were interviewed at diabetic clinics of hospitals and data were collected by using structured questionnaires from their medical records.

Sample size

The sample size was calculated by the formula (Schlesselman and Stolley, 1982):

$$n = \frac{\left\{Z_{\alpha/2}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{P_1(1-P_1)+P_0(1-P_0)}\right\}^2}{(P_1-P_0)^2}$$

Where n = minimum number of diabetics needed for the study; P_o was the proportion of exposure in the control group of 0.23; P_1 was the proportion of exposure in case group of 0.37; $Z_{\alpha/2} = 1.96$ at $\alpha = 0.05$; $Z_{\beta} = 1.28$ at $\beta = 0.10$. The minimum number needed for each group was determined to be 223.

Statistical analysis

The software program SPSS, version 17.0 (IMB, Armonk, NY) was used for the evaluations. Descriptive statistics, such as frequencies, percents, means and standard deviations were used to describe the study subjects. Univariate analysis was performed using the Pearson's chi-square test. Multiple logistic regression was used to determine factors associated with DR after adjusting for confounding factors. Statistical significance was considered to be $p< 0.05$.

RESULTS

Sixty-two percent of the subjects were female, 42% were aged 60-69 years, 75% were married, 55% had a primary school education, 27% had no occupation and 67% had a family income >10,000 Baht per month. Factors associated with DR on univariate analysis are shown in Table 1. An elevated body mass index (BMI) was associated with a greater risk of DR, especially with a BMI ≥ 30 kg/m^2, giving an OR of 1.99 (95%CI: 1.06-3.73) compared to a BMI < 23 kg/m^2. Diabetics with a fasting plasma glucose (FPG) level of 141-160 mg/dl, 161-180 mg/dl and ≥180 mg/dl were 5.70, 3.43 and 3.21 times more likely to develop DR than those with a FPG level ≤ 120 mg/dl (OR= 5.70; 95% CI: 2.34-13.82; OR=3.43; 95% CI: 1.39-8.08; OR= 8.46; 95% CI: 1.27-8.08, respectively). Patients with a hemoglobin A1c (HbA1c) level >9% had twice the risk of developing

Table 1
Association of variables with diabetic retinopathy among study subjects.

Variables	Cases		Controls		OR_c	95%CI	*p*-value
	n	%	*n*	%			
Education							
No schooling	24	10.4	21	9.1	1		
Primary school	135	58.7	120	52.2	0.98	0.52 - 1.56	0.961
Secondary school	59	25.7	71	30.9	0.73	0.37 - 1.44	0.358
Bachelor degree or higher	12	5.2	18	7.8	0.58	0.23 - 1.49	0.259
Occupation							
No occupation	64	27.9	64	27.9	1		
Government employee	19	3.9	10	4.3	0.90	0.34 - 2.36	0.831
Private employee	50	21.7	55	23.9	0.91	0.54 - 1.52	0.718
House wife	29	12.6	26	11.3	1.12	0.59 - 2.10	0.735
Agriculture worker	48	20.9	52	22.6	0.92	0.55 - 1.56	0.764
Merchant	30	13.0	23	10.0	1.30	0.69 - 2.45	0.419
Family income (Baht/month)							
< 5,000	19	8.3	15	6.5	1		
5,000 - 10,000	66	28.7	51	22.2	1.02	0.47 - 2.21	0.956
> 10,000	145	63.0	164	71.3	0.70	0.34 - 1.42	0.323
Age at diagnosis (years)							
< 40	19	8.3	18	7.8	1		
40 - 49	105	45.7	104	45.2	0.96	0.48 - 1.93	0.901
50 - 59	87	37.8	87	37.8	0.95	0.47 - 1.93	0.881
≥ 60	19	8.3	21	9.1	0.86	0.35 - 2.10	0.736
Mean (SD)	49.0 (7.3)		49.2 (7.3)				
Duration since diagnosis (years)							
≤ 9	83	36.1	100	43.5	1		
≥ 10	147	63.9	130	56.5	1.36	0.94 - 1.98	0.106
Mean (SD)	10.1 (4.1)		10.0 (3.9)				
Types of therapy							
Diet and OHA	187	81.3	196	85.2	1		
Diet and insulin	37	16.1	31	13.5	1.25	0.75 - 2.10	0.396
Diet, insulin and OHA	6	2.6	3	1.3	2.1	0.46 - 10.74	0.300[a]
Control food intake							
Yes	199	86.5	186	80.9	1		
No	31	13.5	44	19.1	0.66	0.40 - 1.09	0.102
Exercise							
Yes	101	43.9	110	47.8	1		
No	129	56.1	120	52.2	1.17	0.81 - 1.69	0.400
Smoking							
Never	190	82.6	196	85.2	1		
Ever	19	8.3	18	7.8	1.09	0.56 - 2.14	0.805
Current	21	9.1	16	7.0	1.35	0.69 - 2.67	0.383
Alcohol consumption							
Never	172	74.8	182	79.1	1		
Ever	30	13.0	25	10.9	1.27	0.72 - 2.25	0.412
Current	28	12.2	23	10.0	1.29	0.71 - 2.32	0.400

Table 1 (Continued).

Variables	Cases		Controls		OR_c	95%CI	*p*-value
	n	%	*n*	%			
BMI (kg/m^2)							
< 23	37	16.1	45	19.6	1		
23 - 24.9	64	27.8	53	23.0	1.47	0.83 - 2.59	0.184
25 - 29.9	80	34.8	102	44.3	0.95	0.57 - 1.61	0.860
≥ 30	49	21.3	30	13.0	1.99	1.06 - 3.73	0.032[b]
Mean (SD)	26.3 (3.9)		26.0 (3.5)				
FPG (mg/dl)							
≤ 120	8	3.5	22	9.6	1		
120 - 140	36	15.7	85	37.0	1.16	0.47 - 2.86	0.739
141 - 160	89	38.7	43	18.7	5.7	2.34 - 13.82	<0.001[b]
161 - 180	55	23.9	44	19.1	3.43	1.39 - 8.46	0.007[b]
≥ 180	42	18.3	36	15.7	3.21	1.27 - 8.08	0.013[b]
Mean (SD)	159.0 (25.7)		147.6 (26.0)				
HbA1c (%)							
< 7	33	14.3	44	19.1	1		
7 - 9	138	60.0	151	65.7	1.22	0.73 - 2.02	0.445
> 9	59	25.7	35	15.2	2.25	1.22 - 4.16	0.010[b]
Mean (SD)	26.3 (3.9)		26.0 (3.5)				
Hypertension							
No	96	41.7	122	53.0	1		
Yes	134	58.3	108	47.0	1.58	1.09 - 2.28	0.015[b]
Total cholesterol (mg/dl)							
< 200	107	46.5	100	43.5	1		
≥ 200	123	53.5	130	56.5	0.88	0.61 - 1.27	0.512
Mean (SD)	200.0 (30.8)		201.0 (31.9)				
Triglyceride (mg/dl)							
< 200	136	59.1	146	63.5	1		
≥ 200	94	40.9	84	36.5	1.2	0.83 - 1.75	0.339
Mean (SD)	193.4 (45.2)		187.1 (42.9)				
LDL-Cholesterol (mg/dl)							
< 100 mg/dl	63	27.4	59	25.7	1		
≥ 100 mg/dl	167	72.6	171	74.3	0.92	0.60 - 1.38	0.673
Mean (SD)	116.0 (30.9)		118.1 (31.7)				
HDL-Cholesterol (mg/dl)							
> 40 mg/dl	202	87.8	198	86.1	1		
≤ 40 mg/dl	28	12.2	32	13.9	0.86	0.50 - 1.48	0.580
Mean (SD)	45.3 (4.9)		45.6 (5.1)				

[a]Fisher exact chi-square test; [b]$p < 0.05$; ORc, crude odds ratio; CI, confidence interval; BMI-body mass index; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; LDL, low density lipoprotein; HDL, high density lipoprotein; OHA, oral hypoglycemic agent; SD, standard deviation.

Table 2
Multiple logistic regression analysis of factors associated with diabetic retinopathy among study subjects.

Variables	OR_c	95%CI	OR_{adj}	95%CI	*p*-value
BMI (kg/m^2)					
< 23	1		1		
23 - 24.9	1.47	0.83 - 2.59	1.65[a]	0.88 - 3.10	0.120
25 - 29.9	0.95	0.57 - 1.61	1.03[a]	0.58 - 1.84	0.910
≥ 30	1.99	1.06 - 3.73	2.09[a]	1.04 - 4.19	0.038[b]
FPG (mg/dl)					
≤ 120	1		1		
120 - 140	1.17	0.47 - 2.86	1.46[c]	0.56 - 3.82	0.440
141 - 160	5.7	2.34 - 13.82	7.23[c]	2.80 - 18.72	<0.001[b]
161 - 180	3.43	1.39 - 8.46	4.33[c]	1.66 - 11.33	0.003[b]
≥ 180	3.21	1.27 - 8.08	3.76[c]	1.39 - 10.18	0.009[b]
HbA1c (%)					
< 7	1		1		
7 - 9	1.22	0.73 - 2.02	1.38[c]	0.80 - 2.40	0.252
> 9	2.25	1.22 - 4.16	2.26[c]	1.15 - 4.43	0.018[b]
Hypertension					
No	1		1		
Yes	1.58	1.09 - 2.28	1.80[d]	1.19 - 2.71	0.005[b]

[a]Adjusted for FPG, hypertension, total cholesterol, triglyceride, LDL-Cholesterol, HDL-Cholesterol, age at onset, duration since diagnosis of diabetes, smoking, control of food intake, exercise, alcohol consumption.
[b]$p < 0.05$.
[c]Adjusted for hypertension, total cholesterol, triglyceride, LDL-Cholesterol, HDL-Cholesterol, age at onset, duration of DM, smoking, control of food intake, exercise, alcohol consumption, BMI.
[d]Adjusted for FPG, total cholesterol, triglyceride, LDL-Cholesterol, HDL-Cholesterol, age at onset, duration of DM, smoking, control of food intake, exercise, alcohol consumption, BMI.
FPG, fasting plasma glucose; HT, hypertension; LDL, low density lipoprotein; HDL, high density lipoprotein; DM, diabetes mellitus; BMI, body mass index; HbA1c, hemoglobin A1c; ORc, crude odds ratio; ORadj, adjusted odds ratio.

DR than those with a HbA1c level <7%. Hypertension defined by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of Hypertension (Chobanian *et al*, 2003) was a systolic blood pressure ≥140 mmHg, or a diastolic blood pressure ≥90 mmHg. Those with hypertension had a greater risk of developing DR than those without hypertension (OR = 1.58; 95% CI: 1.09-2.28). Total cholesterol, triglycerides, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, type of diabetic treatment, age at diagnosis of diabetes, duration since diagnosed with DM, type of food consumed, history of exercising, current smoking and current alcohol consumption were not significantly associated with DR.

After controlling for confounding factors using multiple logistic regression analysis, 4 factors were associated with

DR: BMI, FPG level, HbA1c level and hypertension (Table 2). A BMI ≥ 30 kg/m^2 was associated with a greater risk of having DR (OR = 2.09; 95% CI: 1.04-4.19). The risk for developing DR increased 7-fold for diabetics with a FPG of 141-160 mg/dl (OR = 7.23; 95% CI: 2.80-18.72), increased 4-fold for diabetics with a FPG of 161-180 mg/dl (OR = 4.33; 95% CI: 1.66-11.33) and increased 3-fold for diabetics with a FPG >180 mg/dl (OR = 3.76; 95% CI: 1.39-10.18), compared to diabetics with a FPG <120 mg/dl). Diabeties with a HbA1c >9% had a greater risk of DR (OR = 2.26; 95%CI: 1.15 - 4.43) than those with a HbA1c <7%. Having hypertension was associated with an increased risk of DR (OR = 1.80; 95% CI: 1.19-2.71).

DISCUSSION

In this study, hyperglycemia was the main risk factor for DR. FPG and HbA1C were both used as indicators of diabetes control. However, FPG only reflects an isolated period in time. Risk of DR is not greatly affected by short-term improvements in glycemic control, since there is a lag between metabolic control and affect on DR risk (Wong and Klein, 2008). In our study, a HbAlc level >9% was significantly associated with DR after adjusting for other variables. This finding agrees with several other studies (Looker *et al*, 2001; Fosmark *et al*, 2006; Pradeepa *et al*, 2008, Wong *et al*, 2008b). However, one study found no relationship between hyperglycemia and DR (Kifley *et al*, 2007). Both elevated FPG and HbA1c levels were associated with DR in our study. This has been seen in other studies (Keen *et al*, 2001; Maberley *et al*, 2002). Elevated glucose levels have a direct deleterious effect on both pericytes and endothelial cells (Joussen *et al*, 2007). High blood glucose levels are associated with increased retinal blood flow and increased vascular shear stress. The effect of blood flow increase is damage to vessel walls, clogged vessels, hypoxia, ischemia, and proliferating DR (Pradeepa *et al*, 2008). Prolonged elevations in blood sugar result in the occurrence of complications more easily (Wong *et al*, 2008a).

Our study found hypertension was associated with DR, after controlling for other variables. Other studies have found hypertension as a risk factor for DR (Maberley *et al*, 2002, Rani *et al*, 2009). Hypertension influences blood flow in the retina by causing destruction of the blood vessel epithelial cell (Joussen *et al*, 2007; Wong and Klein, 2008). As a result, blood vessels become narrower and there is clogging of the small blood vessels, resulting in soft exudates and accumulation of fat (Joussen *et al*, 2007; Wong and Klein, 2008). Chronic hypertension causes hardening of the blood vessels, resulting in stenosis, clotting of blood in the retina and a cross between veins and arteries (Joussen *et al*, 2007, Wong and Klein, 2008). Overlapping of blood vessels is associated with poor blood circulation and retinal complications (Cugati *et al*, 2006).

A BMI ≥ 30 kg/m^2 was found to be significantly associated with DR. This agrees with several other studies (Wong *et al*, 2008b; Rani *et al*, 2009). Obesity shares many common risk factors with diabetic retinopathy, including hyperglycemia, hypertension and dyslipidemia. (Wong and Klein, 2008). However, the underlying pathophysiological mechanisms of the possible association between obesity and retinopathy are not well understood (Wong and Klein, 2008).

Prevention of vision loss from DR should be a part of diabetes management.

Diabetics should be screened regularly. Elevated blood sugar, blood pressure and body weight were associated with DR in our study. Further study is needed to determine if controlling these factors can reduce the prevalence of DR.

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