Original Article

Effects of Glycemic Control on Diabetic Eyes Diseases in Type 2 Diabetes

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Objective: To evaluate the impact of glycemic control on diabetic eyes diseases. The impact of other clinical features on diabetic eyes diseases, and the effect of glycemic control on other medical complications were also studied.

Materials and Methods: This retrospective comparative study included type 2 diabetic patients who were treated in Endocrinology Unit, faculty of Medicine Vajira Hospital between January 2005 and June 2016. The patients were divided into two groups by their most current Hb1Ac levels as good glycemic control (HbA1c <7%) versus moderate to poor control (HbA1c ≥7%). The effects of glycemic control and other clinical features on the development and progression of diabetic eyes diseases which included diabetic retinopathy [DR] and cataracts were compared.

Results: Among 1,001 diabetic patients included in the study, 341 patients (34.1%) had good glycemic control and 660 (65.9%) had moderate and poor control. The median follow-up of 7.3 years (IQR 4.8 to 8.5 years). We found 140 patients (14.0%) had development and progression of diabetic eyes diseases: 51 patients (15%) of the good glycemic control group vs. 89 patients (13.5%) in moderate to poor glycemic control (HR 1.11; 95% CI, 0.78 to 1.56; $p = 0.570$). Age ≥60 years was the only significant risk factor for diabetic eyes diseases.

Conclusion: Good glycemic control or HbA1c <7% by the current practical guidelines did not have effects on diabetic eyes diseases. Only age was a significant risk factor for diabetic eyes diseases.

Keywords: Diabetes eyes diseases, Diabetic retinopathy, Cataracts

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Patients who have diabetes mellitus have increased risks of many end organs damage from vascular complications, such as, eyes, renal, cardiovascular, and etc[1]. Regarding diabetic eyes diseases, the lesions can be found as diabetic retinopathy [DR], diabetic maculopathy, rubeosis of the iris, secondary glaucoma, complicated cataract, diabetic neuropathy of cerebral nerves supporting ocular muscles, and diabetic neuropathy of optic nerves[2].

DR and cataracts are common causes of visual loss in both type 1 and type 2 diabetic patients. The risk was high especially in the patients with long term diabetes and who had poor glycemic control[3]. Studies in Thailand showed one third of type 2 diabetic patients had DR[4] and about 30% had blindness[5]. In general population, the incidence of cataract was approximately 50% in individuals aged between 65 to 74 years old and increased to 70% in older age than 75 years old[6]. Diabetes increased the risk of cataract 2 to 5 times than non-diabetic patients. The risk was even higher or 15 to 25 times in younger age (<40 years)[7].

Many studies or trials attempted to identify factors which may prevent or reduce the risk of microvascular complications. Unfortunately, data from previous studies were inconsistent. Some showed benefits of strict glycemic control in patients with type 2 diabetes[8] with a 25% risk reduction of microvascular complications[9]. On the contrary, other trials[10,11] could not demonstrate a reduction of DR or

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other major cardiovascular events despite of intensive glycemic control represented by hemoglobin A1c [HbA1c] less than 7%. Another study showed risk of cataract exaggerated with higher HbA1c level. The odds ratio [OR] of cataracts sequentially increased with higher levels of HbA1c: OR 1.04 with HbA1c 6.5 to 7.5% and 1.16 with with HbA1c >8.5[12]. Reduction 1% of HbA1c level could reduce the risk of cataract 19%[13].

Current clinical practice guideline from the Diabetes Association of Thailand recommends target HbA1c less than 7% for prevention of diabetic vascular complications. The endocrinologists generally have common targets in taking care of the diabetic patients. However, a good glycemic control which would lead to different treatment outcomes certainly depends on several factors.

Objective

The present study primarily aimed to assess the effect of glycemic control on diabetic eyes diseases (DR and cataracts) in type 2 diabetic patients who had treatment in our institution. The second objectives were to study the impact of other clinical features on diabetic eyes diseases, and the effect of glycemic control on other medical complications.

Materials and Methods

This retrospective comparative study was approved by Ethical Committee on Human Rights Related to Researches Involving Human Subjects, Faculty of Medicine Vajira Hospital, Navamindradhiraj University. As a routine practice in the Endocrinology Unit, diabetic patients were screened for DR and cataract by fundal photographs assessed by practical nurses at an initial visit and annually afterwards. Diagnoses of DR or cataracts were made when one or both eyes were affected. The patients who had abnormal findings would be referred to an ophthalmologist for a management.

Subjects and data collection

Patients who had type 2 diabetes mellitus and were treated and follow-up at Endocrinology Unit, Vajira Hospital between January 2005 and June 2016 were identified. Eligibility criteria were the patients who had diabetic microvascular screenings including fundal photography and urine albumin, and had baseline (at initial screening) and followed-up HbA1c values. The patients with non-proliferative diabetic retinopathy [NPDR] or cataracts not requiring surgery were defined in our study as mild degree of diabetic eyes diseases were also included. Exclusion criteria were the patients who had onset of diabetes before 30 years of age, pre-existing proliferative diabetic retinopathy [PDR] or previous cataract surgery, had an eye assessment only once during the study period, or had inaccessible or unavailable fundal photography. Data collected from the medical records and electronic medical records of the patients included: age, gender, duration of diabetes, body mass index [BMI], blood pressure, laboratory investigations including fasting plasma glucose, baseline and the most current HbA1c levels, creatinine, and lipid profiles.

Main outcomes and measures

The primary outcome of this study was the impact of glycemic control on the courses of DR and cataracts in diabetic patients after treatment. The impact was measured with the deterioration rates and hazard ratio [HR] of progression of NPDR to PDR, development of NPDR or PDR, or progression of cataracts requiring surgery. The secondary outcomes were the occurrence of major cardiovascular events (non-fatal myocardial infarction and non-fatal stroke), severe hypoglycemia, hyperglycemic crisis, micro- and macro-albuminuria and acute kidney injury [AKI].

Statistical analysis

All data were analyzed using SPSS for windows version 22.0 (IBM Corp, Armonk, NY). Descriptive data were presented with median with interquartile ranges or number with frequency. Data were compared between the patients who had good vs moderate to poor glycemic control with Chi-square or Fisher exact tests as appropriate. Rates of DR and cataracts over time were analyzed by the Kaplan-Meier method and were compared between groups with log rank test. The Cox proportional-hazards model was used to calculate hazard ratio with 95% confidence intervals. Glycemic control at the end of study was determined by the HbA1c levels. Good glycemic control was defined as those who had HbA1c less than 7%. Adverse events incidence rates were calculated per 100 patient-years. The p-value <0.05 was considered significant.

Results

We identified 1,581 diabetic patients during the study period. 527 patients were excluded by the following reasons: 382 had eyes screening test only once, 107 had inaccessible or unavailable fundal photography, and 38 patients were found to have PDR and previous cataract surgery (Figure 1).

Total of 1,001 patients met all inclusion criteria. Approximately two third were female, 656 patients (65.5%). Median age was 59 years (IQR 52 to 67 years) whereas median duration of diabetes was 7.5 years (IQR 3.4 to 12.7 years). Among these, macrovascular complications, strokes or myocardial infarction, were present in 127 patients (12.7%). From baseline eyes screening, 845 patients (84.4%) had normal findings, 84 (8.4%) had evidenced of NPDR, and 72 (7.2%) had cataracts not requiring surgery. Median fasting blood glucose was 138 mg/dl (IQR 115 to 173 mg/dl) whereas the median HbA1c was 7.7% (IQR 6.8 to 9.0). The median values of all lipid profiles were within normal range. Medication review showed 43.4% of the patients received statins, 38.4 % received renin-angiotensin-aldosterone system (RAAS) inhibitors, and 27.7% had antiplatelets. Demographic data of the patients are shown in Table 1.

A median duration of follow-up in our study was 7.3 years (IQR 4.8 to 8.5 years). Median fasting blood glucose was 143 mg/dl (IQR 117 to 178 mg/dl) whereas the median HbA1c was 7.4% (IQR 6.7 to 8.4). Using HbA1c <7%, 341 patients (34.1%) was determined to have good control and 660 (59.9%) had moderate to poor control (Figure 1). The most current eyes screening identified 802 patients (80.1%) had normal findings, 14 (1.4%) had NPDR, 11 (1.1%) had PDR, 82 (8.2% had cataracts not requiring surgery whereas 92 (9.2%) required surgery. We compared the results of the initial and most current eyes screening, we found 140 patients (14.0%) had deterioration of diabetic eyes diseases: 106 of 845 patients (12.5%) who had initially normal test, 7 of 84 patients (8.3%) who had initial NPDR, 27 of 72 patients (37.5%) who initially had cataract not requiring surgery. Detailed findings of the initial and the latest eyes screening are presented in Table 2.

We studied the most current eyes findings according to the status of glycemic control and found 51 patients out of 341 patients who had good glycemic control (15.0%) had deterioration of eyes findings compared to 89 of 660 patients (13.5%) who had moderate to poor glycemic control (HR 1.11; 95% CI, 0.78 to 1.56; $p = 0.570$). Probability of diabetic eyes disease progression between the good and moderate to poor glycemic control is shown in Figure 2.

Data from the last eyes screening (in relation to the initial findings) according to the group of glycemic control are shown in Table 3. To be emphasized, we found slightly higher percentages of the patients who had moderate to poor glycemic control developed PDR than the good control group: 8 patients

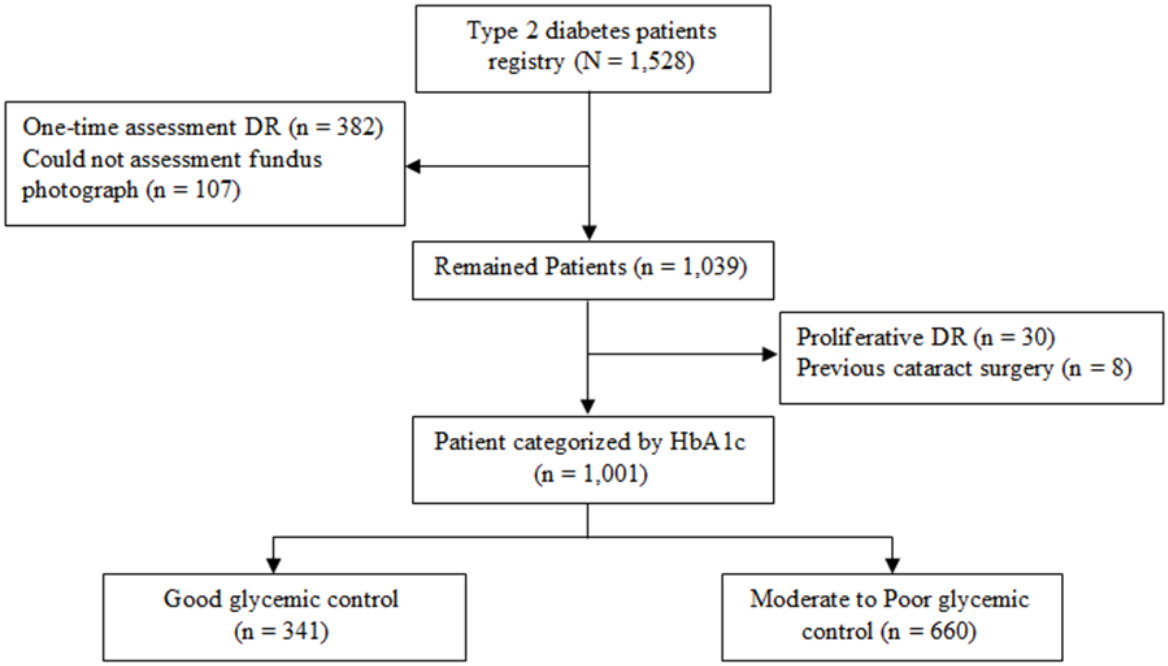

Figure 1. Categorization and follow-up of study participants.

Table 1. Clinical characteristics of diabetic patients (n = 1,001)

Characteristic	Total
Demographic data	
Age (years)	59 (52 to 67)
Duration of diabetes (years)	7.50 (3.42 to 12.75)
Female	656 (65.5)
Established CVD	127 (12.7)
Body Mass Index; BMI (kg/m^2)	26.45 (23.51 to 29.47)
Body weight (kg)	66.0 (57.0 to 75.0)
Systolic BP (mmHg)	135 (123 to 147)
Diastolic BP (mmHg)	77 (70 to 84)
Laboratory findings	
Fasting blood glucose (mg/dL)	138 (115 to 173)
Hemoglobin A1c (%)	7.7 (6.8 to 9.0)
Creatinine (mg/dL)	1.00 (0.86 to 1.20)
Cholesterol (mg/dL)	181 (156 to 207)
HDL-C (mg/dL)	44 (37 to 52)
LDL-C (mg/dL)	106 (85 to 129)
Triglyceride (mg/dL)	129 (96 to 173)
Medication	
Antiplatelets*	277 (27.7)
Aspirin	267 (26.7)
Clopidrogel	26 (2.6)
RAAS Inhibitor*	384 (38.4)
ACEI	233 (23.3)
ARB	161 (16.1)
Statins	434 (43.4)
Diabetic eyes diseases at initial	
Normal	845 (84.4)
NPDR	84 (8.4)
Cataracts not requiring surgery	72 (7.2)

Data are presented as n (%) or median (interquartile range)
* One patient may have one of more drugs
ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; BP = blood pressure; CVD = cardiovascular disease; HDL-C = high density lipoprotein-cholesterol; LDL-C = low density lipoprotein-cholesterol; NPDR = non-proliferative diabetic retinopathy; RAAS = renin-angiotensin-aldosterone system

(1.2%) vs. 3 patients (0.9%), $p = 0.451$. In contrast, the patients with good glycemic control had higher rate of cataracts surgery: 37 patients (10.9%) vs. 55 patients (8.3%), $p = 0.191$.

Aside from glycemic control, we also studied the other clinical factors which may impact the progression of diabetic eyes disease. By univariate analysis, we found age ≥60 years, duration of diabetes ≥10 years, presence of cardiovascular disease, and systolic blood pressure >130 mmHg were risk factors of eyes diseases progression. LDL ≥100 mg/dl appeared to have lower risk. By multivariate analysis, only age ≥60 years was the only significant risk factor. Table 4 shows uni- and multivariate analysis of glycemic control and other clinical factors associated with diabetic eyes diseases.

We studied other medical complications among the diabetic patients with good or moderate to poor glycemic control. Good glycemic control had significantly lower events of micro- and macro-albuminuria: 2.51 per 100 patient-years vs. 3.41 per 100 patient-years ($p = 0.004$) and 0.08 per 100 patient-year vs. 1.30 per 100 patient-years ($p = 0.016$), respectively. No differences of other major cardiovascular events, severe hypoglycemia, hyperglycemic crisis, or AKI were found (Table 5).

Discussion

The present study could not demonstrate an impact of glycemic control in diabetic patients. Previous studies also showed that glucose lowering treatment, especially in a rapid manner, would induce retinopathy or damage retina in type 1 and type 2 diabetic patients[14,15]. Data from the large well recognized trials had inconsistent results. The 2 trials from UK and the USA found favorable out outcomes of tight glycemic control[9,16]. The UK Prospective Diabetes Study [UKPDS][9], with a 10-year follow-up, reported that an intensive diabetic therapy (HbA1c <7%) could significantly decrease risk retinopathy progression 21% and cataract surgery 24%. Another trial, the Action to Control Cardiovascular Risk in Diabetes [ACCORD] Eye study[16], also demonstrated a significant risk reduction of DR with intensive glycemic therapy with the OR of 0.67 compared to standard therapy. However, in accord with our study, the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE][10] and the Veterans Affairs Diabetes Trial [VADT][11] could not demonstrate such a benefit of tight glycemic control compared to standard therapy. Some had proposed the rational why glycemic control did not influence the diabetic eyes diseases. Diabetic patients tend to have microvascular injuries of the end organs especially eyes and kidney. Physiologically, vascular endothelial growth factor [VEGF] is overexpressed during a neovascularization compensatory process. Recent study proposed that a synergistic action of insulin and VEGF might hamper retinal circulation, induced ischemia, and increased diabetic eyes diseases[17].

Table 2. Data in details of the initial and the latest eyes screening (n = 1001)

Initial eyes findings	Latest eyes findings, n (%)				
	Normal	NPDR	PDR	Cataracts, not requiring Sx	Cataracts, requiring Sx
Normal (n = 845)	739 (87.5)	-	7 (0.8)	34 (4)	65 (7.7)
NPDR (n = 84)	63 (75)	14 (16.7)	4 (4.8)	3 (3.6)	-
Cataracts not requiring Sx (n = 72)	-	-	-	45 (62.5)	27 (37.5)
Total	802 (80.1)	14 (1.4)	11 (1.1)	82 (8.2)	92 (9.2)

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; Sx = surgery

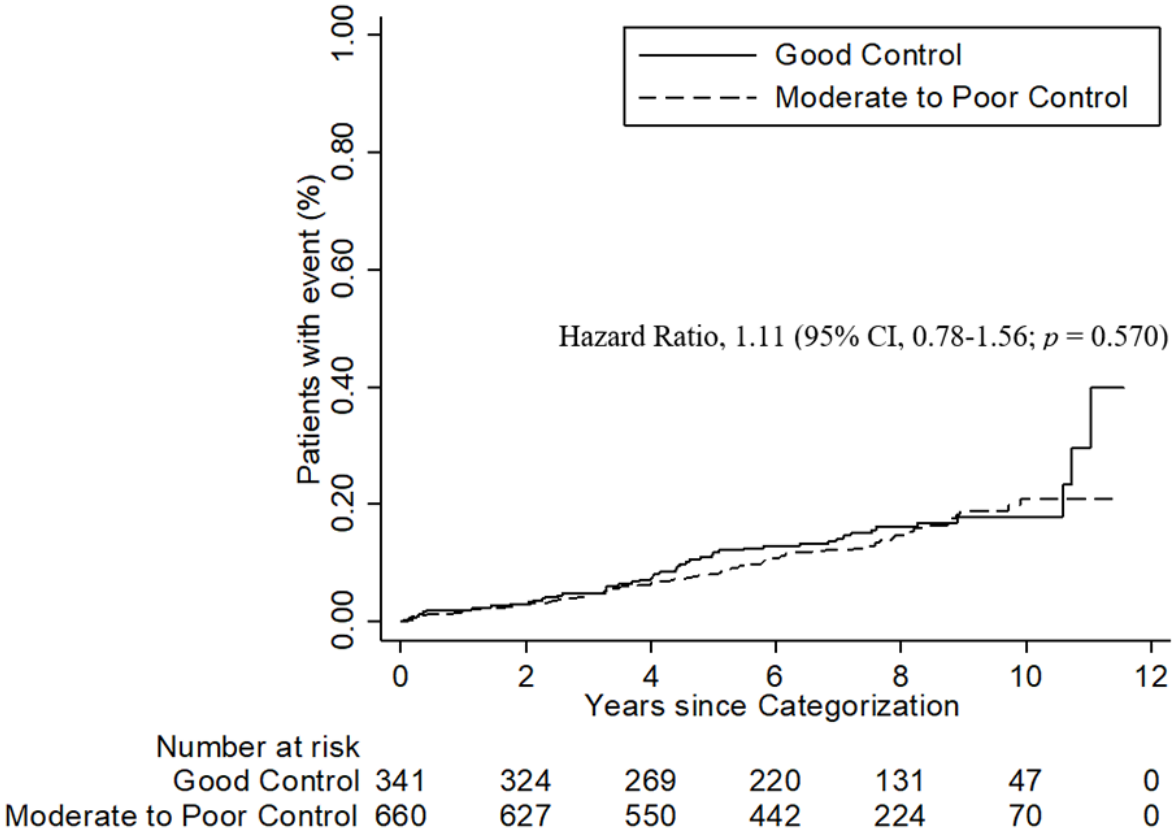

Figure 2. The primary outcome was an event diabetic eyes diseases. The hazard ratio and 95% confidence interval for the primary outcome was estimated with the use of adjusted Cox regression models for all good glycemic control group versus moderate to poor control.

When we focused on the PDR and cataracts requiring surgery which were considered as severe eyes problems, we found lower rate of progression to PDR among those who had good glycemic control. Small numbers of patients with this event may not allow a detection of statistical significant difference. Regarding the contradictory finding of a higher rate of cataracts surgery in the patients with good glycemic control, we explored the possible reasons and found that an ophthalmologist tended to provide surgical

Table 3. Data in details of eyes of the latest eyes screening (in relation to the initial findings) according to the group of glycemic control (n = 1,001)

Initial eyes findings	Latest eyes findings, n (%)				
	Normal	NPDR	PDR	Cataracts, not requiring Sx	Cataracts, requiring Sx
Good Control (n = 341)	267 (78.3)	4 (1.2)	3 (0.9)	30 (8.8)	37 (10.9)
Normal	253 (86.6)	-	2 (0.7)	10 (3.4)	27 (9.2)
NPDR	14 (70.0)	4 (20.0)	1 (5.0)	1 (5.0)	-
Cataracts not requiring Sx	-	-	-	19 (65.5)	10 (34.5)
Moderate to Poor Control (n = 660)	535 (81.1)	10 (1.5)	8 (1.2)	52 (7.9)	55 (8.3)
Normal	486 (87.9)	-	5 (0.9)	24 (4.3)	38 (6.9)
NPDR	49 (76.6)	10 (15.6)	3 (4.7)	2 (3.1)	-
Cataracts not requiring Sx	-	-	-	26 (60.5)	17 (39.5)

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; Sx = surgery

Table 4. Shows uni- and multivariate analysis of glycemic control and other clinical factors associated with diabetic eyes diseases

Factors	Progression of diabetic eyes disease, n (%)	Univariable analysis			Multivariable analysis		
		HR[1]	95% CI	*p*-value	HR[2]	95% CI	*p*-value
Glycemic control							
Moderate to poor control	89 (13.5)	1.00	Reference		1.00	Reference	
Good control	51 (15.0)	1.11	(0.78 to 1.56)	0.570	0.98	(0.69 to 1.39)	0.906
Age (years)							
<60 years	41 (8.0)	1.00	Reference		1.00	Reference	
≥60 years	99 (20.4)	2.64	(1.84 to 3.80)	<0.001	2.46	(1.68 to 3.61)	< 0.001
Duration of diabetes (years)							
<10 years	72 (11.6)	1.00	Reference		1.00	Reference	
≥10 years	68 (17.9)	1.48	(1.06 to 2.06)	0.021	1.09	(0.77 to 1.55)	0.625
Established CVD							
No	113 (12.9)	1.00	Reference		1.00	Reference	
Yes	27 (21.3)	1.56	(1.02 to 2.38)	0.040	1.41	(0.92 to 2.15)	0.117
Systolic BP (mmHg)							
<130 mmHg	46 (12.1)	1.00	Reference				
≥130 mmHg	94 (15.2)	1.23	(0.86 to 1.75)	0.259			
Diastolic BP (mmHg)							
< 80 mmHg	90 (15.5)	1.00	Reference				
≥80 mmHg	50 (11.9)	0.76	(0.54 to 1.08)	0.127			
LDL-C (mg/dL)							
<100 mg/dL	71 (16.5)	1.00	Reference		1.00	Reference	
≥100 mg/dL	69 (12.1)	0.67	(0.48 to 0.94)	0.019	0.72	(0.52 to 1.01)	0.054

HR = Hazard ratio; HRadj = Adjusted hazard ratio; CI = confident interval; BP = blood pressure; CVD = cardiovascular disease; LDL-C = low density lipoprotein-cholesterol

[1] Crude Hazard Ratio estimated by Cox's proportional hazard regression

[2] Adjusted Hazard Ratio estimated by Multivariate Cox's proportional hazard regression adjusted for age, duration of diabetes, established CVD and LDL-C

Table 5. Medical complications after glycemic control on both groups

Event	Good control	Moderate to poor control	*p*-value
	Event per 100 patient-year		
New cardiovascular event	0.61	0.60	0.951
Microalbuminuria	2.51	3.41	0.004
Macroalbuminuria	0.08	1.30	0.016
Severe hypoglycemia	0.20	0.39	0.113
Hyperglycemic crisis	0.05	0.07	0.758
Acute kidney injury (AKI)	0.23	0.30	0.543
Malignancy	0.20	0.21	0.943

treatment when diabetes was well controlled.

The inconsistent results among these studies may be due to many reasons. The characteristic features of the patients in each study may vary, such as, mean age of participants, baseline HbA1c, and duration of follow-up. We also speculated that including cataracts in diabetic eyes diseases in our study may dilute or underpowered the results of glycemic control because cataracts, aside an effect from diabetes and its treatment, may also be contributed to senile change or some other degenerative factors especially after a long period of follow-up.

Aside from diabetic treatment in blood glucose control, other factors may also contribute to the diabetic eyes diseases. We found higher rates of eyes diseases progression among those who aged ≥60 years, had diabetes ≥10 years, presence of cardiovascular disease, and systolic blood pressure >130 mmHg were risk factors of diseases progression especially age which was the only significant factor from multivariate analysis. Other studies also reported association of good blood pressure control and development[11,16,18-21] or progression of DR[22,23]. The possible mechanism of action was atherosclerosis in hypertension may readily lower retinal blood flow inducing ischemia of retinal capillaries. Our study found LDL <100 mg/dl lowered risk of diabetic eyes diseases. Previous studies had inconsistent effect of LDL level and diabetic eyes diseases[24-26].

Although the present study could not demonstrate the benefit of good glycemic control on cardiovascular events, the rates of micro- and macro-albuminuria were significantly reduced compared to moderate to poor control. These findings of our study regarding the benefits on albuminuria by tight glycemic control were consistent with other previous ACCORD, ADVANCE and VADT trials[10,11,16]. This may be explained that the damage of high blood glucose on microvascular structures generally takes place sooner, its recovery is also evidenced in early phase after treatment.

We were aware of some limitations in our study. Being a retrospective study, data were incomplete in many aspects. First, due to a dynamic nature of diabetic treatment, most of these patients had switched medications back and forth among drugs regimens or single or combined drug. Hence, we could not collect and describe the antidiabetic drugs use among our patients. Second, some patients who were recently had their treatment in our clinic may have only a few eyes screening. This may lead to lower detection rate of eyes disease. The last limitation was our study used the most current HbA1c instead of average values over time. This might not reflect the actual effect of glycemic control. Nevertheless, the present study had some strength. Our study had a long follow-up period, median of 7 years and maximum of nearly 12 years. Hence, the findings of eyes disease should be somewhat reliable. Second, we collected data from a large number of patients in clinical practice. Although our evidence would not be as good as data from the prospective randomized trial, this reflected the situation in real practice. Previous studies in the country generally assessed risk or associated factors with diabetic eyes diseases whereas the present study, aside from the risk factors, also evaluated the impact of glycemic control. These data should be informative to the clinicians taking care of diabetic patients.

Conclusion

We could not demonstrate an impact of glycemic control on diabetic eyes diseases. One

observation is a potential benefit of good glycemic control in the progression or development of proliferative diabetic retinopathy. Our study found the benefit of good glycemic control only in renal outcomes represented as lower albuminuria in this group of patients compared to the moderate or poor control. Further studies should explore the benefits of glycemic control on these particular outcomes of proliferative diabetic retinopathy and renal outcomes.

What is already known on this topic?

Diabetic retinopathy and cataracts are the 2 most common diabetic eyes diseases. These, in turn, are also the common cause of blindness especially in young age. Although most diabetic clinical practice guidelines consensus recommend tight glycemic control (HbA1C <6.5 to 7%) aiming to prevent diabetic microvascular complications. However, with controversial findings from large clinical trials, this is still a subject of debates.

What this study adds?

The present study could not demonstrate an impact of glycemic control on overall diabetic eyes diseases. One observation was lower proliferative diabetic retinopathy development in the patients who had good glycemic control than moderate to poor control.

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Potential conflicts of interest

The authors declare no conflict of interest.

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