CORRELATION BETWEEN SYSTEMIC RISK FACTORS AND DIABETIC RETINOPATHY IN PATIENTS WITH DIABETES MELLITUS

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Abstract

Introduction : Diabetic Retinopathy (DR) is a highly specific microvascular complication of both type 1 and type 2 diabetes mellitus (DM) that can cause significant visual impairment in adult populations worldwide. The risk of having and/or developing DR is influenced by many systemic features. Identification and management of particular systemic risk factors as early as possible during the course of DM might lower incidence of further progression and severity of DR.

Purpose : To describe the correlation between systemic risk factors and DR in patients with DM in Cicendo National Eye Hospital on December 1st 2017 – January 31st 2018.

Method : An analytical cross-sectional study. The subjects were all patients diagnosed with DR based on ophthalmology examination at outpatient clinic of Vitreoretinal Division in Cicendo National Eye Hospital. The data were analyzed using chi-square (x2) with significances of $p < 0.05$.

Results : Seventy one eyes were included in this study, among of which has been classified as mild NPDR (n= 1), moderate NPDR (n= 9), severe NPDR (n= 27), and PDR (n= 34). Severe NPDR group had older age distribution at range 51-60 years old (n= 18, 66.7%, p = 0.001). Stage 1 hypertension was found to be dominant in PDR group (n= 18, 66.7%, p = 0.043). Both high total serum cholesterol group (n= 27, 76.5%, p = 0.048) and high fasting blood glucose (n= 27, 79.4%, p = 0.01) were significantly present in patients with PDR. Positive (+1) urine glucose was statistically significant in PDR group.

Conclusion : There were several systemic risk factors from laboratory findings correlated in patient with DR in this study, however further study is needed to determine their role for predicting progression and severity of DR.

Keywords : Diabetic Retinopathy, Diabetes Mellitus, Systemic Risk Factors

INTRODUCTION

Diabetes mellitus (DM) is a global epidemic with significant morbidity. The global prevalence of DM is predicted to increase dramatically from an estimated 422 million in 2014 to 592 million by 2035. According to International Diabetes Federation (IDF), Indonesia has 10.5 million people with DM in 2017 and about 7.7 million of them have not been diagnosed and are at a higher risk of developing harmful complications. World Health Organization (WHO) estimates the prevalence of DM in Indonesia itself will increase to 21.3 million in 2030. Diabetic Retinopathy (DR) is a highly specific complication of DM. It remains the leading cause of acquired vision loss in adult populations worldwide and with the increasing number of people with DM, the number of DR and vision-threatening DR (VTDR) has been estimated to rise to 191.0 million and 56.3 million, respectively by 2030.[1-6]

The risk factors for development and progression of DR can be broadly divided into modifiable factors; hyperglycaemia, hypertension, hyperlipidemia and obesity, and non-modifiable factors such as; duration of DM, puberty and pregnancy. Although there are an increasing number of therapeutic strategies for DR, the best method of minimizing its impact is prevention of ocular complications. Insulin resistance, which often precedes type 2 DM (T2DM), is a component of the metabolic syndrome. Those with DM are more likely to have other components of the metabolic syndrome including abdominal obesity, dyslipidemia, hypertension, prothrombotic state, and a proinflammatory state. Having one or more of these components of the metabolic syndrome has been associated with a higher risk of diabetic complications, including DR itself. [6-9]

The Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) were the two landmark clinical trials that showed intensive glycaemic control could reduce the risk of DR development and progression in diabetic patients. The UKPDS stated that for every 1% decrease in HbA1c, there was a reduction in 40% of DR development, 25% progression to VTDR, 25% need for laser therapy and 15% blindness in people with diabetes. The UKPDS was the first RCT that showed the importance of tight blood pressure (BP) control in reducing retinopathy. It has been shown that every 10mmHg increase in systolic blood pressure was associated with 10% increased risk of early DR and 15% risk of PDR. On the other hand, various studies have reported inconsistent results on the effect of lipid on the development and progression of DR. DCCT showed that the severity of DR correlated positively with increasing triglycerides (TG) and inversely with high-density lipoprotein (HDL) in type 1 DM (T1DM). However, there was no association between total cholesterol and DR shown in the Multi-Ethnic Study of Atherosclerosis (MESA), but of the subset in the lipid panel, TG were shown to be related to the presence of DR. The subgroup of Action to Control Cardiovascular Risk in Diabetes Eye (ACCORD) study has also demonstrated that fenofibrate, a TG-lowering agent, reduced the DR progression at 4 years in T2DM patients, compared to placebo group (6.5% vs 10.2%). [2,8,10,11]

Meanwhile, the influence of BMI on DR had shown conflicting results, more recent reports showed positive correlation of increased BMI with increased risk of DR, although in Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) the association between obesity (BMI >31 for men and >32 for women) versus DR severity and progression (2+ ETDRS steps) was not statistically significant ($P > 0.05$). Also in WESDR, there was a 30% excess risk of DR development in post pubertal period an pregnancy could increased the risk of DR progression by 2.3 times. Taken together, optimization of systemic risk factors is clearly important.[11-14]

Thus, the purpose of this study is to describe the correlation between systemic risk factors and DR in patients with DM.

METHODS

This is an analytical cross-sectional study on subjects diagnosed with DR based on eye examination had been done by consultants, fellows and residents in Vitreoretinal Division outpatient clinic in Cicendo National Eye Hospital between December 1st 2017 – January 31st 2018. Eyes with any severity of DR and no other retinal diseases were included, and patients with incomplete laboratory results were excluded.

Eye examination has done with indirect ophthalmoscope, Classification of DR stage was determined using International Classification of DR Scale. Blood pressure, body weight and height were previously measured by calibrated device provided in the clinic, then the day after all patients

underwent laboratory examination for hematology, urine, renal and liver function, lipid profile, fasting blood glucose, glycosylated hemoglobin, and hemostasis profile.

All data were analyzed using SPSS Statistical software version 21, chi-square test was used to compare categorical variables. A P value < 0.05 was considered to be statistically significant.

RESULTS

Seventy one eyes of 36 patients were enrolled in this study, 1 eye was excluded because of an anophthalmic status, among of which has been classified as mild NPDR (1 eye), moderate NPDR (9 eyes), severe NPDR (27 eyes), and PDR (34 eyes). Patients' demographic characteristics and baseline BP measurement at the time of first visit are reported in Table 1.

Table 1 showed that age distribution and baseline blood pressure have significant differences among all groups of DR with p value 0.043 and 0.001 repectively. Age distribution in range 51-60 years old was mainly found in Severe NPDR group otherwise younger age group at 41-50 years old was found in PDR. Stage 1 hypertesion was dominantly present in both Severe NPDR and PDR group. From all 36 patients included in this study there were 10 patients with stage 1 hypertension at baseline measurement and 8 of them already had previous history of antihypertensive medication.

Table 1. Demographic Patients Data

	Diabetic Retinopathy								P-Value
	Mild NPDR		Moderate NPDR		Severe NPDR		PDR		
	n= 1		n= 9		n= 27		n= 34		
	N	%	N	%	N	%	N	%	
Age									0,001
≤ 40 y.o	0	0,0	2	22,2	1	3,7	1	3,0	
41 - 50 y.o	0	0,0	0	0,0	1	3,7	18	51,5	
51 - 60 y.o	0	0,0	7	77,8	18	66,7	13	39,4	
61 - 70 y.o	1	100,0	0	0,0	5	18,5	2	6,1	
> 70 y.o	0	0,0	0	0,0	2	7,4	0	0,0	
Gender									0,351
Male	1	100,0	7	77,8	13	48,1	18	52,9	
Female	0	0,0	2	22,2	14	51,9	16	47,1	
Region									0,042
West Java	1	100,0	7	77,8	26	96,3	28	82,4	
Outside West Java	0	0,0	2	22,2	1	3,7	6	17,6	
DM type									0,001
T1DM	0	0,0	2	22,2	0	0,0	0	0,0	
T2DM	0	0,0	5	55,6	24	88,9	30	88,2	
DM duration									0,442
≤ 5 years	2	200,0	10	111,1	8	29,6	21	63,6	
5-10 years	4	400,0	4	44,4	6	22,2	14	42,4	
> 10 years	1	100,0	8	88,9	11	40,7	20	60,6	
No Answer	0	0,0	2	22,2	4	14,8	6	18,2	
DM therapy									0,052
Regular	0	0,0	7	77,8	15	55,6	16	47,1	
Irregular	0	0,0	0	0,0	7	25,9	10	29,4	
No therapy	0	0,0	0	0,0	2	7,4	4	11,8	
Blood Pressure									0,043
Normal	0	0,0	1	11,1	8	29,6	4	11,8	
Prehypertension	0	0,0	4	44,4	3	11,1	3	8,8	
Stage 1	0	0,0	0	0,0	9	33,3	11	32,4	
Stage 2	0	0,0	2	22,2	4	14,8	10	29,4	
Urgency/Emergency	0	0,0	0	0,0	0	0,0	2	5,9	

Table 2. Systemic Risk Factors Parameters in Diabetic Retinopathy

	Diabetic Retinopathy										P-Value
	No DR		Mild NPDR		Moderate NPDR		Severe NPDR		PDR		
	n= 1		n= 1		n= 9		n= 27		n= 34		
	N	%	N	%	N	%	N	%	N	%	
Triglyceride											0.355
< 150	1	100.0	1	100.0	3	33.3	16	59.3	14	44.1	
≥ 150	0	0.0	0	0.0	6	66.7	11	40.7	20	55.9	
Total Cholesterol											0.048
< 200	1	100.0	1	100.0	3	33.3	11	40.7	7	23.5	
≥ 200	0	0.0	0	0.0	6	66.7	16	59.3	27	76.5	
LDL											0.421
< 100	1	100.0	0	0.0	4	44.4	10	37.0	8	26.5	
≥ 100	0	0.0	1	100.0	5	55.6	17	63.0	26	73.5	
HDL											
Female											0.375
< 50	0	0.0	0	0.0	2	22.2	12	44.4	10	29.4	
≥ 50	0	0.0	0	0.0	0	0.0	2	7.4	6	17.6	
Male											
< 40	0	0.0	0	0.0	5	55.6	6	22.2	11	32.4	
≥ 40	1	100.0	1	100.0	2	22.2	7	25.9	7	20.6	
PP Blood Glucose											0.46
< 200	0	0.0	1	100.0	5	55.6	9	33.3	13	38.2	
≥ 200	1	100.0	0	0.0	4	44.4	18	66.7	21	61.8	
Fasting Blood Glucose											0.01
< 126	0	0.0	1	100.0	7	77.8	9	33.3	7	20.6	
≥ 126	1	100.0	0	0.0	2	22.2	18	66.7	27	79.4	
HbA1c											
New Onset DM											0.095
< 6.5	0	0.0	1	100.0	2	22.2	2	7.4	1	2.9	
≥ 6.5	0	0.0	0	0.0	0	0.0	3	11.1	7	20.6	
Already on therapy											
< 7	0	0.0	0	0.0	2	22.2	6	22.2	4	11.8	
≥ 7	0	0.0	0	0.0	5	55.6	16	59.3	22	64.7	
Ureum											0.283
< 10	0	0.0	0	0.0	2	22.2	0	0.0	2	5.9	
10-50	1	100.0	1	100.0	4	44.4	19	70.4	17	50.0	
> 50	0	0.0	0	0.0	3	33.3	8	29.6	15	44.1	
Creatinin											0.332
0.5-0.9	0	0.0	0	0.0	0	0.0	7	25.9	7	21.2	
> 0.9	0	0.0	0	0.0	2	22.2	7	25.9	9	27.3	
< 0.6	0	0.0	0	0.0	2	22.2	2	7.4	0	0.0	
0.6-1.1	0	0.0	1	100.0	2	22.2	2	7.4	7	21.2	
> 1.1	1	100.0	0	0.0	3	33.3	9	33.3	11	30.3	
AST											0.665
< 32	0	0.0	0	0.0	2	22.2	13	48.1	13	38.2	
≥ 32	0	0.0	0	0.0	0	0.0	1	3.7	4	8.8	
< 38	1	100.0	1	100.0	7	77.8	11	40.7	17	52.9	
≥ 38	0	0.0	0	0.0	0	0.0	2	7.4	0	0.0	
ALT											0.948
< 31	0	0.0	0	0.0	2	22.2	11	40.7	13	38.2	
≥ 31	0	0.0	0	0.0	0	0.0	3	11.1	3	8.8	
< 41	1	100.0	1	100.0	7	77.8	12	44.4	17	50.0	
≥ 41	0	0.0	0	0.0	0	0.0	1	3.7	1	2.9	
Hb											0.275
<12	0	0.0	0	0.0	2	22.2	6	22.2	4	12.1	
12-16	0	0.0	0	0.0	0	0.0	8	29.6	12	36.4	
<13	0	0.0	0	0.0	3	33.3	9	33.3	12	36.4	
13-18	1	100.0	1	100.0	4	44.4	4	14.8	6	15.2	
WBC											0.934
4000-10600	1	100.0	1	100.0	9	100.0	25	92.6	31	94.1	
>10600	0	0.0	0	0.0	0	0.0	2	7.4	3	5.9	

	Diabetic Retinopathy										P-Value
	No DR		Mild NPDR		Moderate NPDR		Severe NPDR		PDR		
	n= 1		n= 1		n= 9		n= 27		n= 34		
	N	%	N	%	N	%	N	%	N	%	
Thrombocyte											0.468
150000-440000	1	100.0	1	100.0	9	100.0	26	96.3	29	85.3	
> 440000	0	0.0	0	0.0	0	0.0	1	3.7	5	14.7	
Urine protein											0
(-)	0	0.0	0	0.0	5	55.6	1	3.7	0	0.0	
(+)	0	0.0	1	100.0	2	22.2	11	40.7	10	29.4	
(++)	0	0.0	0	0.0	0	0.0	6	22.2	14	35.3	
(+++)	0	0.0	0	0.0	2	22.2	8	29.6	5	17.6	
(++++)	1	100.0	0	0.0	0	0.0	1	3.7	5	17.6	
Urine Glucose											0.042
(-)	0	0.0	1	100.0	6	66.7	5	18.5	5	15.2	
(+)	0	0.0	0	0.0	3	33.3	7	25.9	13	36.4	
(++)	0	0.0	0	0.0	0	0.0	4	14.8	6	18.2	
(+++)	1	100.0	0	0.0	0	0.0	10	37.0	10	30.3	

From laboratory examination listed in Table 2 we found that total serum cholesterol above 200 mg/dl was significantly found in PDR group with p value 0.048, but abnormal value of serum lipid such as Triglyceride (TG), LDL, and HDL was not differ significantly among these groups with p = 0.355, p = 0.421, p = 0.375. Fasting blood glucose exceeded 126 mg/dl had occured significantly in patients with PDR in this study (p = 0.01). It might equivalent with positive elevated glucose urine level happened in the same group (p = 0.042). This result might explain high glycosylated hemoglobin result found in PDR group although that was not statistically significant. Similiar findings also found in serum urea and creatinin, both of these renal function marker were higher in PDR patients but not statistically significant.

DISCUSSION

Diabetes is a chronic condition and managing the disease can be a substantial burden to patients. Diagnosing DR itself can be a pivotal moment in the patients' lives. A threat of vision loss can be a critical wake-up call for patients to invest in habits that will maintain their overall health and the health of their eyes. The risk factors from hematologic and biochemical aspect proposed to be correlated with development and severity of DR are; increase platelet adhesiveness and erythrocyte aggregation, upregluation of VEGF, abnormality of serum lipids, growth hormone and whole-blood viscocity, and local and systemic inflammation, but the precise role of these findings is not well defined. [8, 15]

In this study we have found that stage 1 hypertesion was dominantly present in both Severe NPDR and PDR group. From 36 patients included in this study there were 10 patients with stage 1 hypertension at baseline measurement and 8 of them already had previous history of antihypertensive medication.

Diabetic's patients are particularly susceptible to the effects of hypertension with respect to their risk for developing cardiovascular disease. Hypertension is the most common modifiable risk factor for cardiovascular disease. One mechanism implicates interactions between hormonal control of blood sugar levels in diabetic patients and the renin-angiotensin-aldosterone system (RAAS) at multiple levels and in both directions; those with diabetes have elevation of the RAAS

leading to hypertension. The combination of diabetes and hypertension is associated with an increased mortality rate due to cardiovascular disease also increases a patient's risk of retinal complication. [16-18]

One study by Zheng et al in 2012 found that for every 10 mmHg increase in systolic blood pressure, there was a 1.23 times increased risk of DR and 1.19 times increased risk of VTDR. Including Raum et al and Jin et al in 2015, effective treatment of hypertension with BP less than 150/85, has been shown to reduce the rate of worsening of diabetic retinopathy by 34 % over 7.5 years also lowered the risk of vision loss of three lines or more by 47 %. These matched several earlier studies. The UKPDS showed that the incidence of retinopathy was associated with systolic blood pressure. Of the 1919 patients with older onset T2DM from that study with retinal photographs taken at diagnosis and 6 years later, systolic blood pressure was significantly associated with retinopathy incidence. Those in the top tertile range at baseline (systolic BP ≥140 mm Hg) were 2.8 times as likely to develop retinopathy as people in the lowest tertile range (systolic BP <125 mm Hg). There was no relation of systolic BP at baseline with retinopathy progression. In the WESDR, diastolic blood pressure was a significant predictor of progression of diabetic retinopathy to proliferative diabetic retinopathy over 14 years of follow up in patients with T1DM. However, neither systolic or diastolic BP nor hypertensions at baseline were associated with the incidence and progression of retinopathy in people with T2DM. In the WESDR, patients with T2DM with high BP and retinopathy were at a higher risk of death than people with high BP without retinopathy, and the inability to find a relation between progression of retinopathy and blood pressure may have been due to this selective mortality-at least in part. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial did not find a significant difference in the rates of DR progression between those undergoing intensive blood pressure control (goal systolic blood pressure ≤120 mmHg) and standard management (goal ≤ 140 mmHg), although control of BP to a level of ≤ 140/90 is recommended under the Joint National Committee (JNC) 8 regulations. [19-23]

Elevated serum cholesterol and lipid levels are a known component of the metabolic syndrome. In this study we found that high total serum cholesterol was significantly present in PDR group. Abnormal value of other serum lipids was found in this study in the same group of patients but not statistically significant among all groups. These findings similar to one study by Chew et al has been found that elevated cholesterol and lipid levels have also been linked to higher rates of hard retinal exudates. Compared to those with a cholesterol level ≤200 mg/dL, those with a cholesterol level ≥200 mg/dL were twice as likely to have hard retinal exudates; the effects of HDL and TG in this study were modest and not statistically significant either. However monitoring serum lipids level according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines of cut off LDL ≤100 mg/dL is a reasonable goal. Controlling serum cholesterol and lipids is associated with a lower rate of complications from diabetic eye disease, according to a study by Sen et al in 2002 and Nielsen et al in 2014, Statins and Fibrate are a common treatment for high cholesterol, and their use prior to diabetes diagnosis has been associated with a significantly decreased rate of development of DR and has been linked to better average visual acuity improvement in DR. In this study Body Mass Index (BMI) of each

patients could not be collected properly because some desirable variables are incompletely measured in some patients, so that we can't conclude subjects with high total serum cholesterol to ones with metabolic syndrome for further data analysis related to this study. The Diabetes Incidence Study in Sweden reported significant association between baseline high BMI and severe NPDR and PDR ($p = 0.001$) after 10 years of follow up. Even though the evidence is still equivocal between BMI and DR in other studies, however it is still critical for people with diabetes to maintain an optimal BMI to prevent development and progression of DR and other diabetes-related complications. [9, 24-26]

Elevated fasting blood glucose level exceeded 126 mg/dl occurs significantly in patients with PDR in this study ($p = 0.01$), comparable to another significant result in this study that was positive (+) glucose urine level happened in PDR group also. Hyperglycemia is one of the most important risk factors for DR. Glucosuria only begins to occur at higher than normal plasma glucose levels. Glucosuria in diabetic patients is the result of increased glucose reabsorbtion from glomerular filtrate in people with DM. [27]

Wong et al had meta-analysis of three large population-based studies that found a graded relationship between the level of glycemia and frequency of retinopathy signs. The DCCT showed that intensive glycemic control reduced the incidence of retinopathy by 76 % and progression from early to advanced retinopathy by 54 %. This highlights that strict glycemic control is much more effective in preventing or delaying the onset of DR in patients with DM without DR, rather than limiting the severity of DR after it has occurred. Poor glycemic control should correlate with glycated hemoglobin (HbA1c) level. Multiple studies have consistently shown HbA1c to be an independent risk factor for diabetic retinopathy. The UKPDS stated that for every 1% decrease in HbA1c, there was a reduction in 40% of DR development, 25% progression to VTDR, 25% need for laser therapy and 15% blindness in people with diabetes. However in this study, the PDR group achieved the highest portion of HbA1c $\geq$ 7 but that was not significant statistically. A1c-Derived Average Glucose (ADAG) Study formulated the relationship between blood glucose and HbA1c. In this study, the cut-off point for HbA1c was 6.5% and 7% which is equivalent to 140 mg/dl and 154 mg/dl if converted to ADAG formula respectively. [7, 28]

This study has several limitations due to the nature of its study design. Research subjects are small, many data had not been collected properly at the time of subject recruitment started, and we difficult to analyze the correlation between those systemic factors with progressivity of DR because of relatively short sample collection time. We recommend to make a cut-off point of HbA1c to $\leq$6.5% to all recruited subjects in order to compare the result with fasting blood glucose value equipotentially.

CONCLUSION

Our study demonstrates that particular systemic factors value such as uncontrolled systemic blood pressure, high fasting blood glucose and glucosuria state significantly correlates with severity of DR. Although we still have to unify all parameters needed regarding to this study to prevent any missing data thus many more related variables can be further analyzed.

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