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ASSOCIATION BETWEEN THE DEGREE OF DIABETIC RETINOPATHY AND DIABETIC MACULAR EDEMA

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ABSTRACT

Introduction: WHO estimates more than 150 million diabetes patients worldwide. One of the complications of diabetes is diabetic retinopathy which is recognized as the leading cause of blindness in the working-age population and the cause of 12% of new cases of blindness each year due to macular edema, vitreous haemorrhage, and tractional retinal detachment. Macular edema is the most common cause of decreased visual acuity. The relationship between macular edema and the degree of retinopathy is unclear, so further research is needed. This study aimed to analyze the incidence of macular edema with the degree of diabetic retinopathy. **Method:** This study used a cross-sectional method. Samples were taken from the Retina Data Register at the National Diponegoro Hospital Eye Polyclinic of all diabetic retinopathy patients who attended National Diponegoro Hospital from July to December 2020 who were recruited as participants. The variables measured included the incidence of macular edema and the degree of diabetic retinopathy. Measurements using fundoscopy, slit lamp and condensing lens + 78D according to ETDRS (Early Treatment Diabetic Retinopathy Study) criteria by an ophthalmologist. Data analysis used a bivariate difference test for 2 groups. The statistical test used was the Fisher's Exact Test, which was significant if $p \leq 0.05$. **Results:** In this study, out of 132 eyes diagnosed with diabetic retinopathy, 28 (21.21%) had diabetic macular edema (DME). Seven (5.3%) eyes were diagnosed with non-proliferative diabetic retinopathy (NPDR) and DME, 21 (15.91%) eyes were diagnosed with proliferative diabetic retinopathy (PDR) and DME. There was no significant difference in the incidence of DME between NPDR and PDR. (Fisher's Exact Test, $p = 1.000$). **Conclusion:** There is no significant difference of incidence DME between NPDR and PDR.
Keywords: *diabetic retinopathy, macular edema*

INTRODUCTION

Diabetic retinopathy (DR) is one of the main complications of diabetes mellitus (DM) and is a major cause of visual disturbances. DR affects 75% of people with type 1 diabetes and 50% of people with type 2 diabetes. Visual impairment in DR occurs due to diabetic macular edema (DME), vitreous haemorrhage, and tractional retinal detachment. About 25% of diabetics have DME. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reports a 25-year incidence of macular edema in 29% of people with type 1 diabetes. The Diabetes Control and Complications Trial (DCCT) shows that 27% of people with type 1 diabetes develop macular edema within 9 years since the onset of diabetes. The prevalence of DME in diabetic patients is generally much lower than the prevalence of DR. Diabetic macular edema is a consequence of DR in the macular area, occurs due to damage to the retinal blood barrier triggered by changes in metabolism due to hyperglycemia, the exact mechanism caused is still unclear.[1–3]

Macular edema can occur at any stage of diabetic retinopathy, be it non-proliferative (NPDR) or proliferative retinopathy (PDR). DME occurs more frequently as diabetes duration increases and the severity of DR. The prevalence of DME was 3% in eyes with mild NPDR, 38% in eyes with moderate to severe NPDR, and 71% in eyes with NPDR. Macular thickening involving the fovea or threatening the fovea causes metamorphosis and vision loss.[2] Variation in the incidence and prevalence of DME has also been reported in various epidemiological studies, depending on the type of diabetes (type I or II), treatment modality (insulin, oral hypoglycemic agent, or diet. only), and duration of diabetes.[4]

Another study reported that the majority of PDR patients (65-85%) had little or no concurrent evidence of DME based on clinical examination and thickness of the central sub-plane on OCT. Likewise, the majority of DME patients (80%) had little or no evidence of concomitant neovascularization. Clinical observation shows that the majority of patients with PDR do not show DME even though it is suspected

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that there is a high concentration of VEGF in the eye. The prevalence of DME in PDR patients in the study was similar to the prevalence of PDR (22.5%) in the PDR patient group as in the DRCR S protocol.[5] This study aimed to determine the incidence of DME at various degrees of DR. Whether the heavier the degree of DR, the more the incidence of DME so it is important to prevent the progression of DR before the onset of DME.

METHOD

This research uses the cross-sectional method. Samples were taken from the Retina Data Register at the Eye Polyclinic of National Diponegoro Hospital from all diabetic retinopathy patients who went to the National Diponegoro Hospital from July to December 2020 who were recruited as participants. The variables measured included the incidence of macular edema and the degree of diabetic retinopathy. Measurements using fundoscopy, slit lamp and condensing lens +78D according to ETDRS (Early Treatment Diabetic Retinopathy Study) criteria by an ophthalmologist. Data analysis used a bivariate difference test for 2 groups. The statistical test used was Fisher's Exact Test, which was significant if $p \leq 0.05$.

RESULT

The results of this study, of 75 patients diagnosed with diabetic retinopathy, 150 eyes were examined. The research characteristics are outlined in the table below.

Table 1. Sample's characteristic

Variable	DME		p*
	Yes	No	
Age (Mean±SD)	60.12±0.119	58.14±1.312	0.169**
Male	6 (8%)	25 (33.3%)	0.388**
Female	11 (14.7%)	33 (44%)	

*Chi-square
**Significant if $p \leq 0.05$

The data of this study showed that there was no significant difference in the mean age and gender between the samples (p = 0.388).

Table 2. Differences in the Distribution of Diabetic Macular Edema According to the Degree of Retinopathy

Variable	DME		ODDS RATIO (95% CI OR)	p*
	Yes	No		
NPDR	7 (5.3%)	27 (20.45%)	1.0 (Based value)	
PDR	21 (15.91%)	77 (58.33%)	1.0519 (0.4023 – 2.7507)	1.000**
Total	28 (21.21%)	104 (78.79%)		

*Fisher's Exact Test
**Significant if $p \leq 0.05$

There was no significant difference in the incidence of DME between NPDR with PDR (p = 1.000).

DISCUSSION

In this study, There was no significant difference in the incidence of DME between NPDR with PDR (p = 1.000). The pathophysiology of DME is multifactorial and complex and involves mechanical and biochemical pathways triggered by hyperglycemia. The common pathway leading to macular edema in DME and other exudative retinal disorders is the breakdown of the blood-retinal barrier (BRB). BRB is made up of internal BRB and external BRB, which exist to maintain homeostasis in neural tissue. The internal BRB consists of tight junctions between retinal endothelial cells, the surrounding basal lamina, pericytes, astrocytes, and microglia. The outer BRB is made up of tight junctions between the cells of the retinal pigment epithelium (RPE). The impaired integrity of the BRB leads to the leakage of dissolved plasma substances into the interstitial spaces, causing edema by increasing the osmotic pressure. The fluid is then collected in various spaces within and below the retina.[6]

BRB disruption in diabetic retinopathy results from the release of inflammatory cytokines and growth factors under conditions of chronic hyperglycemia. Important factors involved include VEGF-A, placental growth factor (PlGF), IL-8, IL-6, IL-1p, TNF-α, and matrix metalloproteinase. BRB abnormalities occur in diabetic retinopathy, so the incidence of diabetes is higher in diabetic retinopathy compared to diabetic patients who did not have retinopathy. Therefore, BRB will induce inflammatory reactions and the release of growth factors.[6]

The retina responds to ischemia by stimulating growth factors (VEGF) to produce new blood vessels (neovascularization). Macular edema is the result of microvascular changes in diabetes that cause

edema. Effects of VEGF include stimulation of neovascularization which will later lead to bleeding complications and tractional retinal detachment, as well as increased vascular permeability which causes leakage or extravasation lipid and fluid from blood vessels which causes edema. The higher the degree of retinopathy, the higher chance the retinal gets ischemia or hypoxia. The hypoxic state stimulates VEGF causing more edema.[7,8] In PDR the degree of hypoxia is greater than in NPDR but other factors such as inflammation also play a role and might be the cause of the incidence of DME in PDR is no difference with in NPDR.

Study in Sarajevo distribution of NPDR was 66.27%, and PDR was 33.73%. DME was present in 33.70% of cases. In NPDR, DME was presented in 51% of the cases, while in PDR was presented in 49% of the cases.[9]

The study conducted by Nicolas Leveziel, et al, that DME is significantly more common in more severe stages of DR. With statistical tests, their study also found that DME was significantly associated with lower limb amputation in type 2.[10] diabetes patients. In 2019 a study by Hiroaki Endo, et al. Showed that changes in Central Choroidal Thickness in the eyes of DM patients likely depend on the thickness of the outer layer of the choroid. This is associated with chronic hyperglycemia as a factor that aggravates the disruption of the choroid microcirculation.[11] Pedro Romero-Aroca, et al. Stated that DR and DME are currently considered to be manifestations of parallel neuronal and vascular degenerative processes. Several studies support this view, suggesting that the presence of subclinical neurological disorders before the appearance of vascular lesions is typical of DR. DME is the leading cause of blindness in diabetic patients. Vasogenic changes secondary to hyperglycemia result in rupture of the blood-retinal barrier (BRB), initiating a cascade of macular edema formation. However, the activation of low-grade inflammation in conjunction with vasogenic changes will cause serious retinal damage, and the changes that occur in the macula will be chronically progressive.[12]

Macular edema is strongly associated with the severity of diabetic retinopathy.[7] Two important clinical trials, the United Kingdom Prospective Diabetes Study (UKPDS) and the Diabetes Control and Complications Trial (DCCT) provide strong evidence that tighter glycemic control (via HbA1c 7%) reduces risk. the development and progression of DR in both type 1 diabetes and type 2.[13] diabetes The duration of diabetes is highly correlated with the prevalence and incidence of macular edema, development of retinopathy, and other diabetes complications.[14] The diagnosis of diabetes in type 2 subjects sometimes occurs sometime after subclinical diabetes appears, which results in a minority of patients who may present with macular edema at the time of diagnosis, or even have decreased vision due to macular edema.[7,15]

However, in a retrospective cross-sectional study conducted by Sam Hobbs et al. In 2016, the majority of PDR patients (65-85%) had little or no evidence of an association with DME either based on clinical examination or thickness of the central subfield in OCT. Likewise, the majority of DME patients (80%) had little or no pathophysiological evidence of concomitant neovascularization. The prevalence of DME in PDR patients in this study was similar to the prevalence of DME (22.5%) in a particular group of PDR patients as recently reported in the Diabetic Retinopathy Clinical Research Network (DRCR.net) Protocol S.[5]

VEGF is considered the main target in both DME and PDR, patients with PDR are actively suspected to have high VEGF levels and most of them still do not show signs of DME. Likewise, most patients with DME do not create new blood vessels despite high VEGF levels, which leads us to believe that other molecular factors are involved in the development of DME. It appears that DME and PDR are two independent disease processes from the same spectrum namely diabetic retinopathy. Further analysis of risk factors such as age, sex, type of diabetes, glycemic control, blood pressure, and cholesterol showed no statistically significant association in the incidence of concurrent DME and PDR. This indicates a genetic factor in the development of the disease process.[5]

The weakness of this research is that the sampling time is quite short and the number of samples is relatively small. Patients usually present with severe diabetic retinopathy due to prolonged uncontrolled diabetes mellitus. Diagnosis of macular edema and graded diabetic retinopathy was carried out using stereoscopic fundoscopy, without supporting investigations such as OCT and not observing other factors such as diabetes duration and other comorbidities. Early detection of eye

examinations in people with diabetes mellitus is very important to reduce the impact of diabetic macular edema. Therefore fundoscopy evaluation becomes very important to prevent the occurrence of DR because DME is one of the causes of decreased vision in DM patients.

Early detection of retinal abnormalities is essential to prevent vision loss.[15] Treatments, such as photocoagulation, can reduce the risk of vision loss.[16] However, it is generally not possible to restore visual acuity after deterioration.[17] Benefits of early management, such as intensive diabetes control, visual acuity can persist for years, even with subsequent events of hyperglycemia.[15,16,18] Thus, routine screening and early treatment for DR / DME can potentially save vision for years.

CONCLUSION

In this study, it can be concluded that there is no significant differences in the incidence of macular edema between NPDR and PDR. Early macular edema case finding is expected to provide information to patients to be more alert and have routine examination. Several studies have shown better clinical outcomes if patients are screened and treated early.

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