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HIGH GLYCOSYLATED HEMOGLOBIN INCREASE PREVALENCE OF PROLIFERATIVE DIABETIC RETINOPATHY

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ABSTRACT

BACKGROUND: Diabetic retinopathy (DR) is one of the microvascular complication in diabetes mellitus (DM). Glycosylated hemoglobin (HbA1c) is an indicator that reflects the percentage of blood glucose tied to hemoglobin for the past three months. **AIM:** This study aims to determine if a high level of HbA1c increases the prevalence of proliferative diabetic retinopathy. **METHODS:** Cross-sectional study. The participants were DM patients who were diagnosed with PDR and NPDR for the first time and HbA1c level was checked in the laboratory. **RESULT:** Of the 74 participants, 37 participants were PDR, and 37 participants were NPDR. The ratio of prevalence (PR) was 3.87, with Confident of Interval (CI 95%): 1.96-7.67 and $p < 0.001$. Multivariate analysis shows Odd Ratio (OR) of HbA1c is 18.319 (5.334-62.919) and $p < 0.001$. **CONCLUSION:** High level of HbA1c as a risk factor of high prevalence of PDR.

KEYWORD

Diabetic retinopathy, diabetes mellitus, glycosylated hemoglobin.

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Introduction

DR is a retinal disorder due to microvascular complications of DM. DR is the most common cause of blindness after cataracts. The number of DM patients worldwide is estimated more than 360 million people and expected to increase more than two times by 2030 [1]. The purpose of this study was to find out the glucoregulation of patients with PDR and NPDR, expressed by levels of HbA1c and the specific aim of this study was to determine whether a high level of HbA1c increases the prevalence of proliferative diabetic retinopathy.

Methods

Study Design

A cross-sectional study was conducted to examine whether the high levels of HbA1c lead to increased prevalence of PDR patients with DR at the Internal Medicine clinic in the Endocrine division of Sanglah Hospital, Eye clinic at Sanglah Hospital and Indra Hospital. The study was conducted from October 3, 2014 to January 31, 2015. The inclusion criteria were DM patients who willing to take part in the study and sign informed consent. The exclusion criteria were patients with intraocular infection or inflammation, subjects with abnormalities in anterior and posterior eye's chamber which can interfere visualization during retinal examination other than RD, subjects with anemia, chronic kidney failure, thalassemia, subjects who consumed high doses of vitamin C and E for the last one month, and subjects with obesity.

Sample Recruitment

The samples were selected by a consecutive sampling technique from registered patients. The chosen sample was patients with DM who had either NPDR or PDR in one or both eyes, but if both eyes had different retinopathy degree than the patients were included in the diabetic retinopathy group with a higher stadium (PDR).

The collection of the data was carried out through interviews, physical examination, ophthalmologic examination, and blood sampling. The diagnosis of NPDR and PDR was recorded in an ophthalmological state examination sheet and research questionnaire sheet. Patients with diabetic retinopathy were then determined to have NPDR or PDR and then blood samples and HbA1c levels were tested.

The stages of data analysis include data selection, namely editing, coding and tabulation inserted to file navigator of Statistical Package for The Social Sciences (SPSS) program. Descriptive statistical analysis, the calculation of diabetic retinopathy prevalence, NPDR prevalence, and PDR prevalence, the cutoff point of HbA1c levels was known by using the ROC curve. AUC value is considered well if ≥ 70%. The calculation of the ratio of prevalence (PR) of PDR compared to diabetic retinopathy using a 2x2 table. Logistic regression multivariate analytic was used to look at the risk factor, odds ratio (OR) from the variable age, sex, and the duration of DM to PDR with CI 95% and statistically significant if $p < 0.05$.

Results

A total of 123 DM patients, divided into 74 DM patients with DR and 49 DM patients without DR were evaluated. Seventy four DM patients with DR were divided into two groups, the PDR group and NPDR group, and each group consisted of 37 participants. These two groups underwent laboratory HbA1c testing. Table 1 shows the mean HbA1c level in the PDR group was 9.40 ± 2.17%. The mean HbA1c level in NPDR group was 7.06 ± 1.97%. This study shows that the prevalence of DR in DM patients was 60.16%. This study also shows that among patients with DR, the prevalence of PDR and NPDR in DR was 30.08% each group.

Table 1. Research Subject Characteristic

Characteristic	PDR	NPDR
Age (year) {Mean±SD}	56.00 ± 7.60	57.32 ± 9.74
Sex {n (%)}		
Male/Men	19 (51%)	20 (54%)
Female/Women	18 (49%)	17 (46%)
Duration of diagnosed by DM (year) {Mean±SD}	9.72 ± 3.92	8.50 ± 2.92
High HbA1c {n/∑n (%)}	31/37 (83.8%)	9/37 (24.3%)
Normal HbA1c {n/∑n (%)}	6/37 (16.2%)	28/37 (75.7%)

Receiver Operating Characteristic (ROC) curve is used to see the AUC (Area Under Curve) and to determine the cut off point of HbA1c. Figure 1 shows the ROC (Receiver Operating Characteristic) curve and AUC (Area Under Curve) value. The AUC value was 85.2%, with 95% CI with a lower limit of 76.1% and an upper limit of 94.3% and p <0.001 statistically strong because it was greater than the minimum AUC value expected by researchers, which was 70%. The purpose of the diagnostic test in this study is to determine the cut off point. The cut point with a high sensitivity level needs to be found. The cut point of ROC (cut off point) curve has been selected at sensitivity 0.816 so that a high level of HbA1c was obtained and that was more than 7.77%Figure 1. the ROC (Receiver Operating Characteristic) curve and AUC (Area Under Curve) value.

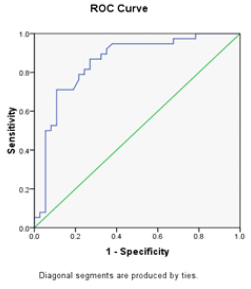

Table 2 shows the logistic regression multivariate analysis between the variables of age, sex, duration of DM, HbA1c levels and PDR. Variables of age, sex, and duration of diagnosed with DM were not significant of the PDR prevalence (p> 0.05). A high HbA1c level (>7.77%) increases the risk of 18.33% of the prevalence of PDR (Odd Ratio = 5.334-62,919). This was statistically significant (p <0.001).

Table 2. Logistic Regression Multivariate Analysis's Result.

Variable	Coefficient	OR (CI 95%)	p
Age	0,294	1,342 (0,351-	0,667
Sex	0,137	0,872 (0,267-	0,820
Duration of DM	0,586	1,797 (0,349-	0,483
HbA1c level	2,908	18,319 (5,334-62,919)	< 0,001
Constant	-2,040	0,130	0,37

Discussion

Important risk factor for diabetic retinopathy to occur in people with DM is age. Several studies have reported that the prevalence of DR has increased with the increasing of age [2]. Ageing can reduce body function which is caused by the cell apoptosis which begins at the age of more than 45 years old. The condition of chronic hyperglycemia, inflammatory reactions and oxidative stress accelerate the apoptosis of cells in the retina resulting in the state of retinopathy. Both of these things explain why older people are more vulnerable to DR which eventually were found to increase with the increasing of age [3]. Research conducted by Xu Jie, et al., (2013) in China found that the average age of NPDR patients 60.75 ± 8.74 years and the average age of PDR patients were 58 ± 5 years [4]. Studies above did not differ much from the results of this study. Logistic regression multivariate analysis in this study found that age increased risk of 1.3% of the prevalence of PDR.

Gender is an important risk factor besides age in PDR and NPDR patients. Some studies show differences in sex characteristics in PDR and NPDR patients. Some studies in Spain reported the prevalence between men and women with NPDR was the same, that was 50%. Another study found 55% of women, but a study in Portugal reported that 63.2% of the men in their study were in the NPDR group [5], [6], [7]. Research by Dirani, et al. (2011) found that 51.11% of PDR patients were men. Research by Funatsu, et al. (2011) in Japan reported that PDR was found in 50% of men and 50% of women [6]. However, there were several studies which show the opposite. Hartnett (2010), showed that 54.4% of PDR patients were women [8]. The sex characteristics of the PDR and NPDR groups in this study are almost similar to some previous studies. Lifestyle and economic status like the habits of men who mostly smoke, consume coffee, alcohol, soft drinks, and minimal activity often increase the progression of diabetic retinopathy to PDR [8], [9]. Other factors that support the tendency of PDR patients are men, namely factors that men tend to ignore the early symptom so that patients often come to treatment when the symptoms get worse [2], [6], [10].

Duration of DM is one of the factors that associated with the increase of the occurrence of DR [11], [24]. Hyperglycemia exposure for a long time can increase biochemical and physiological changes, in the form of cellular changes in the basement retinal cell membrane resulting in the damage of the retinal capillary arteries, endothelial cell proliferation and thickening of the basement membrane resulting in capillary occlusion and nonperfusion of the retina. Capillary occlusion will cause bleeding and the emerge of the new fragile blood vessels so that it can cause recurrent bleeding which can reduce the sharpness of the vision [13]. Several studies have shown some variations in the duration of suffering from DM until later they found the NPDR and PDR complications. The incidence of diabetic retinopathy after 4 years of follow-up was around 50% in type 1 and type 2 DM, and after 10 years of follow-up it became 74% [14]. The study by Tarr et al (2013) in India found that the duration of DM was the strongest predictor on the development and progression of retinopathy diabetic (p = 0.001) [15]. The results of this study were almost similar to studies that have been done before, the multivariate analysis showed that the duration of diagnosis of DM increased the risk by 0.59% of the prevalence of PDR.

HbA1c levels indicate the amount of glycated hemoglobin due to the long-term serum glucose exposure. High levels of HbA1c indicate an uncontrolled condition of hyperglycemia for the past 3 months [7]. The effect of this blood sugar control is related to the complications of DM that occur. Good HbA1c control (<7%) can reduce the progressivity of the complication that occur [16].

Some studies show that DM control was said to be good if the HbA1c number is <6.5%. Research by Dirani, et al (2011) shows that the cut-off point of diabetic retinopathy patients is ≥ 7.6% with AUC (area under the curve) 82% [10]. The study of Lee, et al (2010) showed a cut-off point of diabetic retinopathy patients ≥ 7.3% [17]. Mitchell (2010)'s research showed that the cut-off point of diabetic retinopathy patients was ≥7.8% [12]. In this study, the prevalence ratio (RP) of PDR had been obtained at 3.87, with CI 95% (1.96 - 7.67) with p <0.001. The prevalence ratio (RP) > 1 and CI was always above

1, having the understanding that high HbA1c is a risk factor for PDR and high HbA1c increases the prevalence of PDR. These studies prove that poor HbA1c control will increase the incidence of microvascular complications in DM, one of which is diabetic retinopathy. In conclusion, HbA1c increased the prevalence of PDR. The level of HbA1c>7.7% increased the prevalence of PDR 3.87 times compared to the level of haemoglobin glycosylate (HbA1c) <7.7%. Multivariate analysis showed a stronger relationship, where haemoglobin glycosylate levels (HbA1c) > 7.7% increased the prevalence of PDR 18.32 times in compared to haemoglobin glycosylate (HbA1c) levels <7.7%.

Further research is needed to evaluate the further consequences of high HbA1c levels. This study is a cross-sectional study where the data collection was done at one point in time, so we cannot determine the lasting influence of high HbA1c levels on the progression of DR in patients with DM and poor glycemic control.

Conflicts of Interest
The author reports no conflicts of interest in this work.

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