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CORRELATION BETWEEN HBA1C LEVELS AND SEVERITY OF DIABETIC RETINOPATHY

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ABSTRACT

Background: In recent years, Diabetes Mellitus (DM) has emerged as the world's leading cause of death with the potential to develop micro vascular complications in the form of retinopathy. One of the tools as an indicator to identify hyperglycemia and plays an important role in monitoring the development of complications due to DM is HbA1c. This study is important to prove the reliability of HbA1c as a prognostic indicator of the development of retinopathy, especially in Indonesia, because there are differences in results from studies outside Indonesia regarding HbA1c levels with the development of retinopathy. Therefore, study is undertaken determine the relationship between HbA1c levels and the severity of diabetic retinopathy in DM patients in Semarang, Indonesia. **Aim:** To identify the relationship between HbA1c levels and different stages of diabetic retinopathy. **Method:** An analytic observational, cross sectional design, using patients' medical record. Patient data consisted of gender, age, DM duration, HbA1c levels, and stages of diabetic retinopathy. Non parametric correlation Spearman's rho was chosen for statistical analysis. **Result:** A total of 72 DM patients consisted of 29 men and 43 women with a mean DM duration 10.4 years. A total of 37 patients were diagnosed with diabetic retinopathy with 30 NPDR respondents (41.7%) and 7 PDR respondents (9.7%). The average HbA1C levels based on the patient's diabetic retinopathy stages, as follows; normal attained 6.49% (SD ± 0.95), NPDR 8.17% (SD ± 1.77), and PDR 8.47% (SD ± 1, 10). Spearman's non-parametric test showed a strong and significant relationship ($p < 0.001$) between HbA1c levels and the degree of diabetic retinopathy. **Conclusion:** There was a strong significant positive correlation between HbA1c levels and the severity of diabetic retinopathy. As the HbA1c level increased severity of the diabetic retinopathy also increased.

Keywords: *diabetes mellitus, diabetic retinopathy.*

INTRODUCTION

Diabetes mellitus (DM) describes as a metabolic syndrome identified by the presence of hyperglycemia with varying etiopathogenesis, including abnormalities in insulin secretion, insulin action, or a combination of both, followed by metabolism disturbances in carbohydrate, fat, and protein.[1] According to International Diabetic Federation (IDF) 9th edition, DM kills 1 person every 8 seconds and is considered as the main cause of 11.3% of global adult mortality in the 20-79 years age group and estimated will increase dramatically to be 16,6 millions in 2045.[2] Indonesian Endocrinology Association (Perkeni) 2015, stated that DM is the third highest cause of death in Indonesia, thus making Indonesia an epidemic of type 2 diabetes.[3]

Diabetes Mellitus leads to micro vascular complication which occurs due to the disturbances in retinal blood flow in Diabetic Retinopathy (DR) which conducts to vision loss in adult populations worldwide.[4] Several pathogenesis theories of hyperglycemia result in retinal capillary endothelial permeability abnormality leads to serum leakage which generate edema in the retina and macula due to biochemical changes.[5] The risk factors for progression of DR divided into modifiable factors specifically; glycemic control, hypertension, obesity, and vitamin D deficiency. Whereas non-modifiable factors such as; duration of DM, age and puberty.[6]

According to American Academy of Opthalmology (AAO), DR falls into three main classes which can be differentiated using funduscopy. The stages are normal, Non-Proliferative Diabetic Retinopathy (NPDR) and Proliferative Diabetic Retinopathy (PDR). NPDR is an early stage in diabetic retinopathy characterized by micro vascular damages and obstructions, distinguish as microaneurysms, dot-blot hemorrhage, venous beading, and/or cotton wool spots in funduscopy. NPDR has the potential to develop into PDR with a percentage of 6.1% in the first year of suffering from diabetes. Proliferative diabetic retinopathy (PDR) is marked by the presence of neovascularization of the disc (NVD) or elsewhere (NVE) or vitreous hemorrhage.[7]

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The biochemical parameter to evaluate the long-term metabolic control in DM patients in this experiment is using the HbA1c levels, as it describes blood plasma sugar levels for 8-12 weeks due to the erythrocyte cycle in the human body for 120 days.[4,8] In a regular blood sugar test which frequently used in Indonesia, the tool measured the blood sugar level at that time which can change throughout the day, depending on what the patient consumed before the test. The results of the HbA1c has low variability and will not be fluctuated by food and drink intake at the time of the test, so there is no need for special preparations such as fasting. Measurement of HbA1c more accurately identify the risk for clinical outcomes than the commonly used measurement of fasting glucose. Each 1% increase in HbA1C from baseline was associated with a more than 2-fold risk of DR. Many other epidemiological studies confirm that uncontrolled HbA1c is an important risk in the development of diabetic retinopathy. [8-10]

The delay in early detection of the development of diabetic retinopathy which has the potential for blindness can be avoided by routine HbA1c testing in DM patients.[6] In the research literature conducted in Indonesia, the majority use regular blood sugar tests as an indicator of the development of DR, and in fact, HbA1c levels are rarely examined in patients with DM or DR. While the International Committee and WHO have since 2009 recommended HbA1c as a biomarker for the development of diabetes complications, including DR.[11-12] It causes there has been no research in Indonesia regarding the relationship between HbA1c levels and the stages of diabetic retinopathy in DM patients. This study is also important to prove the reliability of HbA1c as a prognostic indicator of the development of DR, especially in Indonesia, because there are differences in results from studies outside Indonesia regarding HbA1c levels with the development of DR.[13] The researchers are interested in further proving the HbA1c modality as an accurate screening method for identifying the degree of eye damage's progression due to DM. Therefore, this study was conducted to determine the relationship between HbA1C levels and the stages of diabetic retinopathy in DM patients.

OBJECTIVE

This study aims to determine the relationship between HbA1c levels and different stages of diabetic retinopathy.

METHODS

This is an analytical cross-sectional study including 72 type 2 DM patients aged 35-75 years and had HbA1c laboratory examination data checked less than 3 months from outpatients ophthalmic clinic Diponegoro National Hospital, Amanda Clinic, and Safira Clinic in Semarang, Central Java, Indonesia participated during July until October 2020. The exclusion criteria were eye disorders that could interfere the HbA1c levels such as anemia, bleeding, episodic hemolysis, and chronic renal failure. Patients' data taken from medical records consisted of gender, age, duration of DM, HbA1c levels, and stages of diabetic retinopathy. This study had been approved by Ethical Commission of Medical Research on Faculty of Medicine Diponegoro University with number 138/EC/KEPK/FK-UNDIP/VI/2020.

All the data were analyzed using SPSS Statistical software version 21, non parametric correlation Spearman's rho was chosen to find the significance of study parameters and P value <0.05 was taken as significance.

RESULT

Seventy-two respondents consisted of 29 men and 43 women whose ages ranged from 36 years to 71 years with a mean of ages was 54.12 years. Table 1 showed that the overall prevalence of DM (43.1%) were between the ages of 51 - 55 years. As 72 respondents involved, all of them were type 2 DM patients with DM duration ranging from 1 month to 20 years.

Table 1. Characterization based on gender, age, and duration of DM

Character	Frequency	%
Gender		
Male	29	40.3
Female	43	59.7
Age		
35 – 40 years old	4	5.6
41 – 45 years old	4	5.6
46 – 50 years old	10	13.9
51 – 55 years old	19	26.4

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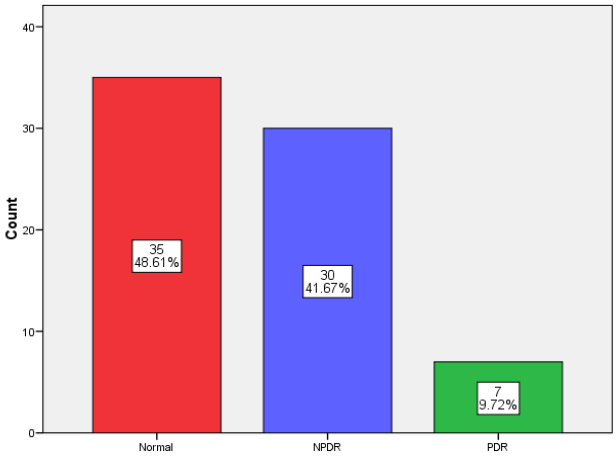
56 – 60 years old	31	43.1
61 – 65 years old	2	2.8
66 – 70 years old	1	1.4
71 – 75 years old	1	1.4
DM Duration		
<1 year old	2	2.8
1 – 5 year(s) old	46	63.9
6 – 10 years old	12	16.7
11 – 15 years old	6	8.3
>15 years old	6	8.3

The distribution of patients' stages of DR shown as picture 1 below. The data on the stages of diabetic retinopathy showed that 35 patients (48.61%) out of 72 patients were normal.



Picture 1. The distribution of patients' stages of DR

Normality test using Kolmogorov Smirnov for HbA1c levels distribution showed abnormalities, with p = 0.019 (p> 0.05). This is due to the large gap in HbA1c levels between patients. The lowest HbA1c level in the respondents was 4.3% and the highest was 12%. The mean of HbA1c levels among respondents was 7.38% and the HbA1c levels were mostly found in respondents was 6.7%.

Glycated hemoglobin A1c levels were defined controlled if < 6.5 % and uncontrolled if > 6.5 % on table 2. Controlled HbA1c levels in type 2 DM patients in this study were 17 people (23.6%) and uncontrolled HbA1c levels were 55 people (76.4%).

Table 2. Distribution of HbA1c levels

No	HbA1c levels	Amount	
		N	%
1.	Controlled	17	23.6
2.	Not controlled	55	76.4
	TOTAL	72	100

Table 3. Stages of Diabetic Retinopathy and HbA1c Levels.

Stages of DR	Average HbA1c levels	Amount
Normal	6,49 ± 0.95	35
NPDR	8,17 ± 1.77	30
PDR	8,47 ± 1.10	7

Tabel 4. Spearman Correlation Test Results

		HbA1c Levels
Stages of DR	r	0.535
	p	<0.05
	n	72

Table 3 showed the mean levels of HbA1c levels based on the severity of the respondents' diabetic retinopathy were, respectively, normal (6.49%) were 35 people, NPDR (8.17%) were 30 people, and PDR (8.47%) were 7 people.

The Spearman non-parametric correlation test obtained a correlation coefficient (r) of (r = 0.535) which indicates a strong positive correlation. As the relationship between the two variables is positive and interpreted that the higher the HbA1c level, the worse the severity of diabetic retinopathy will be. It is known that the significance value (Sig. 2 tailed or p) is p = 0.000 (p <0.05), which means there is a significant relationship between the stages of diabetic retinopathy and the HbA1c level. In this study, it was found that patients with Hba1c levels of 6.49 % do not yet have microvascular complications of DM on the retina, while the HbA1c level which reached a value of 8.17 % could indicate that the patient already had NPDR stage diabetic retinopathy, and an HbA1c level of 8.47 % as a marker that the patient had reached the PDR stage.

DISCUSSION

In this study we have found that gender distribution of women amounted to 43 (69.7%) of respondents and men amounted to 29 (40.3%) respondents. The result obtained are in accordance with previous study by Rahmanian, et al (2016), it was found that 12.1 % of type 2 DM patients were female, but not significantly. Gender is also influenced by complex interactions between many factors, including genetics, endocrine, and lifestyle.[14]

Women are more at risk of developing diabetes because the estradiol and progesterone show a

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positive association with temporary insulin resistance. Insulin resistance increases during the ovulation phase and reaches peak levels in the lutheal phase.[11] When menopause is reached, physiologically body fat is easily accumulated, so menopausal women have 2 times higher visceral abdominal fat and subcutaneous adipose tissue than premenopausal women. Visceral fat is reported to be associated with increased lipolysis (breakdown of triacylglycerol (TG) to glycerol and free fatty acids (FFA)), which results in increased flow of FFA to the liver and increases hepatic insulin resistance.[14-15]

The lowest age in this study was 41 years and the highest was 65 years old, with a mean age of the respondents was 54 years. A total of 43.1% of T2DM patients are aged 51 – 55 years old. The results obtained are per Perkeni 2019 statement where the age at risk of suffering from T2DM in Indonesia is over 45 years of age.[16] Age of onset diabetes 31– 45 years is associated with an increased risk of developing diabetic retinopathy, regardless of diabetes duration.[17] This can be caused by the aging process of organs in the body including the pancreas causing disruption of homeostasis and glucose metabolism.[18]

Based on this study, the mean DM durations was 10.4 years, with the highest DM duration reaching 22 years and the lowest duration was 1 month. Patients with diabetes for 1-5 years were the most common DM duration, with a total of 46 patients (63.9%). The same thing was found by Ria Arisandi (2018), that type 2 DM patients with a DM 1– 5 years duration were the most common DM duration (57.5%). DM duration is one of the triggers for complications of T2DM, including macro vascular complications of CVD and micro vascular, such as neuropathy, nephropathy and retinopathy. Diabetic retinopathy pop up in DM patient with more than 10 years DM duration, but in fact it is onerous to determine the duration.[19]

The mean of HbA1c levels was 7.5% and the most HbA1c levels found in respondents was 6.7%. Controlled HbA1c levels found in 17 respondents (23.6%), while uncontrolled HbA1c levels shown up in 55 respondents (76.4%). Ria Arisandi's (2018), also found that uncontrolled HbA1c levels were the most respondents, reaching 85%.[17] Indeed, according to the 2019 Riskesdas, the achievement of health services for DM patients in Central Java has not yet reached the standard, which is 2%.[21]

Diabetic Retinopathy incidence in T2DM patients at the Diponegoro National Hospital, Safira Clinic, and Amanda Clinic in Semarang City was 51.4% with data distribution of NPDR found in 30 patients (41.7%) and PDR consisted of 7 patients (9.7%). These results are conformable with the American Diabetes Association (ADA) 2016, which stated that NPDR is the most common type of retinopathy. NPDR has the potential to develop into PDR with a percentage of 6.1% in the first year of suffering from diabetes and increasing to 11% after 10 years.[7] In this study, the majority of respondents had DM with a duration of 1-5 years, so the results of this study found that the majority were at the NPDR stage.

Based on the research that has been done, it is found that there is a significant and strong relationship between the stage of diabetic retinopathy and HbA1c levels, in type 2 DM patients at Diponegoro National Hospital, Safira Clinic, and Amanda Clinic in Semarang City. The results of this study are relevant to research conducted by Lokesh S. (2018), that the higher the HbA1c level, the worse the severity of diabetic retinopathy. The Lokesh S (2018) study, showed that the stages of diabetic retinopathy severity (including severe NPDR and PDR) was more distributed among patients with high HbA1c compared with low HbA1c group. The milder forms of diabetic retinopathy (mild and moderate NPDR) were more prevalent in patients with HbA1c <10% compared to patients with HbA1c> 10%. In their study, it was found that the percentage number of patients with HbA1c levels < 8.0% having DR was 41.17%, HbA1c levels 8.0-10.0% with DR was 73.33%, and HbA1c levels > 10.0% with DR was 77.77%.However, in their study, Lokesh did not exclude eye disorders that could interfere with the HbA1c levels such as anemia, bleeding, episodic hemolysis, and chronic renal failure.[22]

The results obtained prove the author's initial hypothesis that there is a relationship between HbA1C levels and the stages of diabetic retinopathy. This hypothesis is based on research by Khalid M Alabdulwahhab (2019) which showed that HbA1c levels have a significant relationship with the degree of diabetic retinopathy with a p value <0.001. In their study, it was found that the HbA1c level of 9.32%

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was associated with the involvement of DR in patients, and patients who have high HbA1c levels have 1.995 times more chances to develop DR. Their further logistic regression analysis showed that uncontrolled HbA1c levels had a 66.61% chance of developing diabetic retinopathy.[23]

The Barbodose study by Leske et al (2005), found that every 1% increase in HbA1c from baseline was associated with a more than 2-fold risk of diabetic retinopathy. Up to 4 years of follow-up study period showing a linear association of HbA1c levels with the development of diabetic retinopathy.[24] Many other epidemiological studies confirm that uncontrolled HbA1c is an important risk in the development of diabetic retinopathy.[8-10]

This study has limitations in data collection, because it only uses secondary data from existing patient medical records which the opportunity to meet with research subjects in order to explore other risk factors and information needed is limited. This study also uses the age limit is too broad and includes the elderly, so that it can be biased in research. In future research, it is recommended that data collection does not only use secondary data from patient medical records. It is also important to limit the age so that it is not too old and broad. It is necessary to carry out further analysis of variables that could have an effect such as gender, spesific age, duration of DM, blood sugar level, and comorbidities, so that the exploration of risk factors and the necessary information can be carried out completely.

CONCLUSION

From this study, author conclude that there was a strong significant positive correlation between HbA1c levels and the severity of diabetic retinopathy. As the HbA1c level increases severity of the diabetic retinopathy also increases. Hence, it is advisable to include HbA1c a screening tool in the evaluation of DM, so that it can easily predict the development of diabetic retinopathy and treat it at an early stage. Retinal screening routinely under the supervision of an ophthalmologist. Health care providers must empower patients with comprehensive knowledge of DM, so that patients are empowered to make lifestyle changes (diet and exercise).

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