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Correlation Between Diabetic Retinopathy And *C-Reactive Protein* In Patients With Type 2 Diabetes Mellitus

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ABSTRACT

Background: Diabetic Retinopathy (DR) is one of the complications due to diabetes mellitus (DM). Pathogenesis of DR is microvascular disorder because of long term hyperglycemia. The trigger mechanism is activated by metabolic pathways, oxidative stress and inflammation. C-reactive protein (CRP) is one of the inflammatory markers. This study aims to determine the correlation between CRP level and stagging of DR.

Method: This study was a cross-sectional study in Sanglah eye clinic, in August until October 2017, a total of 51 sample with DR. The samples were categorized based on DR staging, namely Non Diabetic Retinopathy (NDR), Non-Proliferative Diabetic Retinopathy (NPDR), and Proliferative Diabetic Retinopathy (PDR) respectively. Each group of staging was performed CRP examination. This study assessed the correlation between CRP levels and staging of DR using Spearman correlation test.

Result: The result of this study obtained correlation coefficient (r) value of 0,396 (p=0,004), showed positive correlation between CRP level and staging Of DR. The regression equation correlation between CRP level and DR staging is expressed by regression equation: CRP = 0,119 + 0,847 (DR staging), this equation shows that if not found DR (NDR=0), CRP level 0,119 mg/L, each 1 staging increase of DR will decrease 0,847 mg/L CRP levels. The correlation between CRP level and DR staging after controlled with independent variables obtained by DR was correlated significantly with DR staging (p=0,037).

Conclusion: This study showed there is positive correlation between plasma CRP levels and the staging of DR, increasing level of CRP correlated with increasing staging of DR.

Keyword: C-Reactive Protein, Diabetic Retinopathy, Diabetes Mellitus
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INTRODUCTION

Diabetic Retinopathy (DR) is a complication of Diabetes Mellitus (DM) and as the leading cause of blindness worldwide. Pathogenesis of DR is a microvascular disorder caused by long term hyperglycemia.[1,2] Based on WHO data, approximately 5 million people suffer from DR worldwide. This prevalence is estimated to increase to 150 million and 75% predicted from developing countries by 2025.

Diabetic retinopathy can be divided into two major parts: non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR).[1,3] Epidemiologic studies show increased blood sugar, long duration of DM, hypertension and hyperlipidemia as risk factors for progression and DR. These risk factors explain only a portion of the DR and other risk factors such as chronic inflammation should be examined and evaluated.[5] Mechanisms that occur in the DR are triggered by metabolic pathways, oxidative stress, and subclinical inflammation.[2] Therapeutic approaches to inflammatory targets in the DR have been widely practiced, such as intravitreal injections of corticosteroids or VEGF agents.[5]

C-reactive protein (CRP) is an inflammatory biomarker that plays a role in endothelial dysfunction and atherogenesis.[6] C-reactive protein is a protein in the acute phase and is produced mainly by the liver and adipose tissue when microbial invasion or tissue injury occurred.[2,6] C-reactive protein (CRP) is elevated in cardiovascular disorders and diabetes and associated with micro albuminuria or macro albuminuria in DM patients or in general population.[5] The relationship between CRP and DR is still not known with certainly. Clinical studies investigating the relationship between CRP and DR levels are still unclear. Several studies have suggested an association between DR and CRP and are associated with the severity of the disease. Other studies have found opposite results.[2] Based on the reason above, the aim of this study is to assess the correlation between CRP level and staging of DR.

METHOD

This study was an observational analytic study with cross-sectional approach to find out the relationship between C-Reactive Protein (CRP) and Diabetic

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Retinopathy (DR). This research was conducted at Eye Polyclinic Sanglah Central General Hospital (RSUP), Denpasar, Bali from August 2017 to October 2017. Total of 51 patients with DM were included in this study with consecutive sampling technique. The inclusion criteria were DM patients aged 30 years or older and had DM for 5 years and were willing to take blood for CRP examination. The study exclusion criteria were patients with type 1 diabetes mellitus or patients with autoimmune diseases such as lupus, patients with treatment or steroid use, oral contraceptives or immunosuppressive drugs, patients with malignancy, and infections such as tuberculosis and also women with pregnancy.

All samples identified which fulfilled the inclusion and exclusion criteria were included in this study. Analysis of demographic data was done included age, sex, education, long suffering from DM, history of hypertension and BMI. The data were entered into SPSS version 17.0 and analyzed to find a relationship between CRP and staging of DR using Spearman correlation test and Ancova regression with p> 0.05.

RESULT

The study sample was selected consecutively with diabetes mellitus (DM) who came to Sanglah Central Hospital Denpasar from 1 August 2017 to 31 October 2017. Fifty-one patients were enrolled in this study. Characteristics of the study sample are shown in table 1 consist of gender, age, duration of diabetes mellitus, history of hypertension, and body mass index (BMI). Total 33 patients were male (64,7%) and 18 patients were females (35,3%). Mean age of patients was 51 ± 9.16 years old and the age range varies from 41 to 77 years old. The mean onset of DM is 10.51 ± 4.91 years and 22 patients with history of hypertension (43.1%), 22 patients have body mass index (BMI) above normal levels (43.1%).

Table 1. Baseline Characteristics

Variables	Descriptive
Sex	
Male	33 (64,7%)
Female	18 (35,3%)
Age {(year)(Mean±SD)}	51 ± 9,16
Onset of Diabetes Mellitus {(Age)(Mean±SD)}	10,51 ± 4,91
History of hypertension	
Yes	22 (43,1%)
No	29 (56,9%)
Body mass index	
Normal	29 (56,9%)
Overweight	20 (39,2%)
Obesity	2 (3,9%)

Levels of CRP in each staging of DR can be seen in table 2. NDR group obtained as many as 9 samples (17.6%) with an average CRP level of 1.19 ± 1.79 mg / L, in DR staging NPDR obtained 7 samples (13.7%) with a mean CRP level of 1.23 ± 0.81 mg / L, in DR staging of PDR obtained as many as 35 samples (68.6%) with a mean CRP level of 2.71 ± 2.45 mg / L. The relationship of CRP and staging of DR was analyzed using Spearman correlation test, where the lower CRP level was found to be lower staging of DR, with correlation coefficient (r = 0.396) which statistically significant (p = 0,004).

The regression equation between CRP level and staging of Diabetic Retinopathy is expressed by regression equation: CRP = 0,119 + 0,847 (staging of DR). This equation shows if there is no DR (NDR = 0) so the CRP level = 0,119 mg / L, increasing each one level of DR staging will increase 0.847 mg / L CRP levels.This shows there is a significant relationship between CRP levels and DR staging (R = 0.291, R2 = 0.085, p = 0.038). The relationship between CRP and DR staging after controlled with independent variables ie sex, age, duration of DM, history of hypertension, and BMI are presented in **Table 3.**

After controlled with the baseline characteristics variables (sex, age, onset of DM, history of hypertension, BMI), the analysis found a significant correlation between DR and CRP levels (t = 2.150; p = 0,037).

DISCUSSION

This is an observational analytic study with cross-sectional design. Total of fifty-one samples were included after passed inclusion and exclusion criteria. The samples then grouped into diabetic retinopathy staging (DR), ie non-diabetic retinopathy (NDR), non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR). The samples were interviewed, taken the blood sampling, and measurement of CRP level. Characteristics of the subjects of this study include sex, age, duration of diabetes, history of hypertension, BMI and CRP levels.

Gender as a risk factor for diabetic retinopathy is still debatable. Several studies have shown differences in sex characteristics in diabetic retinopathy patients. Stratton et al. (2012) in Spain

Table 2. Level of CRP at Any staging of DR

Staging	Total (N)	%	Min.	Max.	Mean ± SD
NDR	9	17,6	0,00	5,33	1,19±1,79
NPDR	7	13,7	0,59	3,05	1,23±0,81
PDR	35	68,6	0,30	9,69	2,71±2,45
Total (N)	51	100,0	1,44	6,80	2,24±2,28

NDR : Non Diabetic Retinopathy
NPDR : Non Proliverative Diabetic Retinopathy
PDR : Proliferative Diabetic Retinopathy

Table3. The relationship between CRP and DR staging after controlled by sex, age, duration of DM, history of hypertension, BMI

Variables	T	*P*
Staging of DR	2,150	0,037
Sex	0,471	0,640
Age	1,082	0,285
Onset of DM	-0,547	0,547
History of hypertension	0,700	0,488
BMI	0,657	0,515

reported the prevalence between men and women with diabetic retinopathy was equal (50%).[7] Study by Hartnett et al., 2000 obtained diabetic retinopathy was more common in females (55%) than in males (45%).[8] Studies in China and Singapore conducted by Wang et al., 2009 and Wong et al., 2008 show there were not differences in the prevalence of diabetic retinopathy.[9,10] Other studies also concluded that there is no relationship between sex and the severity of diabetic retinopathy.[11] This study showed diabetic retinopathy was more common in males (64.7%) than in women (35.3%).[11] Male gender has certain lifestyle such as smoking, drinking alcohol, drinking sodas which increase the risk factor of diabetic retinopathy. According to the American Academy of Ophthalmology and Staff (2015), male sex is one of the risk factors of diabetic retinopathy that is more often influenced by lifestyle, drinking alcohol and soda.[1,12]

Important risk factors for diabetic retinopathy in people with diabetes are age. Several studies reported the prevalence of DR increased with age.[13] Research conducted by Xu Jie, et al., 2013 in China showed that the mean age of patients with NPDR 60.75 ± 8.74 years and mean age of PDR patients was 58 ± 5.0 years.[14] The study conducted by Sulaiman, et al., (2010) found that the mean age of patients with NPDR was 60.22 ± 8.71 years and mean age of PDR patients was 64.31 ± 7.92 years.[15] The result of this study also found that the average age of DR patients was 51 ± 9.16 years.

The effect of hypertension on diabetic retinopathy in DM patients is due to the occurrence of thickening of arterial blood vessels which causes the blood vessel diameter to become narrowed. This will disturb the glucose transporting process.[16] A study conducted by Elwali et al in Sudan in 2016 showed a positive correlation between the history of hypertension and the staging of diabetic retinopathy.[17] Research conducted by Zong et al obtained different results.[12] Zong et al in China found hypertension did not correlate significantly with the staging of diabetic retinopathy.[12] This study obtained DR patients who had a history of hypertension as much as 22 (43.1%) of the sample and did not correlate significantly with the staging of DR

This study examined levels of CRP in 51 samples. In DR of NDR staging, there were 9 samples (17,6%) with average CRP level 1,19 ± 1,79 mg / L, at NPDR level was obtained 7 samples (13,7%) with CRP of 1.23 ± 0.81 mg / L, in PDR level as many as 35 samples (68.6%) with average CRP levels of 2.71 ± 2.45 mg / L. The correlation between CRP and staging of DR was analyzed using Spearman correlation test and showed a significant correlation with correlation coefficient of r = 0,396 and statistically significant (p = 0.004).

Song, et al., conducted a meta-analysis in 2015 of 22 studies and obtained mixed results among the studies. The study consisted of 2 cross-sectional studies and 20 case-control studies with a total of 3679 participants. Song, et al., obtained CRP levels in the blood of diabetic retinopathy cases were higher than patients without diabetic retinopathy as controls. Results of CRP patients with PDR were also higher than in NPDR patients.[2] This result is similar to that of Kaur et al., with study conducted on 60 diabetic retinopathy patients and divided into 20 cases without diabetic retinopathy, 20 cases of NPDR and 20 cases of PDR. CRP levels in the control group were found to be 2.43 ± 2.9 mg / dl, in the group without diabetic retinopathy 2.98 ± 4.2 mg / dl, in the NPDR group found 7.49 ± 8.37 mg / dl, and group PDR 6.67 ± 4.3 mg / dl, which are statistically significant.[18]

These results were agreed with findings by Kulkar and Kodliwadmath, Peng et al., Mahdy and Abdoel, Van Hecke et al., which resulted in a statistically significant increase in blood

plasma levels of CRP.[19,20,21,22] Increased CRP suggests inflammatory activation in cases of diabetic retinopathy. The inflammatory pathway is associated with dysfunction of the endothelium and the pathogenesis of blood vessels leading to the development and progression of the complications of Diabetes mellitus.[2,18]

This study found CRP levels increased linearly with the increased staging of diabetic retinopathy. Peng et al., 2015 says CRP inhibits endothelium-dependent nitric oxid-mediated dilatation and thus has the potential to facilitate the development of retinal vascular disease. CRP also stimulates interactions between leukocytes and endothelias, decreased endothelial nitric oxide, interferes with the number and function of progenitor cells, and causes endothelial dysfunction.[20,22,23] Hyperglycemic status in diabetic patients of retinopathy may be responsible for changes in inflammatory immune pathways and stimulate production of non-enzymatic glycation in accumulated of lysine and argin residues which play a role in the pathogenesis of diabetic complications.[23]

Research conducted by Pertami (2014) showed that Astaxanthin given to patients with mild NPDR could reduce inflammation characterized by decreased levels of IL-6 in the body. Astaxanthin in the eyes have anti-inflammatory and antioxidant effects.[24] Astaxanthin in DM has a role in reducing the severity of the disease by slowing down the sugar toxicity and protecting pancreatic β cells from malfunctioning due to oxidative damage.[24] Research on the administration of Astaxanthin is also done by Laksmi (2014) obtained decrease in Vascular Endothel Growth Factor.[25] Research conducted by Nada and Abdoel (2017) obtained the results of laser therapy without the provision of anti-inflammatory in patients with PDR decreased levels of average CRP after 4 weeks of therapy but not significant.

Hypertension, obesity, age and sex allegedly increased levels of CRP in the blood. Hypertension, heart disease and dyslipidemia are examples of illnesses thought to have a role in elevated levels of CRP in the blood.[26] In this study, the correlation between staging of DR and CRP after controlled by sex, age, duration of diabetes, history of hypertension and BMI had significant results (t = 2,150, p = 0,037). Significant results are only obtained on the staging of diabetic retinopathy. Research conducted by Chu et al., in China, showed no significant relationship between sex and CRP levels. Research conducted by Chu et al also obtained BMI not related to CRP. Timpson et al state that CRP and BMI showed strong association analysis with p = 0.0001. [26,27]

CONCLUSION

Based on the results of this study, there is a positive correlation between C - reactive protein (CRP) levels and staging of Diabetic Retinopathy (DR). The worsening of DR staging, the higher of CRP level. Other variables such as gender, age, onset of DM, history of hypertension and BMI did not have a significant relationship with plasma CRP levels.

REFERENCE

1. American Academy of Ophthalmology and Staff. *Retina and Vitreous*. United State of America: *American Academy of Ophthalmology*. 2015-2016: p. 109-32.
2. Song, J., Chen, S., Liu, X., Duan, H., Kong, J., Li, Z. Relationshhip between C-Reactive Protein Level And Diabetic Retinopathy: A Systemic Review And Meta-Analysis. *Plos one*.2015: VOL: 10(12)
3. Kulkarni, R.P., Kodliwadmath, M.P. Oxidative Stress and High Senstivity C-Reactive Protein In Diabetic Retinopathy. *International Journal of Pharma and Bio Sciences*. 2013: 4.p; 1306-1310.
4. American Diabetes Association. Position Statement: Standards of Medical Care in Diabetes 2010. *Diab Care*, 2010: 33;Suppl.1
5. Yang, X., Deng, Y., Gu, H., Lim, A., Snellingen, T., Liu, X., Wang, N., Domalpally, A., Danis, R., Liu, N. C-Reactive Protein and Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes Mellitus. *Int J Ophthalmol*. 2017: Vol: 9.p.111-118
6. Mocano, V., Timar, R., Horcat, R., Bucur, A., Serban, V. C-Reactive Protein And Body Mass Index In Patients With Type-2 Diabetes Mellitus And Diabetic Retinopathy. *Romanian Journal Of Diabetes Nutritioon And Metabolic Disease*. 2013: 20.p; 127-133
7. Stratton, I.M., Adler, A.I., Neil, H.A.W., dkk. Intensive Blood Glucose Control with Sulphonylureas or Insulin Compared with Conventional Treatment and Risk of Complications in Patients with Type 2 Diabetes. *Lens Diabetes Journal*. 2012: 352;p.837-853
8. Harnett, M.E., Stratton, D.R., Browne, R.W. Serum Markers of Oxidative Stress and Severity of Diabetic Retinopathy. *Diabetes Care*.2000: 23; p.234-240
9. Wang, F.H., Liang, Y.B., Zhang, F., dkk. Prevalence of diabetic retinopathy in rural China: the Handan eye study. *Ophthalmology*.2009: .116(3);p.461-467
10. Wong, T.Y., Cheung, N., Tay, W.T., dkk. Prevalence and risk factors for diabetic retinopathy: the Singapore Malay eye study. Ophthalmology. 2008: 115(11);p.1869-1875.
11. Grigsby, J.G., Allen, D.M., Richard, B.C., dkk. The Role of Sex Hormones in Diabetic Retinopathy. *Intech*. 2012: p.331-56
12. Kastelan, S., Tomic, M., Antunica, G.A., dkk. Body Mass Index: A Risk Factor for Retinopathy in Type 2 Diabetic Patients. Hindawi. 2013;p.1-8
13. Zhang,W., Liu, H., Rojas, M., Caldwell, R.W, and Caldwell, R.B. Anti inflammatory Therapy for Diabetic Retinopathy. *Immunotherap*. 2011: 5.; 609-628

14. Xu Jie, Du, Kui Fang, dkk. Diabetic Retinopathy in Diabetes Mellitus Patient. *Journal of Ophthalmology*. 2013: 20;p.24-28
15. Sulaiman, S., Mkthar, A.N., Ismail, Jeriah. Glycemic Control Among Type II Diabetics Patients in Kelatan. *NCD Malaysia*. 2010: 3(3);p.1-5
16. Zieve, D. Hypertension-Overview. 2012. Available from: http://nlm.nih.gov/medlineplus/ency/anatomyvideos/000072.htm [Accessed: 12 November 2017]
17. Elwali, E.S. *et al.* Frequency of Diabetic Retinopathy and Associated Risk Factors in Khartoum, Sudan: Population Based Study. *Int J Ophthalmol.*2017: 10(6). p948-954
18. Kaur, S., Singh, P., Grewal, R.K., Kaur, N., Agarwal, A. Serum Haptoglobin, Ceruplasmin and CRP Levels: Markers of Diabetic Retinopathy. *Global journal of Medical Research.* 2012: 12; 35-45.
19. Willard, A.L. and Herman, I.M. Vascular complications and diabetes: Current therapies and future challanges. *Journal of Ophthalmology*. 2012:1-14
20. Peng, D., et al. C-Reactive Protein Genetic Variant is Associated with Diabetic Retinopathy in Chinese Patients with Type 2 Diabetes. *BMC Endocrine Disorder.* 2015: 15(8)
21. Marshall, G., Garg, S.K., Jackson, W.E., Holmes, D.L., Chase, P. Factors influencing the onset and progression of diabetic retinopathy in subjects with insulin-dependent diabetes mellitus. *Ophthalmology.* 2003:100; 1133-39
22. Maa, A.Y.,&Sullivan, B.R. Relationship of HbA1c with the Presence and Severity of Retinopathy Upon Initial Screening of Type II Diabetes Mellitus. *American Journal of Ophthalmology*. 2009:114. p.17-18
23. Nada, W.M., dan Abdel-Moety,A. Serum C-Reactive Protein and Diabetic Retinopathy. *Open Journal of Opthalmology.* 2017: 7;73-78
24. Pertami, D.I.A. Astaxanthin Menurunkan Kadar Interleukin-6 Plasma pada Non Proliverative Diabetic Retinopathy Ringan: Uji Klinis Terkendali. *Medicina.* 2014:3; 23 -38.
25. Laksmi, U.N.M., Astaxanthin Menurunkan Kadar Vascular Endothelial Frowth Factor Plasma pada Non Proliverative Diabetic Retinopathy Ringan: Uji Klinis Terkendali. *Medicina.*2014:4; 20-25.
26. Nanda, K., Sadanand, G., Muralidhara Krishna, C.S., Mahadevappa K.L. C-Reactive Protein as a Predictive Factor of Preeclampsia. *Int J Biol Med Res*. 2012; 3(1); 1307-1310.
27. Timpson, N.J., et al. C-Reactive Protein Levels and Body Mass Index: Elucidating Direction of Causation Through Reciprocal Mendelian Randomization. *Int J Obes.* 2011: 35(2);300-308.