Indian Journal of Clinical and Experimental Ophthalmology 2022;8(2):245–249

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Original Research Article

Correlation of serum D-dimer levels with stages of diabetic retinopathy and gycosylated hemoglobin levels

Kiran Shetty[1], Lakshmi K[1,*], Sarita Lobo[1], Vivekanad U[2]

[1]*Dept. of Ophthalmology, Father Muller's Medical College, Mangalore, Karnataka, India*
[2]*Dept. of Ophthalmology, ASRAM Medical College, Godavari, Andhra Pradesh, India*

ARTICLE INFO

Article history:
Received 17-01-2022
Accepted 21-02-2022
Available online 29-06-2022

Keywords:
Diabetic retinopathy
D Dimer
Glycosylated hemoglobin

ABSTRACT

Diabetic retinopathy is a disorder where the perfusion of the retina may be affected owing to the microvascular changes taking place in the retinal blood vessels due to hypergycemia.
D-dimer level has been used as a biomarker of hypercoagulability and fibrinolytic activity since it is a product of fibrin degradation. D-dimer level (as a marker of coagulation cascade/fibrinolysis activation) assessment in type 1 and type 2 diabetics and its correlation with diabetic retinopathy stages have shown positive correlation. The findings in present study endorse the view that Elevated D dimer levels in severe forms of diabetic retinopathy. 26.9% patients with D dimer values more than 1000 have had severe NPDR to proliferative diabetic retinopathy, while 80% patients with normal values have shown to have no diabetic changes in fundus. Poor glycemic control (>6.5%) becomes a strong predictor for occurrence of severe form of diabetic retinopathy. 92.3% patients have shown the same. Hence, this study showed a positive correlation between increased blood sugar levels, elevated glyco Hb levels and severity of diabetic retinopathy. Hence, prompt understanding and treatment of hyperglycemia may prevent complications of diabetic retinopathy. The levels of Plasma D dimer is higher in type 2 diabetes mellitus complicated with microangiopathy. D-dimer is an important marker for thrombus formation hence may play an important role in the pathogenesis of diabetic microangiopathy. Prophylactic anticoagulant therapy and strict diabetic control can help in halting the progression of diabetic retinopathy.

1. Introduction

Type 2 diabetes mellitus is a frequent and important global health problem that has evolved in response to rapid cultural and social changes, such as population ageing, urbanisation, dietary changes, decreased physical activity, and other harmful lifestyle and behavioral habits. There is mounting evidence that recognised risk factors for diabetic retinopathy, such as diabetes duration, hyperglycemia, and hypertension, only account for a small portion of the diversity in diabetic retinopathy risk.[1,2] The most prevalent microvascular consequence of diabetes is diabetic retinopathy. Which has a pathology that isn't fully understood. The length and intensity of hyperglycemia affect the risk of diabetic retinopathy and other microvascular consequences of diabetes.[2,3] Diabetic retinopathy is a disorder where the perfusion of the retina may be affected owing to the microvascular changes taking place in the retinal blood vessels due to hyperglycemia.

Proliferative diabetic retinopathy is a condition in which new blood vessels form on the disc or in other parts of the retina.[4,5] Activation of protein kinase C, stimulation of the polyol pathway, activation and release of reactive oxygen species, activation of the fructose-6-phosphate pathway, and increased production and release of advanced glycation end

* *Corresponding author*.
E-mail address: gonsalvessarita@gmail.com (Lakshmi K).

https://doi.org/10.18231/j.ijceo.2022.049

products like D-dimer could all be involved in diabetic retinopathy retinal changes. Changes in the coagulation cascade have been implicated in the pathogenesis of the vascular diabetic complications. Advanced stages of diabetic retinopathy can lead to blindness. There are not many studies done comparing the stages of diabetic retinopathy with serum glycosylated hemoglobin levels with advanced glycation end products like D-dimer. D-dimer level has been used as a biomarker of hypercoagulability and fibrinolytic activity since it is a product of fibrin degradation.

A positive link has been shown between D-dimer levels (as a measure of coagulation cascade/fibrinolysis activation) and diabetic retinopathy stages in type 1 and type 2 diabetics.[6] It's critical to understand which factors play a role in causing retinal alterations in diabetic patients, as well as their relationship to the severity of hyperglycaemia. The link between d dimer, a serum inflammatory marker, and the various stages of diabetic retinopathy is investigated in this study.

2. Materials and Methods

To find the correlation between HbA1c levels in various diabetic retinopathy stages. To find the relation between serum D dimer levels in various stages of diabetic retinopathy

Analytical hospital-based cross-sectional study. The study included 77 pre-diagnosed diabetic patients over the age of 45 who had a fasting plasma glucose of more than or equal to 126 mg/dl, a 2-hour post glucose load plasma glucose of more than or equal to 200 mg/dl, or a random plasma glucose of more than or equal to 200 mg/dl in the presence of hyperglycemia symptoms. The Epi Info software was used to compute the sample size. Values less than 500, between 500 and 1000, and greater than 1000 were used to classify D dimer levels and correlate them with retinopathy stages. The research was carried out in a tertiary care hospital in south India's ophthalmology department. The institutional ethical committee granted permission to proceed. Patients over 45 years of age and with diabetes mellitus were included in the study.

Patients with opaque/hazy ocular media that made the fundus difficult to see were excluded from the study. Those with any of the confounding conditions that can influence D dimer levels, such as fever, active systemic infections, pregnancy, chronic inflammatory illnesses, cancer, trauma, post-surgery, liver disease, and heart disease, were also excluded from the study. A detailed medical history was collected, including the duration of diabetes and the existence of hypertension. A Snellen's chart was used to re-measure the patient's visual acuity, and an anterior segment slit lamp examination was performed. The Goldman's applanation tonometer was used to measure intraocular pressure. Direct slit lamp ophthalmoscopy and indirect ophthalmoscopy were used to examine the fundus. The ETDRS scale was used to categorise the stages of diabetic retinopathy. Patients are divided into three groups: Group A, which has no diabetic retinopathy, Group B, which has mild to moderate nonproliferative diabetic retinopathy, and Group C, which has both nonproliferative and proliferative diabetic retinopathy. Blood sugar levels were taken at random, as well as serum glycosylated hemoglobin and serum d dimer levels. HbA1C readings are classed as normal (5.7), pre-diabetic (5.7 to or = 6.5), or diabetes (>6.5) according to NICE recommendations. The patients were divided into groups based on their diagnoses. All patients' D dimer levels were evaluated. The results have been correlated and tabulated.

3. Results

There were a total of 77 participants in the study. There were 25 females and 52 guys in all. There were no diabetic retinopathy alterations in 25 of them. There were mild to moderate diabetic retinopathy changes in 25 people, and severe diabetic retinopathy changes in 26 people. In 8 cases, glycosylated hemoglobin levels were less than 5.7 percent, between 5.7 and 6.5 percent in 26 subjects, and greater than 6.5 percent in 43 subjects (Tables 1 and 3 showing the age, sex distribution of study subjects with correlation of glyco Hb levels). The results of this investigation support the theory that elevated D dimer levels are associated with severe forms of diabetic retinopathy. Patients with D dimer values more than 1000 had severe NPDR to proliferative diabetic retinopathy, whereas patients with normal values showed no diabetic changes in the eyes. (Glyco Hb and D dimer values are shown in Table 2) Poor glycemic control (>6.5%) is a major predictor of the development of severe diabetic retinopathy. The same has been demonstrated by 92.3 percent of patients. (Tables 4 and 6) As a result, our research found a link between high blood sugar levels, high Glyco Hb levels, and the severity of diabetic retinopathy. (Tables 7 and 8). As a result, early recognition and treatment of hyperglycemia may help to prevent diabetic retinopathy problems.

4. Discussion

In type 1 diabetes, inflammatory markers are cross-sectionally linked to microvascular problems and cardiovascular disease.[7] While inflammation is thought to be a pathogenic element in the formation and progression of diabetic retinopathy, several studies have revealed conflicting results when it comes to systemic markers of inflammation, such as serum CRP, and diabetic retinopathy.[8] Several studies have compared levels of vitreous advanced glycation end products (AGEs) and D-dimer with the various stages of diabetic retinopathy, but only a few have assessed the correlation between blood

Table 1: Showing the age and sex distribution of study subjects, grades of diabetic retinopathy, glycosylated Hb and D dimer levels

		Count	Column N %
Gender	F	25	32.5%
	M	52	67.5%
Grade of DR	NO DRNO DR	25	32.5%
	Mild MOD DR	26	33.8%
	Severe DR, PDR	26	33.8%
Grade of DR	No DRNO DR	25	32.5%
	DR Present	52	67.5%
HBA1C	<5.7%	8	10.4%
	5.7 To 6.5%	26	33.8%
	>Or=6.5%	43	55.8%
D Dimer	<500	40	51.9%
	Until 1300	30	39.0%
	>1300	7	9.1%

Table 2: Showing glycosylated Hb levels and D dimer levels in the study subjects

		Grade of DR						Grade of DR			
		No DRNO DR		Mild MOD DR		Severe DR, PDR		No DRNO DR		DR Present	
		Count	Column N %	Count	Column N %	Count	Column N %	Count	Column N %	Count	Column N %
Gender	F	7	28.0%	7	26.9%	11	42.3%	7	28.0%	18	34.6%
	M	18	72.0%	19	73.1%	15	57.7%	18	72.0%	34	65.4%
HBA1C	<5.7%	6	24.0%	2	7.7%	0	0.0%	6	24.0%	2	3.8%
	5.7 to 6.5%	17	68.0%	7	26.9%	2	7.7%	17	68.0%	9	17.3%
	>Or=6.5%	2	8.0%	17	65.4%	24	92.3%	2	8.0%	41	78.8%
D Dimer	<500	20	80.0%	16	61.5%	4	15.4%	20	80.0%	20	38.5%
	Until 1300	5	20.0%	10	38.5%	15	57.7%	5	20.0%	25	48.1%
	>1300	0	0.0%	0	0.0%	7	26.9%	0	0.0%	7	13.5%

Table 3: Shows the stages of diabetic retinopathy in the study population

	N	Mean	Std. Deviation	Anova p value	
No DRNO DR	25	57.64	9.291	.079	NS
Mild MOD DR	26	61.23	11.190		
Severe DR, PDR	26	64.15	9.821		
Total	77	61.05	10.359		

Table 4: Correlation of stages of diabetic retinopathy with HBA1c and serum D dimer levels

		N	Mean	Std. Deviation	95% Confidence Interval for Mean		Anova p value	
					Lower Bound	Upper Bound		
HBA1C	No DRNO DR	25	5.980	.3884	5.820	6.140		
	Mild MOD DR	26	7.735	1.7951	7.010	8.460	.000	HS
	Severe DR, PDR	26	9.408	1.9223	8.631	10.184		
D Dimer	No DRNO DR	25	399.60	154.447	335.85	463.35		
	Mild MOD DR	26	601.15	381.652	447.00	755.31	.000	HS
	Severe DR, PDR	26	897.69	465.010	709.87	1085.51		

Post hoc analysis

Table 5:

Multiple Comparisons		
Bonferroni		
(J) Grade of DR	Bonferroni P value	
Mild MOD DR	.000*	HS
Severe DR, PDR	.000*	HS
NO DRNO DR	.000*	HS
Severe DR, PDR	.001*	HS
NO DRNO DR	.000*	HS
Mild MOD DR	.001*	HS

Table 6: Confidence levels in Hb A1c and Dimer levels in the study population

D Dimer	**No DRNO DR**	**Mild MOD DR**	**.149**	
		Severe DR, PDR	.000*	HS
	Mild MOD DR	No DRNO DR	.149	
		Severe DR, PDR	.012*	sig
	Severe DR, PDR	No DRNO DR	.000*	HS
		Mild MOD DR	.012*	sig

*. The mean difference is significant at the 0.05 level

Table 7: P value for the above comparison

		N	**Mean**	**Std. Deviation**	**95% Confidence Interval for Mean**		**t test p value**	
					Lower Bound	Upper Bound		
HBA1C	NO DRNO DR	25	5.980	.3884	5.820	6.140	.000	HS
	DR Present	52	8.571	2.0259	8.007	9.135		
D Dimer	No DRNO DR	25	399.60	154.447	335.85	463.35	.000	HS
	DR Present	52	749.42	447.005	624.98	873.87		

Table 8: P value for the above comparison

		Chi square test/Fishers exact test p value			
		Grade of DR		**Grade of DR**	
Gender	P=	.419	NS	.562	NS
HBA1C	P=	.000	HS	.000	HS
D Dimer	P=	.000	HS	.002	HS

Table 9: Logistic regression analysis– unadjusted odds ratio Dependent variable DR present (1) vs absent (0)

	P	**odds ratio**	**95% C.I. for odds ratio**	
			Lower	**Upper**
HBA1C	.000			
HBA1C (5.7 to 6.5%)	.613	1.588	.264	9.538
HBA1C(>OR=6.5%)	.000	61.500	7.243	522.202
	P	**odds ratio**	**95% C.I. for odds ratio**	
			Lower	**Upper**
D Dimer (>500)	.001	6.400	2.071	19.773

Table 10: Adjusted odds ratio

		P	**Odds ratio**	**95% C.I. for odds ratio**	
				Lower	**Upper**
Step 1[a]	D Dimer (>500)	.161	2.853	.659	12.360
	HBA1C	.000			
	HBA1C (5.7 TO 6.5%)	.467	2.011	.306	13.206
	HBA1C (>OR=6.5%)	.000	53.802	6.094	474.990

haemoglobin A1C (HbA1c) levels and serum d dimer levels with the pathological changes in the retina. Common systemic markers of inflammation, such as CRP and IL-6, were also found to be unrelated to diabetic retinopathy in several investigations.[9] Changes in findings between studies are most likely due to differences in diabetes type, sample numbers, or insufficient control for confounding factors. The findings of our investigation back with several prior studies that found elevated D-dimer levels in those with diabetes. The discovery that plasma D-dimer levels increase with disease progression, from pre-diabetes to different stages of progression of diabetic retinopathy[9,10] is well recognised. However, few studies have compared D dimer levels to glycosylated haemoglobin levels and different phases of diabetic retinopathy. The mean level of D-dimer in the control group is lower than in the diabetes group, as shown in the results. (p,0.001). The findings imply that D-dimer has a complementary role in the early detection of diabetes complications and the progression of diabetic retinopathy alterations. Furthermore, our findings show that high levels of glycosylated haemoglobin and D-dimer are linked to advanced stages of diabetic retinopathy.

5. Conclusion

In type 2 diabetes mellitus exacerbated by microangiopathy, plasma D dimer levels are greater. Because D-dimer is a key marker for thrombus development, it could play a role in diabetic microangiopathy pathogenesis. Diabetes retinopathy can be slowed down with prophylactic anticoagulation treatment and strict diabetic control.

6. Source of Funding

None.

7. Conflict of Interest

The authors declare no conflict of interest.

References

1. Mohamed Q, Gillies MC, Wong TY. Management of diabetic retinopathy: a systematic review. *JAMA*. 2007;298(8):902–16.
2. Nguyen TT, Wang JJ, Wong TY. Retinal vascular changes in pre-diabetes and prehypertension: new findings and their research and clinical implications. *Diabetes Care*. 2007;30(10):2708–15.
3. Maurya RP. Diabetic retinopathy: My brief synopsis. *Ind J Clin Exp Ophthalmol*. 2015;1(4):189–90.
4. Garg P, Misra S, Yadav S, Singh L. Correlative Study of Diabetic Retinopathy with HbA1c and Microalbuminuria. *Int J Ophthal Res*. 2018;4(2):282–6.
5. Loho T, Venna V, Setiabudy RD, Sukartini N, Immanuel S, Kumalawati J, et al. Correlation Between Vitreous Advanced Glycation End Products, and D-dimer with Blood HbA1c Levels in Proliferative Diabetic Retinopathy. *Acta Med Indones*. 2018;50(2):132–7.
6. Simó-Servat O, Planas A, Ciudin A, Simó R, Hernández C. Assessment of advanced glycation end-products as a biomarker of diabetic outcomes. *Endocrinol Diabetes Nutr*. 2018;65(9):540–5.
7. Gündüz K, Bakri SJ. Bakri Management of proliferative diabetic retinopathy. *Compr Ophthalmol Update*. 2007;8(5):245–56.
8. Choudhuri S, Dutta D, Sen A, Chowdhury IH, Mitra B, Mondal LK, et al. Role of N-ε- carboxy methyl lysine, advanced glycation end products and reactive oxygen species for the development of nonproliferative and proliferative retinopathy in type 2 diabetes mellitus. *Mol Vis*. 2013;19:100–13.
9. Brazionis L, Rowley K, Harper CA. Markers of inflammation are cross-sectionally associated with microvascular complications and cardiovascular disease in type 1 diabetes Homocysteine and diabetic retinopathy. *Diabetes Care*. 2008;31:50–6.
10. Long ZF, Qu GY, Xu M. Relationship between the level of plasma D-dimer and diabetic microangiopathy. *Hunan Yi Ke Da Xue Xue Bao*. 2001;26(5):434–6.

Author biography

Kiran Shetty, Associate Professor

Lakshmi K, Junior Resident

Sarita Lobo, Associate Professor

Vivekanad U, Professor

Cite this article: Shetty K, Lakshmi K, Lobo S, Vivekanad U. Correlation of serum D-dimer levels with stages of diabetic retinopathy and gycosylated hemoglobin levels. *Indian J Clin Exp Ophthalmol* 2022;8(2):245-249.