ISSN No:-2456-2165

Effect of Variability of Hemoglobin Value on Type and Severity of Diabetic Retinopathy in Adult Type II Diabetes Mellitus Patients

Dr. Mehrin Samed[1*] (***correponding author***), Dr. Nashwa Abdul Gaffoor[2], Dr. Babitha V[3], Dr. Padma B Prabhu[4]
[1,2] MBBS-Intern, [3]Associate professor, [4]Additional professor
[1,2,3,4] Govt. Medical College Kozhikode, Kerala, India

Abstract:-
Background: Anemia has been identified as a risk factor for Diabetic Retinopathy, a leading cause of blindness worldwide. However the "at risk" values of hemoglobin in prognosticating diabetic retinopathy has not been defined. This study intends to evaluate the relation between level of hemoglobin and type and severity of diabetic retinopathy among type 2 DM.

Methodology: design - descriptive cross sectional study; duration-6months, study setting- tertiary care hospital in North Kerala, study population- type II DM Patients, age> 40years with diabetic retinopathy, sample size-87 cases. Variables - gender, age, duration of disease, stages of Retinopathy, Hb, HbA1C, RFT. p value <0.05 considered as statistically significant. Data analyzed using chi square and one way anova with PASW statistics 18.0.0.

Results: Male female ratio=1.2:1. Mean age - 59.83 ± 6.201, mean duration of disease- 11.06± 5.564. Mean Hb was 11.65 ± 1.89. 81.6% of subjects were anemic. 50.6% subjects had PDR and others had NPDR. 69% of patients had maculopathy. Anemia was more prevalent in PDR patients and those with maculopathy . Among NPDR and PDR, anemic had severe disease. The mean Hb values showed a statistically significant relationship with type and severity of retinopathy irrespective of gender and nephropathy. Mean Hb and type of retinopathy had a statistically significant relationship among subjects with poor glycemic control. The lower mean Hb related to male gender and normal HbA1c values among maculopathy cases.

Conclusion: Lower hemoglobin values correlated with the severity of diabetic retinopathy and presence of maculopathy independent of gender and presence of nephropathy. Correcting anemia and maintaining a normal Hb value may delay the onset and progression of diabetic retinopathy and maculopathy in type 2 diabetic adults.

Keywords:- *Diabetic Retinopathy, Nephropathy, Anemia, Maculopathy.*

I. INTRODUCTION

[1]Diabetic retinopathy (DR), including diabetic maculopathy, is a microvascular complication of DM and the [2]leading cause of blindness worldwide. [3,4,5]Various factors are associated with the development and severity of DR including high blood pressure, proteinuria, duration of DM, administration of insulin, hyperglycemia and renal disease. [6,7]Anemia is more prevalent in persons with diabetes. [3]Many studies have shown a link between low Hb level and hypoxia induced organ damage.

We designed the study to assess the effect of variation of haemoglobin level on type and severity of diabetic retinopathy and also its association with blood urea, serum creatinine and Hba1c values.

II. SUBJECTS AND METHODS

The study was conducted in a tertiary care hospital at north Kerala among diabetic retinopathy patients with type II diabetes mellitus and age >40 years having evidence of DR on fundus examination. Permission from the Institutional Research Committee and Ethical Committee was obtained. There was no financial burden to the study participants. A descriptive cross sectional study was conducted for duration of 6 months.

A total of 87 cases (based on the formula 4pq/d2, where p=32, d= 10, p is the prevalence and q=100-p) by convenient sampling was taken. DR patients with age of onset of type II DM <40 years, gestational diabetes, pancreatic disease induced diabetes, steroid induced diabetes, type I diabetes mellitus were excluded.

Data about age, gender, duration of type II DM, type of DR, value of hemoglobin, blood urea, serum creatinine, Hba1c were collected. Type of retinopathy was classified as non proliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR). Patients with NPDR were further grouped according to the severity as mild, moderate, severe; and PDR as early PDR and high risk PDR (HRPDR). Patients also evaluated for presence and absence of maculopathy. Data was collected using proforma, lab values from records, and retinal examination. The data was analysed using chi square test and one way anova. p value< 0.05 is considered to be statistically significant.

ISSN No:-2456-2165

From the data collected the patients were grouped into anemic and non anemic based on the Hb value. [8]In males Hb<13.5 g/dL (normal Hb value in males =13.5 to 17.5 g/dL) and in females Hb<12.0 g/dL (normal value in females=12.0 to 15.5 g/dL) is considered as anaemic. According to age, patients were divided into 2 groups as <60 and ≥60 years, data also grouped into two as duration of DM <10 and ≥10 years. Presence of nephropathy was determined with blood urea level [9]normal= 7 to 20 mg/dL) and serum creatinine level (8normal: males (M) = 0.9 TO 1.3 mg/dL, females (F) = 0.6 to 1.1 mg/dL). Patients with blood urea >20 mg/dL and creatinine >1.3 mg/dL in males and >1.1 mg/dL in females were considered to have elevated RFT values. Hba1c values were used to assess whether the patient had uncontrolled or controlled DM. [10]Hba1c ≤ 7 was considered as controlled (short term) diabetes.

III. RESULTS

The study population included 87 diabetic subjects. Among them 55.2% were male. The age varied from 47 to 75 years, mean age was 59.83 ± 6.201 and median 60 years. 44.8% were aged < 60yrs. Duration of type II DM ranged from one year to 25 years with a mean of 11.06 ± 5.564 and median of ten years. Duration of type II DM >10yrs in 62.1% (n=54). PDR in 50.6% (n=44). Among the subjects with Nonproliferative diabetic retinopathy (NPDR), 18.6% (n=8) had mild, 34.9% (n=15) moderate and 46.5% (n=20) severe NPDR. And among PDR 45.5% (n 20) had early PDR, 54.5% (n=24) had high risk PDR (HRPDR). 69% (n=60) had evidence of maculopathy.

Value of Hba1c varied between 4.6 to 14.6% with a mean of 8.06 ± 1.5 and median eight. Hba1c ≤7% considered as good control of DM. 78.2% (n=68) had poor short term control of DM. Hemoglobin value ranged from 8.4 to 15.6 g/dL with a mean of 11.65 ± 1.89 and median 11.6. Among the subjects 81.6% (n=71) were anemic. The minimum blood urea level found in the subjects was 14mg/dL and maximum 118 mg/dL, with a mean of 34 ±18.3 and median of 28. In which 86.2% (n=75) had elevated blood urea level. The serum creatinine level varied from 0.6 to 7.1 mg/dL with a mean of 1.42 ± 0.90 and median equals 1.2. 47.1% (n 41) had high creatinine value. Patients with either elevated urea or creatinine were considered to have nephropathy. Thus 86.2% (n=75) had nephropathy.

The distribution of cases based on presence of anemia, type of retinopathy and its severity is given in table-1. Presence of anemia showed statistically significant relation with type of retinopathy (p=0.02) as well as severity of NPDR (p=0.017) and severity of PDR (p=0.036).

Table 1: Relationship between presence of anemia, type of retinopathy and its severity
** p<0.05 (statistically significant)

Type of retinopathy	N	Non Anemic n(%)	Anemic n(%)	p value
NPDR	43	12(27.9)	31(72.1)	
Mild	8	5(62.5)	3(37.5)	0.017**
Moderate	15	5(33.3)	10(66.7)	
Severe	20	2(10)	18(90)	
PDR	44	4(9.1)	40(90.9)	
Early	20	4(20)	16(80)	0.036**
HRPDR	24	0(0)	24(100)	
Total	87	16(18.4)	71(81.6)	0.022

Presence of anemia and maculopathy was compared. 86.7% (n=52) of patients with maculopathy had anemia while 70.4% (n=19) of diabetic cases without maculopathy had anemia. Though p value was 0.06, this observation is clinically relevant.

Relation between presence or absence of anemia and normal or abnormal creatinine and urea values is shown in table 2.

54.9% of anemic subjects had high serum creatinine (p=0.02). 87.3% had high urea levels (p=0.384). Presence of anemia did not show statistically significant correlation with duration of diabetes(p=0.398) or short term glycemic control as evidenced by HbA1C values (p=0.093)

Table 2: Relation between presence or absence of anemia and RFT
** p<0.05 (statistically significant)

	Serum creatinine				Blood urea			
	n	Normal n(%)	High n(%)	p	n	Normal n(%)	High n(%)	p
Non anemic	16	14 (87.5)	2 (12.5)	0.02**	16	13 (18.8)	13 (81.3)	0.384
Anemic	71	32 (45.1)	39 (54.9)		71	9 (12.7)	62 (87.3)	

Based on gender

The subjects were grouped based on gender and Hb values were compared with type of retinopathy using one way anova. Table 3 and figure 1 represents the relation between

Hb value and type of retinopathy based on gender. A statistically significant relation was observed for both males and females with p value 0.003 and 0.001 respectively.

Figure 1: Relation between Hb value and type of retinopathy based on gender

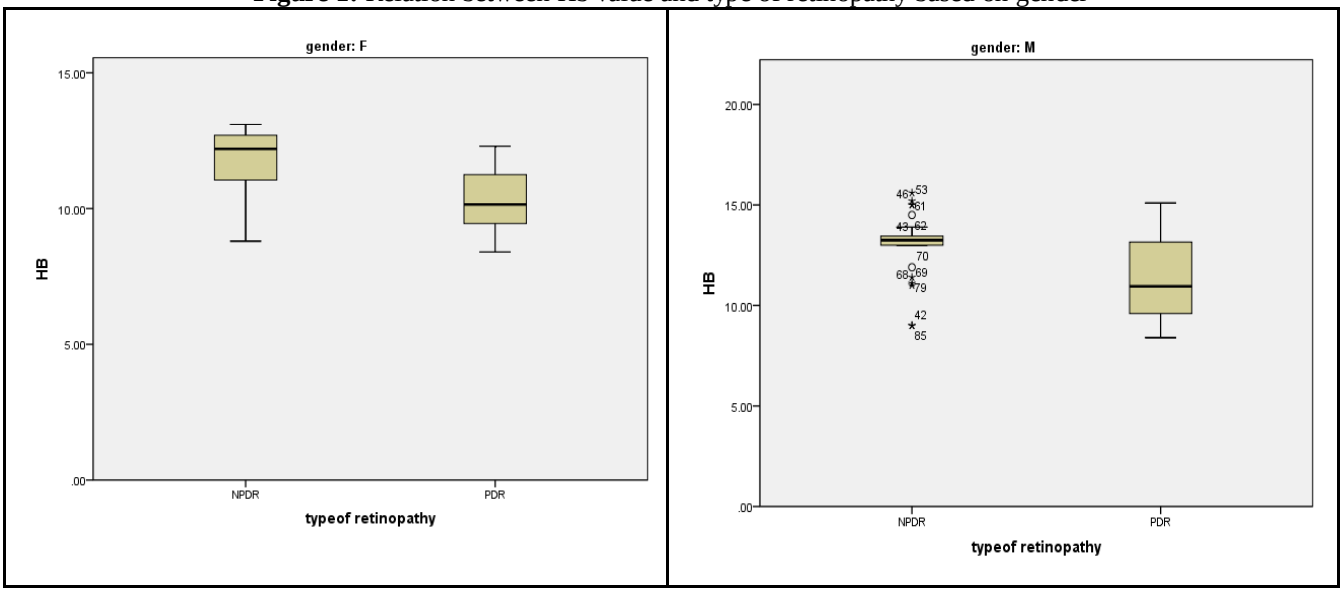


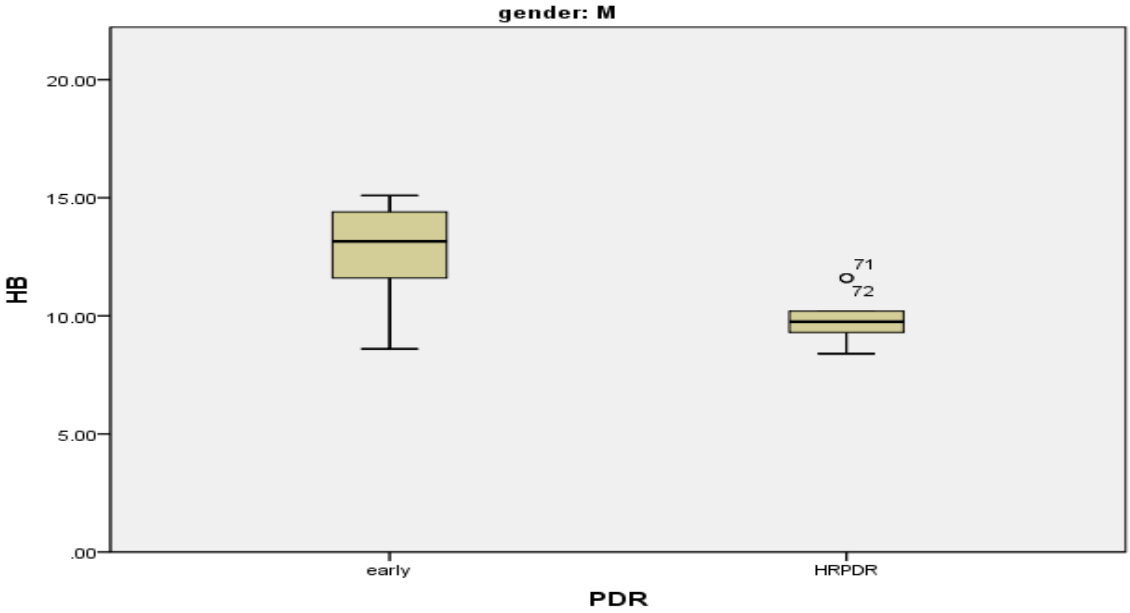
Table 3: Relation between Hb value and type of retinopathy based on gender
** p<0.05 (statistically significant)

Gender		n	Mean Hb	SD	95% CI		Min	Max	p
					Lower	Upper			
F	NPDR	15	11.7	1.26	11.0	12.4	8.8	13.1	0.001**
	PDR	24	10.3	1.15	9.8	10.7	8.4	12.3	
	Total	39	10.8	1.35	10.4	11.28	8.4	13.1	
M	NPDR	28	13.0	1.57	13.6	13.6	9.0	15.6	0.003**
	PDR	20	11.3	2.18	12.3	12.35	8.4	15.1	
	Total	48	12.3	2.01	12.8	12.89	8.4	15.6	

ISSN No:-2456-2165

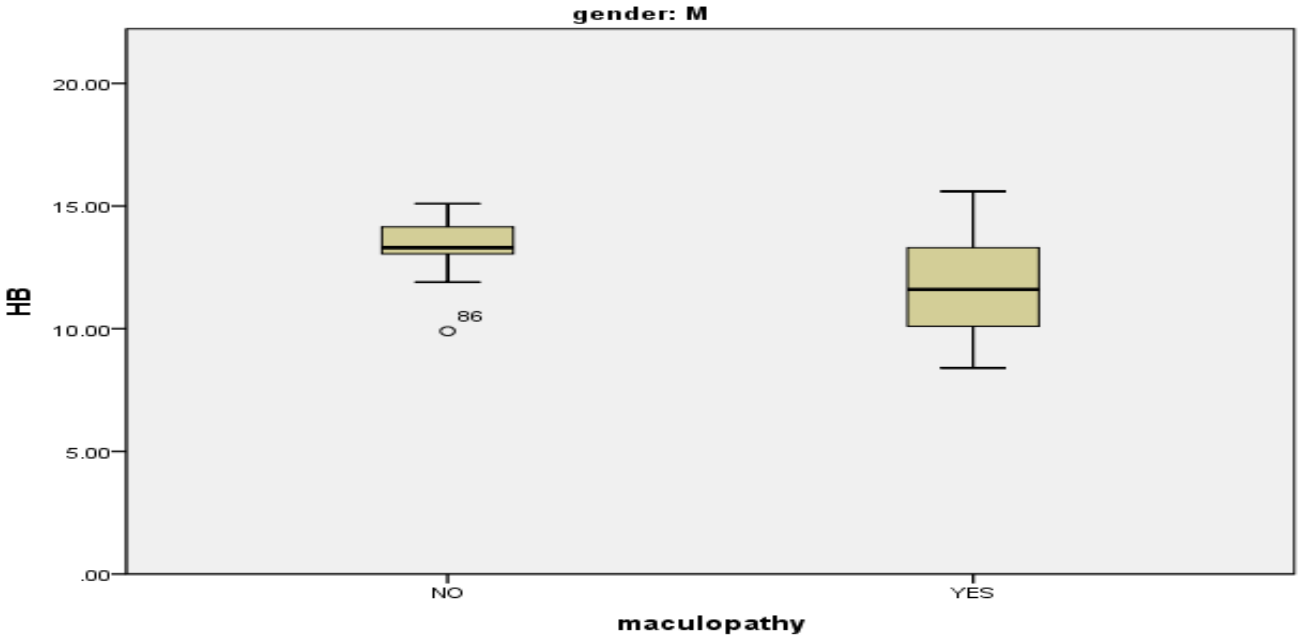
Among those with NPDR, as severity of the disease increased Hb value decreased but it was not found to be statistically significant in both genders. Among those with PDR Hb was less when severity of disease increased in both genders. But the observation was statistically significant only in males (p=0.001). In males for early PDR mean Hb value was 12.7±2.05, 95% confidence interval =11.31 to 14.24 and no extreme values present; for HPDR mean Hb value was 9.88±1.08, 95% confidence interval = 9.10 to 10.65 with two extreme values. Figure 2 shows a box plot representing relation between types of PDR and Hb value in males.

Figure 2: Relation between types of PDR and Hb value in males.



Among males, those without maculopathy had a near normal mean Hb value (13.43gm%). Those with maculopathy had a lower mean Hb value of 11.7± 2.07 (95% CI= 10.37 to 11.47). The relation was statistically significant with a p value of 0.007. In females no such relation was observed between presence of maculopathy and Hb value. Figure 3 shows a box plot representing the presence of maculopathy and Hb values in males.

Figure 3: Relation between presence of maculopathy and Hb values in males



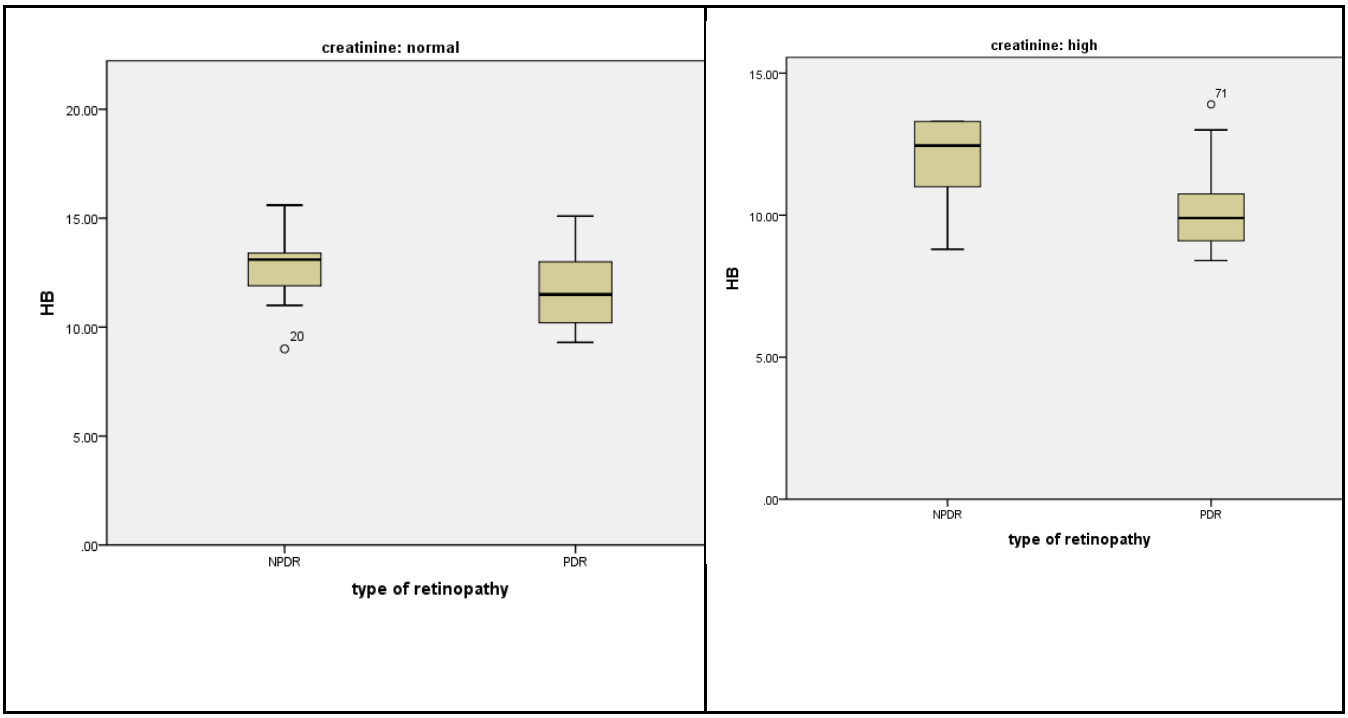
Based on variation in serum creatinine values

Serum creatinine is a more reliable indicator of renal function than blood urea nitrogen because it is less influenced by diet and hydration. Hence the subjects were grouped based on presence or absence of elevated serum creatinine and Hb values were compared with type of retinopathy. The relation was found to be statistically significant in both high and normal creatinine groups with a p value 0.001 and 0.025 respectively. Table 4 shows an analysis between Hb values and type of retinopathy in subjects with normal and elevated serum creatinine values. The same is represented by a box plot in figure 4.

Table 4: Relation between Hb and creatinine value with types of retinopathy
** p<0.05 (statistically significant)

Serum creatinine		n	Mean Hb	SD	95% CI		Min	Max	p
					Lower	Upper			
Normal	NPDR	29	12.8	1.48	12.3	13.4	9	15.6	0.025**
	PDR	17	11.7	1.82	10.79	12.6	9.3	15.1	
	Total	46	12.4	1.69	11.9	12.9	9	15.6	
High	NPDR	14	11.8	1.63	10.9	12.8	8.8	13.3	0.001**
	PDR	27	10.17	1.44	9.5	10.7	8.4	13.9	
	Total	41	10.7	1.70	10.2	11.2	8.4	13.9	

Figure 4: Relation between Hb and creatinine value with types of retinopathy



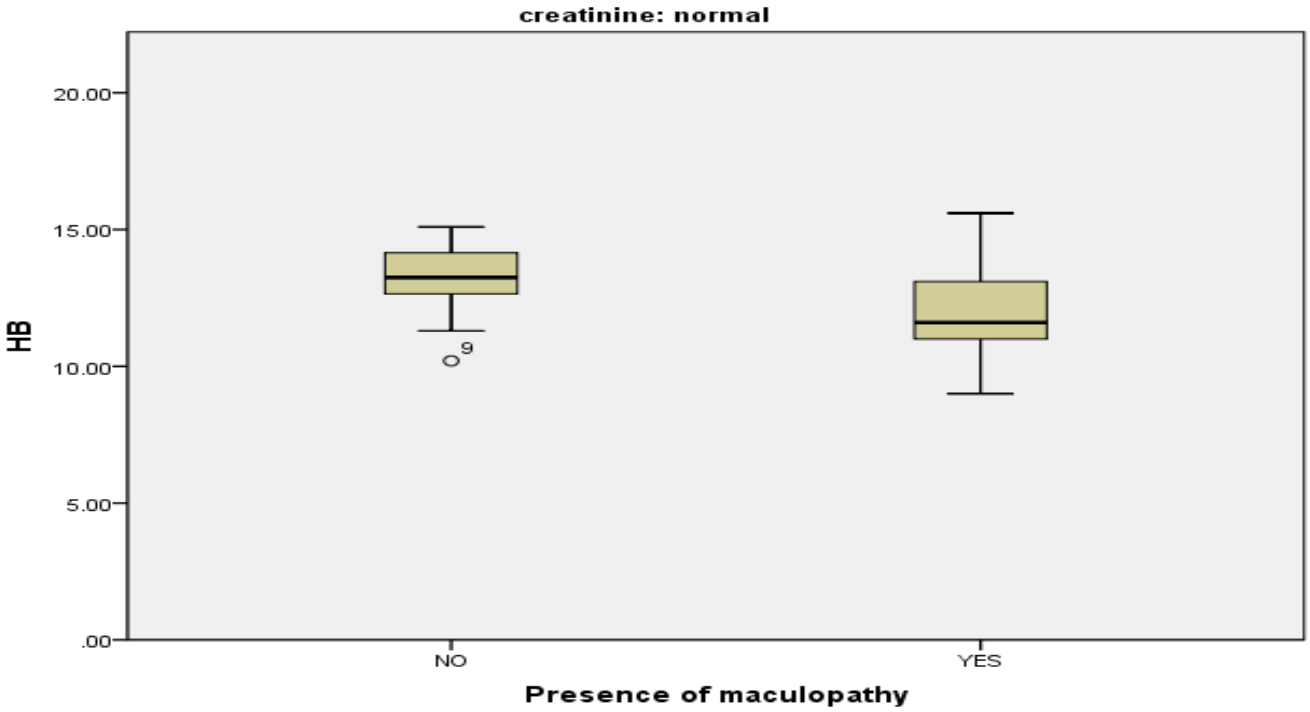
The subcategories of NPDR and PDR were compared with Hb values. Even though the Hb values were less as severity of NPDR increased in both groups no statistically significant relation was found. In PDR for both groups, mean Hb decreased as disease severity increased, but a statistically significant relation was found only in patients with normal creatinine value not in elevated creatinine value. Among them, the mean Hb value for early PDR was 12.6 ± 1.67 (95% CI 11.4 to 13.8) and for HRPDR was 10.3 ± 1.0 (95% CI 9.4 to 11.3). P value was 0.005. Mean Hb of patients with elevated creatinine was lower than those with normal values.

Hb was lower in patients with maculopathy than without maculopathy in both groups irrespective of presence of elevated serum creatinine values. Anemia and presence of

ISSN No:-2456-2165

maculopathy showed a significant association in subjects with no nephropathy (p 0.022). In this category, patients without maculopathy had a mean Hb of 13.2± 1.34, 95% CI= 12.5 to 13.94, and for those with maculopathy mean Hb= 12.4± 1.73, 95% CI= 11.4 to 12.7. Figure 5 shows a box plot showing relation between Hb value and presence of maculopathy in subjects with normal serum creatinine.

Figure 5: Relation between Hb value and presence of maculopathy in subjects with normal serum creatinine



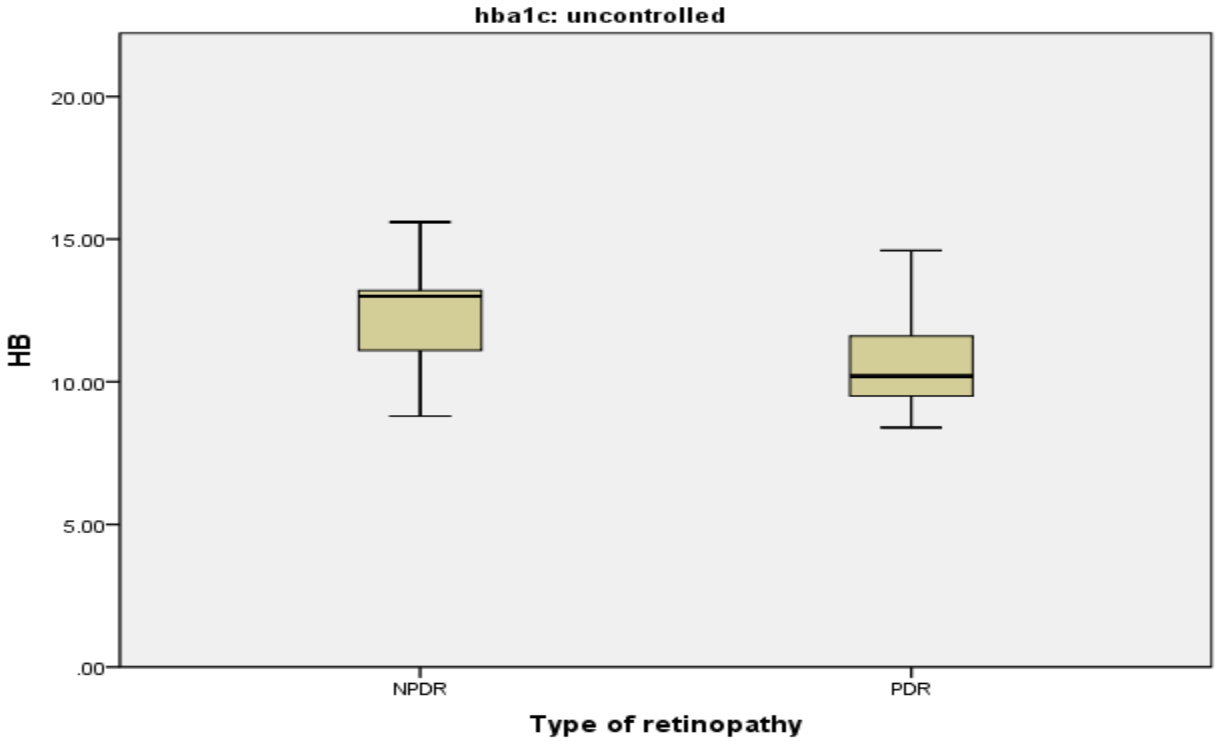
Based on diabetic control

Subjects were divided on the basis of diabetes control, and then the relation between Hb level and type of retinopathy assessed. The mean Hb value was less among PDR cases irrespective of the short term glycemic status. A statistically significant relation was observed among those with poor control (table 5, figure 6).

Table 5: Relation between Hb and short term glycemic control with type of retinopathy
** p<0.05 (statistically significant)

Control of DM		n	Mean Hb	SD	95% CI		Min	Max	p
					Lower	Upper			
Controlled	NPDR	13	12.9	1.5	12.0	13.88	9	15	0.108
	PDR	6	11.35	2.6	8.5	14.1	8.5	15.1	
	Total	19	12.4	2.03	11.47	13.4	8.5	15.1	
Uncontrolled	NPDR	30	12.3	1.6	11.7	12.9	8.8	15.6	0.001**
	PDR	38	10.6	1.6	10.1	11.2	8.4	14.6	
	Total	68	11.4	1.8	10.98	11.8	8.4	15.6	

Figure 6: Relation between type of retinopathy and Hb level in those with uncontrolled diabetes

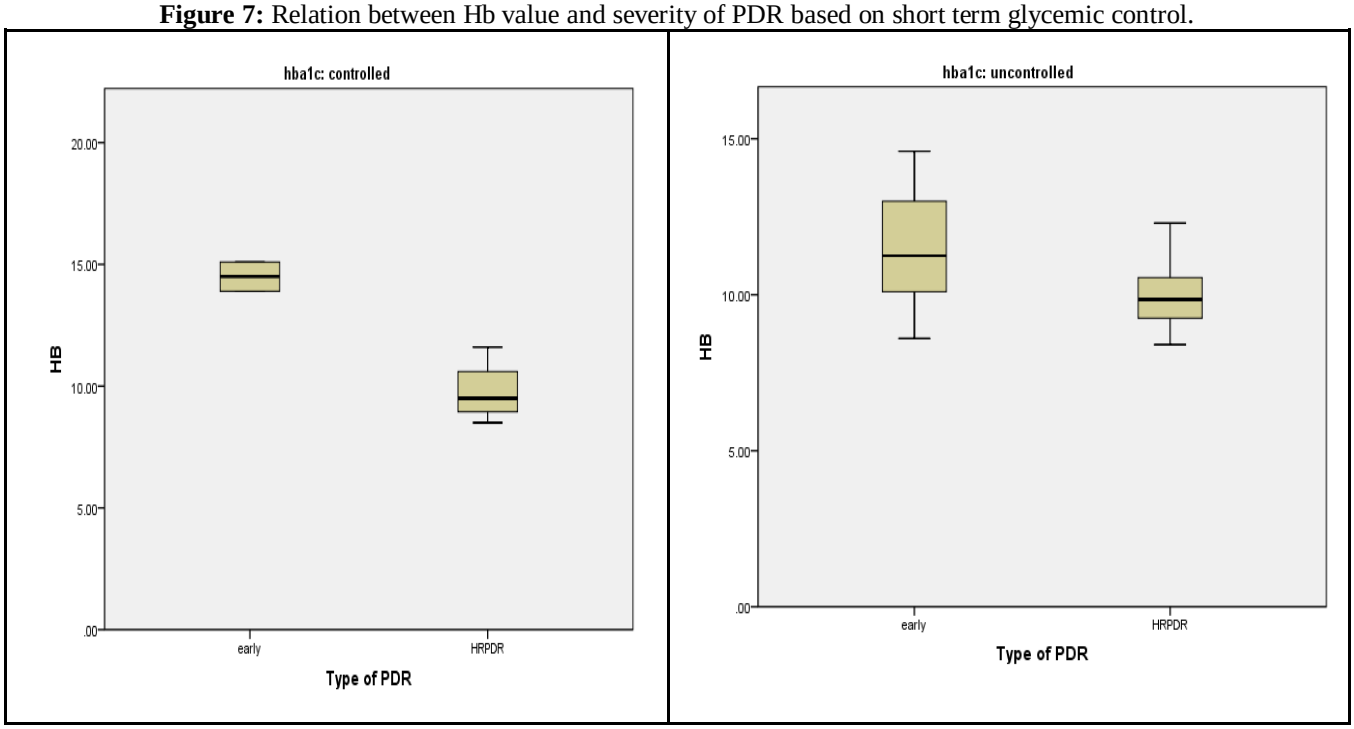


In the case of NPDR, no relation was found between severity of disease and Hb value. In PDR, both controlled and uncontrolled DM groups had statistically significant relations (table 6, figure 7).

Table 6: Relation between Hb value and severity of PDR based on short term glycemic control.
** p<0.05 (statistically significant)

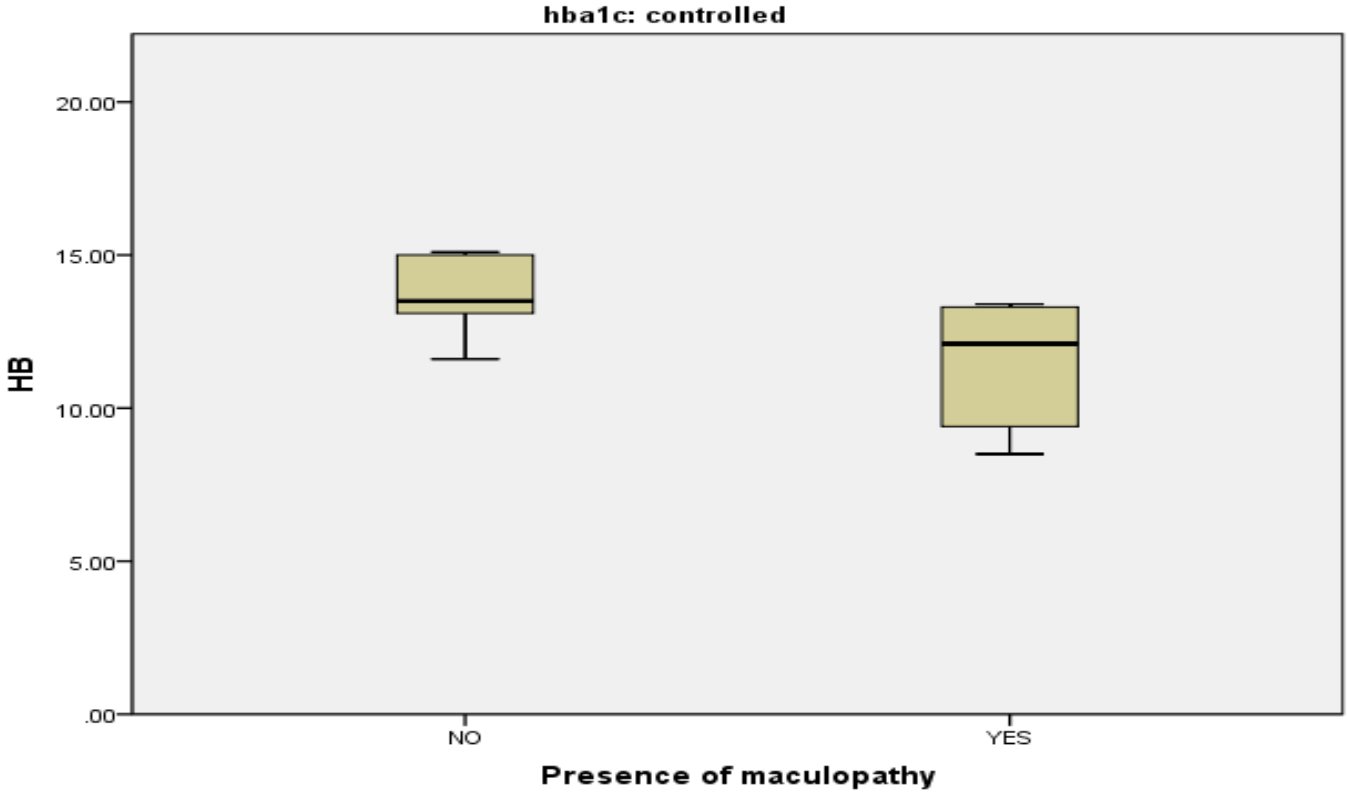
Control of DM		n	Mean Hb	SD	95% CI		Min	Max	p
					Lower	Upper			
Controlled	Early	2	14.5	0.8	6.8	22.1	13.9	15.1	0.011**
	HRPDR	4	9.7	1.3	7.6	11.8	8.5	11.6	
	Total	6	11.3	2.6	8.5	14.1	8.5	15.1	
Uncontrolled	Early	18	11.4	1.7	10.5	12.2	8.6	14.5	0.006**
	HRPDR	20	10	1.1	9.4	10.5	8.4	12.3	
	Total	38	10.6	1.6	10.1	11.2	8.4	14.6	

Figure 7: Relation between Hb value and severity of PDR based on short term glycemic control.



It was observed that the maculopathy and anemia had a significant relation among the subjects with controlled diabetes (p 0.011). Among patients with good short term glycemic control, those with no maculopathy had a mean Hb value of 13.6 gm% ± 1.23, 95% CI =12.7 to 14.5, and those with maculopathy had a mean Hb value of 11.39 gm% ± 2.05, 95% CI= 9.9 to 12.8 (figure 8)

Figure 8: Relation between presence of maculopathy and Hb in controlled diabetes patients



IV. DISCUSSION

Type II Diabetes mellitus is a common disease with an increased incidence in recent decades. Diabetic retinopathy (DR), including diabetic maculopathy, is a microvascular complication of DM and the leading cause of blindness worldwide. [11]The lesions observed in these patients are secondary to microangiopathy and result in increased vascular permeability in the form of edema. Hypoxia is a stimulus for the production of erythropoietin (EPO) and for vascular endothelial growth factor (VEGF). Both EPO and VEGF are neuroprotective factors that possess likely angiogenic potential, leading to an increase in the proliferation of new retinal vessels and thus inducing the development of proliferative retinopathy. Macular edema (ME) may appear at any stage of DR. It is an increase in tissue fluid, which causes a thickening of the retina and secondarily causes structural and functional alterations of retina. [12]Anemia can lead to falsely low HbA1c levels, which may result in under treatment of hyperglycemia, which in turn will contribute to the progression of both microvascular and macrovascular diabetic complications. The etiology of low hemoglobin (Hb) level in diabetes is multifactorial and includes inflammation, nutritional deficiencies, renal disease, concomitant autoimmune disease, drugs and hormonal changes. Anemia is associated with hypoxia. Retinal hypoxia is observed in DR.

The study assessed the association of hemoglobin level and diabetic retinopathy among patients with type II DM and age more than 40 years. It was found that PDR patients were more anemic than NPDR. As the hemoglobin level decreased the disease severity increased.

A positive relationship was observed between anemia and diabetic retinopathy in individuals with type 2 DM. Similar observations were made by [3]Chung JO et al. Anemia was prevalent in the majority of the cases. Anemia causes tissue hypoxia, which is a critical etiology of diabetic retinopathy. Retinal hypoxia is proposed to stimulate synthesis of vascular endothelial growth factor (VEGF), a strong stimulant of neovascularization. This factor also increases vascular permeability and retinal exudates. Individuals with anemia have been reported to have increased systemic levels of VEGF. Therefore, decreased oxygen delivery due to anemia might have detrimental effects on the retina of individuals with diabetes. Additionally, anemia might contribute to increased oxidative stress due to a decrease in the absolute number of red blood cells with antioxidant defense and enhanced free radical production. Irace C and others reported association among low whole blood viscosity, haematocrit, haemoglobin and diabetic retinopathy in subjects with type 2 diabetes. The author comments that Haemoglobin, haematocrit and whole blood viscosity were significantly lower in subjects with retinopathy compared to subjects without retinopathy in both gender. A multiple logistic regression analysis confirmed the independent inverse association among viscosity, haematocrit, haemoglobin and retinopathy ($p<0.01$). [12]Padmaja Kumari Ranil and others observed that presence of diabetic retinopathy with OR 1.82 (95% CI 1.22-2.69) is an independent risk factor for development of anemia.

Anemia was more prevalent in subjects with deranged RFT values. [13]E Ritz and others has noted that anaemia is a frequent complication of diabetic nephropathy. In diabetic patients anemia is seen not only in preterminal renal failure, but also frequently in patients with only minor derangement of renal function. [14]Maurizio Li Vecchi and others mentions that anemia is more frequent in the diabetic patients with CKD than in the non-diabetic patients with CKD (61.7 vs. 52%, $p < 0.05$).

Anemia was more common in subjects with poor diabetic control than that of others. [6]Sharif A and others noticed a higher incidence and risk of anemia poorly controlled diabetes (49.5%) compared to those with controlled diabetes ($p < 0.05$).

Among both genders, PDR patients were more anemic than NPDR. In either group, as the disease severity increased the Hb was found to decrease. In the study by [11]Travaset and others, it is observed that Individuals with severe DR showed significantly lower hemoglobin, hematocrit, and erythrocyte levels compared with those with mild disease. Hemoglobin was the only factor that showed a significant inverse association with the severity of DR [beta-coefficient = -0.52, P value = 0.003]. [15]Irace C Et al found that Haemoglobin, haematocrit and whole blood viscosity significantly decreased with increasing severity of retinopathy.

As blood urea can be affected by hydration and diet, serum creatinine was considered a more reliable parameter than blood urea value for determining nephropathy. Hemoglobin level in PDR was lower than NPDR irrespective of presence of nephropathy. The same was observed in the severity of NPDR and PDR. Among subjects with PDR, a significant relation occurred only in case of non nephropathic patients. Thus anemia can be an independent risk factor determining the type and severity of diabetic retinopathy. [16]Wang J and others reports that DKD severity and anemia had joint effect on NPDR (OR = 2.29, 95% CI = 1.32–3.96) and PDR (OR = 11.31, 95% CI = 5.95–21.51). [17]according to Lee w j and others proliferative diabetic retinopathy is associated with microalbuminuria and DR is associated with overt nephropathy in DM patients.

In subjects with uncontrolled diabetes mellitus, hemoglobin was lower in those with PDR than NPDR. Among those with poor glycemic control, a lower Hb value was observed as the disease severity of NPDR and PDR increased. Anemia with uncontrolled sugar level may determine the type and severity of diabetic retinopathy. [18]Chatziralli IP and others have shown that glycemic control remains an important factor for the presence and progression of DR. HbA1c seems to be an indicator which cannot demonstrate exactly the degree of glycemic control, while sudden variations of blood glucose may play an important

role in DR. Therefore glycemic variability may be useful to predict DM complications, such as DR.

Subjects with anemia had more risk of developing maculopathy, especially males. According to [11]Travaset and others, lower hemoglobin concentration Is associated with retinal ischemia and the severity of Diabetic Retinopathy in Type 2 Diabetes. The authors report that hemoglobin showed a significant inverse association with retinal ischemia [beta-coefficient = -0.49, P value = 0.001]. Lower erythrocyte level showed a marginally significant association with macular oedema [beta-coefficient = -0.86, P value = 0.055].

Anemia and presence of maculopathy showed a significant association in subjects with no nephropathy. However Hb was lower in patients with maculopathy than without maculopathy in both groups. In the study conducted by [19]Eli A Friedman and others, all subjects reported subjective improvement in well-being, including enhanced effort tolerance following an increase in hematocrit from a baseline level of to 29.6 +/- 2.0% to a level of 39.5 +/- 2.4% after one year of treatment with erythropoietin (P = <0.0005). Three patients with macular edema evinced substantive improvement-based stable vision and documented resolution noted in fluorescein.

It was observed that the maculopathy and anemia had a significant relation among the subjects with controlled diabetes. [20]Suto C and others, found that the progression rate of diabetic maculopathy was significantly higher in the group that underwent rapid glycemic control (*P* = .02). [21]S., Kajal and others concluded that the stage of diabetic retinopathy rather than metabolic status is a strong predictive factor for the development of diabetic macular edema.

Limitations of the study:

Smaller subgroup population which might have affected analysis of secondary objectives because of Covid 19 pandemic. Shorter study duration as we did this during internship. Selection bias and berksonian bias can be there because of convenient sampling from hospital visiting people.

V. CONCLUSION

Lower hemoglobin values correlated with the severity of diabetic retinopathy and presence of maculopathy independent of gender and presence of nephropathy. Correcting anemia and maintaining a normal Hb value may delay the onset and progression of diabetic retinopathy and maculopathy in type 2 diabetic adults. Glycemic control also has a role in severity and progression of diabetic retinopathy. Rapid glycemic control can worsen maculopathy among anemics.

REFERENCES

[1]. Ramanjith Sihota and Radhika Tandon. Parson's Diseases of the eye. 23rd edition. Elsevier India 2019.
[2]. www.who.int
[3]. Chung JO, Park SY, Chung DJ, Chung MY. Relationship between anemia, serum bilirubin concentrations, and diabetic retinopathy in individuals with type 2 diabetes. Medicine. 2019 Oct;98(43).
[4]. Bahar A, Kashi Z, Amiri AA, Nabipour M. Association between diabetic retinopathy and hemoglobin level. Caspian Journal of Internal Medicine. 2013;4(4):759.
[5]. A K Khurana. Comprehensive ophthalmology. 7th edition. Jaypee Brothers Medical Publishers 2019.
[6]. Sharif A, Younus S, Baig K, Ali NH. Prevalence and risk of anemia in type-2 diabetic patients. Health. 2014 Jun 9;2014
[7]. Jenchitr W, Samaiporn S, Lertmeemongkolchai P, Chongwiriyanurak T, Anujaree P, Chayaboon D, Pohikamjorn A. Prevalence of diabetic retinopathy in relation to duration of diabetes mellitus in community hospitals of Lampang. J Med Assoc Thai. 2004 Nov;87(11):1321-6. PMID: 15825707.
[8]. www.mayoclinic.org
[9]. www.urmc.rochester.edu
[10]. Damodaran M, Vasudevan and S. Sreekumari.Textbook of Biochemistry for Medical Students. 9th edition. Jaypee Brothers Medical Publishers 2019.
[11]. Traveset A, Rubinat E, Ortega E, Alcubierre N, Vazquez B, Hernández M, Jurjo C, Espinet R, Ezpeleta JA, Mauricio D. Lower hemoglobin concentration is associated with retinal ischemia and the severity of diabetic retinopathy in type 2 diabetes. Journal of Diabetes Research. 2016 Apr 20;2016.
[12]. Ranil PK, Raman R, Rachepalli SR, Pal SS, Kulothungan V, Lakshmipathy P, Satagopan U, Kumaramanickavel G, Sharma T. Anemia and diabetic retinopathy in type 2 diabetes mellitus. J Assoc Physicians India. 2010 Feb 1;58:91-4.
[13]. Ritz E, Haxsen V. Diabetic nephropathy and anaemia. Eur J Clin Invest. 2005 Dec;35 Suppl 3:66-74. doi: 10.1111/j.1365-2362.2005.01544.x. PMID: 16281961.
[14]. Li Vecchi M, Fuiano G, Francesco M, Mancuso D, Faga T, Sponton A, Provenzano R, Andreucci M, Tozzo C. Prevalence and severity of anaemia in patients with type 2 diabetic nephropathy and different degrees of chronic renal insufficiency. Nephron Clin Pract. 2007;105(2):c62-7. doi: 10.1159/000097600. Epub 2006 Nov 29. PMID: 17135770.
[15]. Irace C, Scarinci F, Scorcia V, Bruzzichessi D, Fiorentino R, Randazzo G, Scorcia G, Gnasso A. Association among low whole blood viscosity, haematocrit, haemoglobin and diabetic retinopathy in subjects with type 2 diabetes. British Journal of Ophthalmology. 2011 Jan 1;95(1):94-8.

[16]. Wang J, Xin X, Luo W, Wang R, Wang X, Si S, Mo M, Shao B, Wang S, Shen Y, Chen X, Yu Y. Anemia and Diabetic Kidney Disease Had Joint Effect on Diabetic Retinopathy Among Patients With Type 2 Diabetes. Invest Ophthalmol Vis Sci. 2020 Dec 1;61(14):25. doi: 10.1167/iovs.61.14.25. PMID: 33351059; PMCID: PMC7757636.
[17]. Lee WJ, Sobrin L, Lee MJ, Kang MH, Seong M, Cho H. The relationship between diabetic retinopathy and diabetic nephropathy in a population-based study in Korea (KNHANES V-2, 3). Investigative ophthalmology & visual science. 2014 Oct 1;55(10):6547-53.
[18]. Chatziralli IP. The Role of Glycemic Control and Variability in Diabetic Retinopathy. Diabetes Ther. 2018 Feb;9(1):431-434. doi: 10.1007/s13300-017-0345-5. Epub 2017 Nov 30. PMID: 29190012; PMCID: PMC5801231
[19]. Friedman EA, Francis Jr A, Brown CD, Berman DH. Treating azotemia-induced anemia with erythropoietin improves diabetic eye disease: Management of comorbidities in kidney disease in the 21st century: Anemia and bone disease. Kidney International. 2003 Nov 1;64:S57-63.
[20]. Suto C, Hori S, Kato S, Muraoka K, Kitano S. Effect of perioperative glycemic control in progression of diabetic retinopathy and maculopathy. Arch Ophthalmol. 2006 Jan;124(1):38-45. doi: 10.1001/archopht.124.1.38. PMID: 16401783.
[21]. S., Kajal, Jayalekshmi T., Manasa S., & Prasenna M.. "Effect of glycemic control on diabetic retinopathy and diabetic macular edema: a prospective observational study." International Journal of Advances in Medicine [Online], 8.2 (2021): 177-182. Web. 8 Jul. 2021