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Is it of Importance to Estimate Hba1c Excursion among Type 2 Diabetis Mellitus Patints with Diabetic Retinopathy

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Abstract
Diabetic Retinopathy (DR) continued to be the leading cause of sight threatening in the middle – age population with diabetes mellitus that affect job performance and quality of life for millions of people word wide. Glycated hemoglobin (HbA1c) identified as modifiable risk factors for DR, in addition to its importance in the diagnosis and as an index of glycemic control, so that the absolute HbA1c value and/or variability were included in many studies and researches for their implication to both microvascular and macrovascular complications of diabetes. The study aims to see the pattern and risk factor(s) of DR, and whether the estimation of HbA1c excursion is of importance as associated risk or index in among type 2 diabetic patients. This is an observational descriptive cross sectional study involved 404 type 2 diabetic patients attending Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC) and the outpatient clinic in Faiha Teaching Hospital, in Basra, Southern Iraq between May2017–August2018. All of them were registered in the center, with their demographic, clinical, and biochemical parameters and at least 3 HbA1c readings in the last year that were taken for estimation of HbA1c mean and excursion, and they were send for full comprehensive ophthalmological assessment. The total number of the patients were 404, 157 (38.9%) male, 247 (61.1%) female. Mean age was 56.12 ± 9.58, range 31-88 years. The mean HbA1c was 9.86 ± 2, the mean HbA1c excursion evaluated in 266 patients was 2.49±1.73, the positive excursion was 2.26 ± 1.63 and the negative excursion was – 2.7 ±1.78. Diabetic retinopathy was found in 168(41.6%), background diabetic retinopathy 50 (12.4%) preproliferative diabetic retinopathy 10(2.5%), proliferative diabetic retinopathy 47(11.6%). Maculopathy found in 71 (17.6%), with exudative type 62 (15.3 %) and ischemic type in 9 (2.2 %). Conclusions: Age ≥85, duration of diabetes ≥8years, the mean maximum HbA1c ≥12.8 are independent risk for the development of DR, Age ≥45, duration of diabetes ≥4 years, BMI ≤37.5 the mean HbA1c ≥10 were independent risk for the development of diabetic maculopathy. Mean HbA1c excursion has no relation with development of DR or maculopathy, but only with subtypes of DR (background diabetic retinopathy, proliferative diabetic retinopathy).
Keywords: Diabetic retinopathy (DR), Maculopathy, HbA1c, HbA1c excursion

Abbreviations :

DR Diabetic retinopathy .

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BGDR Background diabetic retinopathy
PPDR Preproliferative diabetic retinopathy.
PDR Proliferative diabetic retinopathy.
FDEMC Faiha Specialized Diabetes, Endocrine and Metabolism Center.
T1DM Type 1 DM
T2DM Type 2 DM
FBG Fasting blood glucose.
PPG Postprandial glucose.
CGM Continuous glucose monitoring.
i CGM intermittently viewed glucose monitoring.
MAGE Mean amplitude glucose excursion.
HbA1c Glycated hemoglobin
DCCT Diabetes Control and Complications Trial
UKPDS United Kingdom Prospective Diabetes Study
ACCORD Action to Control Cardiovascular Risk in Diabetes
DESIR Data from an Epidemiological Study on the Insulin Resistance Syndrome
NSC National Screening Committee
OCT Optical coherence tomography
WESDR Wisconsin Epidemiologic Study of Diabetic Retinopathy

Introduction

Patients with diabetes often develop ophthalmic complications, such as corneal abnormalities, glaucoma, iris neovascularization, cataracts, and neuropathies. Diabetic retinopathy (DR) is the most common and potentially most blinding of these complications. [1, 2, 3] Risk factors for developing/worsening of DR include; the modifiable risk factors like the glycemic control, systemic hypertension, blood lipids, and smoking in type 1 diabetes, and non-modifiable risk factors like the duration of diabetes, age, genetic predisposition, ethnicity, and pregnancy. [4, 5]

It is expected that by 2035,there will be 592 million of peoples worldwide will have diabetes [6], and because T2DM account for more than 90-95%of diabetic population so they account for higher fraction of patient with vision loss due to DR, that result from chronic eye damage from hyperglycemic in both type 1 and type 2 diabetes, and well –established chronic microvascular complication that eventually afflict all patients with diabetes mellitus ,[7] and continued to be the leading cause of vision deterioration in the middle – age population with diabetes mellitus that affect job and quality of life for millions of people word wide. The National Health and Nutrition Examination Survey suggest that lack of awareness among patients at risk of vision loss from diabetic eye complications and inadequate evaluation in risky patients for visual loss, [8] are the main causes, so that it necessitate well understanding the associated risk factors for the progression of DR, and early detection with improved strategies for follow up and better efforts for good glycemic control.

Physicians in daily practice, utilize quantitative parameters such as fasting, postprandial glucose and Glycated hemoglobin (HbA1c). HbA1c is the current gold standard for assessing glycemic control, which represent the percentage of circulating hemoglobin that is glycated, and is used as an index of blood glucose monitoring, which estimate the average blood glucose in the preceding few months in addition to its value as modifiable risk factors for DR. [9,10] However HbA1c it only provides

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approximate measure of glucose control, and not link to short term glycemic variability or events of hypoglycemia , because for a given HbA1c value there is a wide range of mean glucose concentration values and for any given mean glucose value there is a wide range of HbA1c value , and does not reflect the glycemic excursion which have been linked to both microvascular and macro vascular complications of diabetes [11] .The absolute value and variability of HbA1c were included in many studies and researches for different purposes ,and the HbA1c variability proposed to contribute to development of microvascular complications in T1DM in diabetes control and complications trial (DCCT) like retinopathy and nephropathy . [12]
Fasting blood glucose (FBG) and HbA1c were well studied in the Data From an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) Study, in which evaluation for DR in 235 individuals with diabetes and 227 individuals with impaired fasting plasma glucose levels. [13] The study found that the risk of developing DR at 10 years was higher in individuals with a FBG level of more than 108 mg/dl and HbA1c level of more than 6%. The DCCT showed that intensive insulin therapy in T1DM, reduced or prevented the development of retinopathy by 27% as compared with conventional therapy. Also, intensive therapy reduced the progression of DR by 34–76%, and need for ocular surgery later. This improvement was achieved with an average 10% reduction in HbA1c from 8% to 7.2%. Similar benefit also demonstrated for T2DM. The results of the DCCT, United Kingdom Prospective Diabetes Study (UKPDS), and Action to Control Cardiovascular Risk in Diabetes (ACCORD) Eye Study showed that; while intensive therapy does not prevent retinopathy completely, it reduces the risk of the development and progression of DR, and this effect is not persistent and declined over time. [14]

The glycemic control monitoring was extensively studied using several indices that have been proposed for quantitative evaluation the glycemic variability in addition to the conventional methods by HbA1c value and variability like fasting (FBG) and postprandial sugar (PPG), continuous or intermittently viewed glucose monitoring (CGM, iCGM), real time CGM (rt CGM) and mean amplitude of glycemic excursion (MAGE).The CGM provide additional details on the patterns of glucose variability and glycemic excursions. The importance of the later measures have been studied for monitoring glycemic control and the results were varies, one of the studies showed that in T2DM patients, the continuous variability of FBS was found to have association with DR progression in a 5 year follow-up, [15] while in other study in elderly patients, it was found that it is the magnitude of hyperglycemia, measured by mean FBG and HbA1c, that strongly predicted the development and progression of DR [16]. Furthermore, it has been reported that patients with more advanced DR didn't get or spent enough time stabilized in the target range and have higher measures of glucose variability. [17]

Based on the way how to estimate the MAGE, we estimate the HbA1c excursion from the serial readings of HbA1c, [18, 19]

Methodology

This is an observational descriptive cross sectional study involved 404 T2DM patients attending Faiha Specialized Diabetes, Endocrine and Metabolism Center (FDEMC) and outpatient clinic in Faiha Teaching Hospital, in Basra, Southern of Iraq

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between May2017–August 2018. Patients fit the criteria were involved in the study after taken a verbal consent. The inclusion criteria were those who fit the definition of T2DM and have previous record at least one year with or without treatment, and excluded patients were T1DM, gestational or drug related DM, previous eye surgery or blindness in one or both eyes .All of them were registered in the center, with their demographic, clinical, and biochemical parameters and at least 3 HbA1c readings in the last year to estimate mean HbA1c, but the serial readings HbA1c more than 3 were used for estimation of the excursion of HbA1c, and the results were either in a positive , negative or neutral .And they were send for comprehensive ophthalmological assessment ,the examination included visual functions like visual acuity by Snellen chart, visual field examination by standard perimeter and also anterior and posterior examination of the both eyes by Zeiss type slit lamp with or without auxiliary lenses. The posterior pole of the eyes examined by optical coherence tomography (Zeiss Ciruss HD- OCT), fundus florescence angiography and OCTA. Intraocular pressure (IOP) was measured in all patients by Tomey automated air-puff tonometer.

DR was classified according to National Screening Committee (NSC). The NSC classification adopts a simplified approach for grading of DR, which is proposed for use in population screening, based on features which a non-ophthalmologist / accredited photographic grader might be faced with in a population of diabetic patients, which have simplicity and average similarity with other many other classifications.[20]

For HbA1c analysis, all the samples were analyzed at FDEMC laboratory by using Bio-Rad Variant II Turbo (Bio-Rad, USA) Ion exchange HPLC method.

The definition of T2DM and the reference ranges of blood glucose and HbA1c were depended on the guidelines from American Diabetes Association. [21]

Statistical analysis

Data statistical analysis was by using IBM SPSS Statistic for Windows, version 23.0 (IBM Corp.,Armonk , NY,USA). [22] Univariate analysis was done using chi-square test for categorical variable, while a student t-test or the one way ANOVA with post hoc analysis were used for continuous variables. Binary logistic regression or multinomial logistic regression as appropriate were used for defining independency of the factors affecting retinopathy and maculopathy. HbA1c excursion was calculated as the difference between each successive readings of HbA1c, taking only the highest excursion for each patient and omitting the other values, and by calculation of the mean of the unsigned values of these maximum excursion for all the patients we got the mean of the absolute excursion. By using only the highest positive excursion for each patient we got the positive HbA1c excursion, and by using only the maximum negative excursion.

Data were presented as number and percent or mean and standard deviation. A p-value of less than 0.05 was considered as significant.

Results

The total number of the patients were 404, 157 (38.9%) male, 247 (61.1%) female. Mean age was 56.12 ± 9.58 SD, range 31-88 years. The mean duration of diabetes was 11.09 ±7.74 SD , with minimum duration one year .The mean HbA1c was 9.86 ± 2 SD, the mean HbA1c excursion evaluated in 266 patients was 2.49±1.73 SD , the positive excursion was 2.26 ± 1.63 and the negative excursion was – 2.7 ±1.78SD. Diabetic retinopathy (DR) was found in 168(41.6%), background diabetic retinopathy

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(BGDR) 50 (12.4%) preproliferative diabetic retinopathy (PPDR) 10(2.5%), proliferative diabetic retinopathy (PDR) 47(11.6%). Maculopathy was found in 71 (17.6%), with exudative type 62 (15.3 %) and ischemic type in 9 (2.2 %). Ten patients were have coexistent of both DR and maculopathy. The age, duration of diabetes, body mass index (BMI), insulin use, mean and maximum HbA1c value were strongly related to DR, while in patients with maculopathy BMI did not show this relationship. HbA1c excursion also did not show significant association with DR nor maculopathy. Binary logistic regression revealed that only the duration of diabetes was an independent factor for the development of DR. However, if we omit the duration of diabetes and the age from the equation (obviously they are strongly correlated $r = 0.31$, $p<0.001$), then BMI and insulin usage appeared as independent factors. For maculopathy, binary logistic regression showed that only duration of diabetes was an independent factor, and with the exclusion of both the age and duration of diabetes from the equation, only insulin usage remains as an independent factor for the development of maculopathy.

In evaluation of subtypes of DR, Post Hoc multiple comparison analysis showed that the mean duration of diabetes in patients with PDR is significantly higher than that of patients with BGDR, and that a significantly higher BMI and a higher Positive HbA1c excursion was found in patients with BGDR than in patients with PPDR. With multinomial logistic regression, it appears that only a higher absolute excursion of the HbA1c is significantly associated with BGDR.

In tables 6 and 7, nearly all the risk factors apart of gender, have significant relation, while by binary logistic regression ; age ≥58, duration of diabetes ≥ 8 years, and the mean of maximum HbA1c ≥ 12.8 , were independent risk for DR, while age ≥ 45 years , duration of ≥ 4 year ,BMI ≤ 37,5, and mean HbA1c ≥ 10 , were independent higher risk for maculopathy.

Discussion

The natural history of progression of DR from no or mild stage of non-proliferative (NPDR) preproliferative diabetic retinopathy (PPDR), to advanced state proliferative diabetic retinopathy (PDR), with high risk of visual problems. While macular edema, can develop at all stages of retinopathy. In people with T2DM, retinopathy may be present in 21% to 39% soon after clinical diagnosis, but is sight-threatening in only about 3%, and most develop some degree of retinopathy over time. [23] The Liverpool Diabetic Eye Study reported the 1-year cumulative incidence of sight-threatening diabetic retinopathy in individuals with T2DM ,who at baseline had no DR, had BGDR or had mild NPDR, the incidence was 0.3%, 5.0% and 15.0%, respectively. [24]

In this study, DR was seen in 41.6% and maculopathy in 17.6% of the studied sample. The age, duration of DM, insulin therapy, and the mean HbA1c were associated with DR. This is explained after looking to the general characteristics of the patients enrolled in this study, were most of them are old age (21%more than 65 year, and more than 50% age 51-65 year) and have long duration of the DM (85% , 8-≥15 years), and have high HbA1c(more 59% of patients HbA1c 9-≥11%). Most of these finding are in agreement with many published studies. DR is the most frequent

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cause of new cases of blind-ness among adults at the age 20 –74 years. Retinopathy may be seen during the first two decades of disease, where nearly all patients with T1DM and60% of patients with T2DM have DR. In the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR), 1.6% of T2DM were legally blind. In this group, in which other eye diseases were common, one third of the cases of legal blindness were due to DR. [25] The duration of diabetes is closely associated with onset and severity of DR since nearly all patients with T1DM and 60% of patients with T2DM develop some degree of retinopathy after 20 years, [26, 27, 28] and HbA1c high levels have strong relation with maculopathy and a severe form of DR , [29] and in three landmark trials in patients with type 2 DM showed that lower HbA1c levels are associated with reduced onset or progression of some microvascular complications. [30,31,32] , In evaluation of BMI in patients with DR and the subtypes in this study, more than 65% of patients BMI above 30%, and only 10% their BMI was more than 40%, show a statistical significance with DR, while didn't show that with maculopathy group. Although both BGDR and PDR have same percentage, but the BMI was different where higher BMI in the former and low in the later and this may be explained by the decrease in the BMI with advance in the age, which may be explained by decrease in the muscle mass with long duration of the disease (sarcopenia) [33], which is seen in this study .This differ from the findings from Turkish study that revealed a significant direct relationship between BMI and PDR. [34]

HbA1c excursion estimation didn't show significance only when compared to the subtypes of DR, where positive HbA1c excursion have a relation with BGDR and PDR, and no relation to the subtypes of maculopathy. The use of continuous glucose monitoring CGM can improve the MAGE results which in turn reflected as glycemic control in persons with type 2 DM [35], but the MAGE, in published studies didn't reflected by the HbA1c value, in contrary it overcome the limitations of HbA1c in diabetes management. The hypothesis for the HbA1c excursion estimation was built from a literature namely "A view beyond HbA1c: Role of Continuous Glucose Monitoring", [36] that discuss the impact of novel metrics on diabetes related complications, the usefulness of CGM in the treatment of T2DM, and the impact of newer glucose lowering therapies like SGLT inhibitors or GLP-IRAs, noval long-acting insulin analogs, and ultra-fast acting prandial insulin that reduce glycemic variability. Until this issue was addressed, no previous studies mentioned it, and its role or validity perhaps may be related to the changes or variability of HbA1c itself, and may need to be reevaluated again.

The relation of insulin therapy with progression of DR in this study was obvious for both retinopathy and maculopathy, although the indication , types and the protocol of insulin therapy as adjuvant or intensification or initial therapy, and the duration since it was started were not included or focused on, to prove this association. And this finding strengthen by the observation from DCCT and other studies. In a summary of the important studies and the controversies about this topic, it was found in UKPDS that 21% reduction in one year rate of progression of DR and with DCCT, there was 70% reduction in the rate of development of any retinopathy by intensive glycemic control in T1DM, and 54% reduction of established retinopathy in comparison with conventional therapy group, the same benefit also seen in T2DM. While other finding from DCCT, that the development or progression of retinopathy may be accelerated by sudden, rapid improvement in glycemic control, pregnancy and in those with nephropathy, a relationship between the degree of improvement in HbA1c and

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progression of retinopathy 2 years after the start of insulin therapy in type 2 diabetic patients. [37] And in a in a prospective, observational case-control study, 42 T2DM patients were examined at baseline and 1, 3, 6, 12, 24, and 36 months after change to insulin therapy, there was a relationship found with high IGF-1 levels, [38] and a relationship between the degree of improvement in HbA1c and progression of retinopathy 3 years after the start of insulin therapy in type 2 diabetic patients, may be explained by a lack of decrement in IGF-1, after 3 years from start of insulin therapy . [39] The later study was small but raises questions about the relationship between DR, hyperglycemia, insulin therapy, and IGF-1.

The established risk factors for DR or maculopathy are; longer duration of diabetes, elevated HbA1c, were also seen in this study, but other factors like; increased blood pressure (BP), dyslipidemia, anemia, pregnancy (with type 1 diabetes), proteinuria weren't evaluated in this study. [40]

Conclusion:

Mean HbA1c excursion may have doubtful relation association or as a risk with development of DR or maculopathy, but only with subtypes of DR (BGDR, and PDR). Age ≥85, duration of diabetes ≥8years, the mean maximum HbA1c ≥12.8 are independent risk for the development of DR, Age ≥45, duration of diabetes ≥4 years, BMI ≤37.5, the mean HbA1c ≥10 were independent risk for the development of diabetic maculopathy. Also there is a raised question about the relation of increased DR in insulin treated patients, that necessitate more awareness when start or intensify insulin therapy by close and regular follow up.

Recommendation:

Every patients newly diagnosed DM, and some other subset of patients should have ophthalmologic assessment, and special care to those who need to be changed or intensified therapy by insulin therapy. Also this concept of relation of insulin therapy with development or progression of DR need to be clarified more.

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Tables and figures

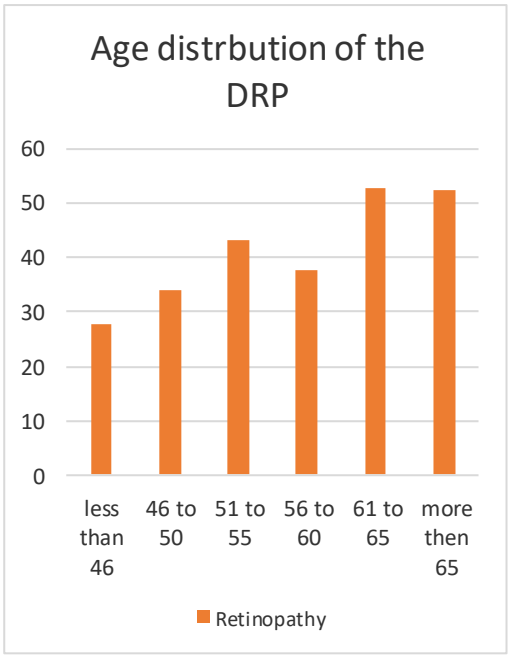
Table 1 general characteristics of the patients
N=404

		N or mean	% or SD	Range	
				Minimum	Maximum
Age		56.12	9.58	31	88
Gender	Males	157	38.9	-	-
	Females	247	61.1	-	-
Duration of Diabetes		11.09	6.74	1	35
BMI		30.60	5.54	17.70	51.10
On insulin	yes	291	72	-	-
	no	113	28	-	-
Mean A1c		9.86	2.00	4.90	15.20
Max a1c		10.87	2.29	4.90	19.5
Min a1c		8.96	2.04	4.90	15.20
Abs A1c excursion*		2.49	1.73	0.00	8.60
Positive excursion**		2.26	1.63	0.20	8.40
Negative excursion***		-2.70	1.78	-8.60	-0.20
Retinopathy		168	41.6	-	-
BGDR		50	12.4	-	-
PPDR		10	2.5	-	-
PDR		47	11.6	-	-
Maculopathy		71	17.6	-	-
Exudative MP		62	15.3	-	-
Ischemic MP		9	2.2	-	-

*n=266, **n=117, ***n=147

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
Received 25 April 2021; Accepted 08 May 2021.

Figure 1 percentage of DRP.



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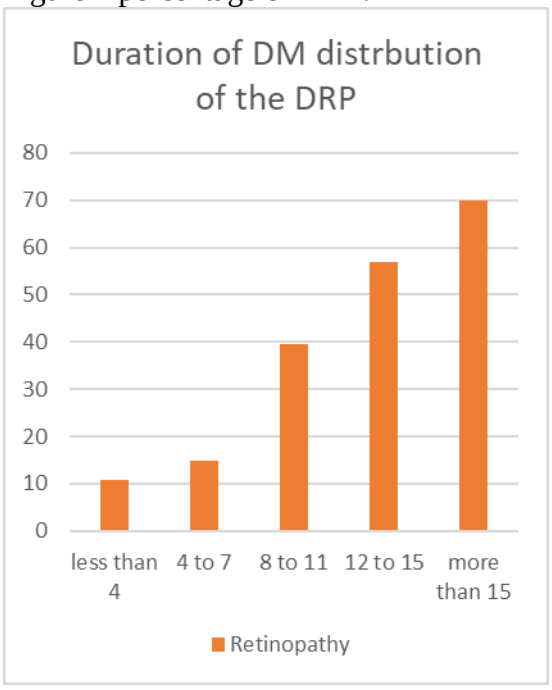
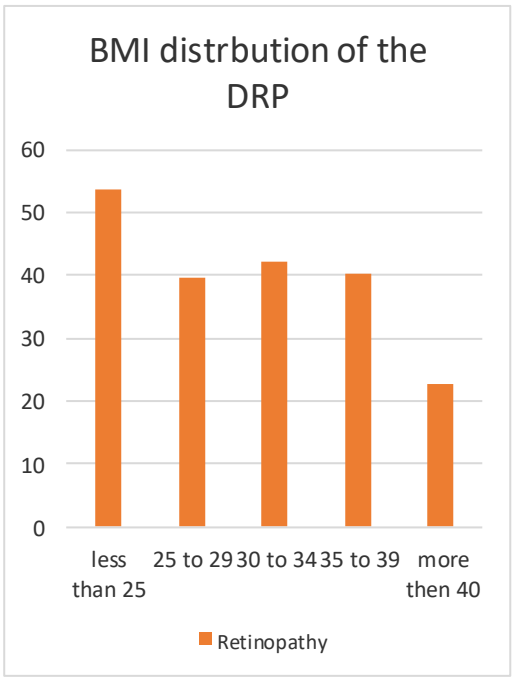


P<0.001



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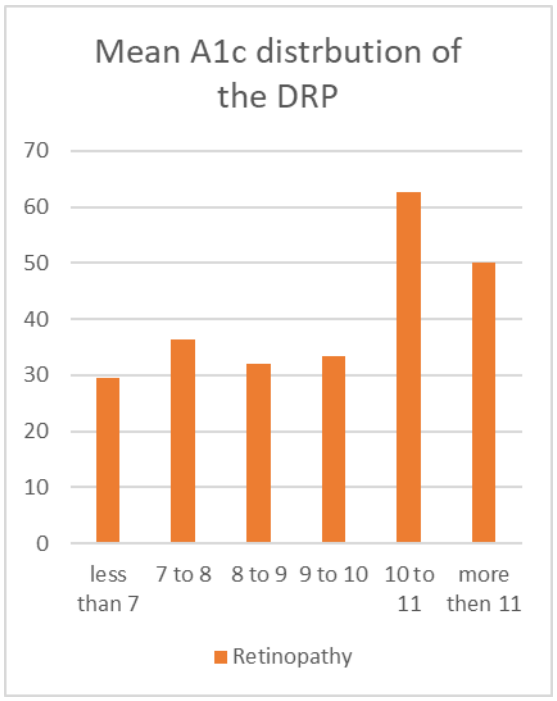


P=0.019

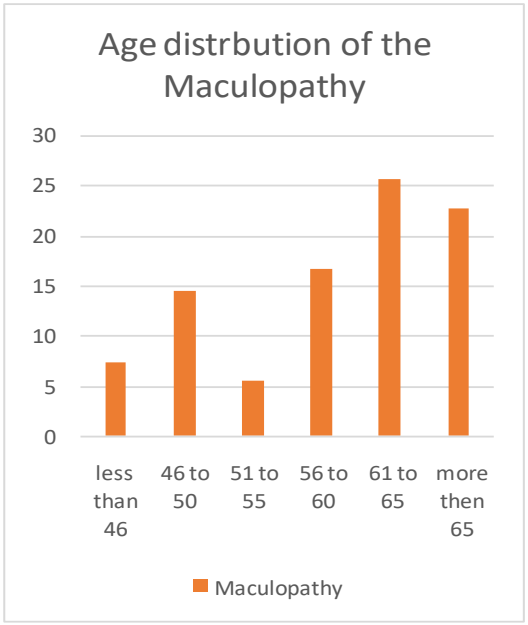
Table 2 general characteristics of the patients with DRP N=404			
	DRP		P
	Yes	No	

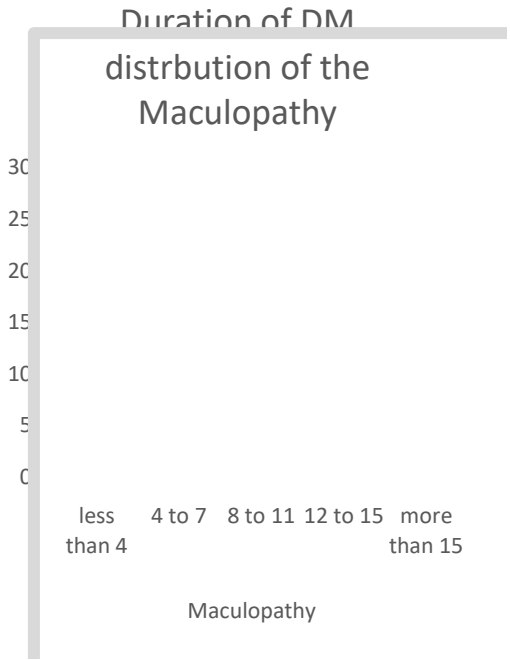
Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
Received 25 April 2021; Accepted 08 May 2021.

		N or mean	% or SD	N or mean	% or SD	
Age		57.90	8.96	54.86	9.82	0.002
Gender	Males	103	61.3	144	61.0	0.518
	Females	65	38.7	92	39.0	
Duration of Diabetes		14.30	6.42	8.81	6.00	<0.001
BMI		29.95	5.27	31.06	5.70	0.048
On insulin	yes	145	86.3	146	61.9	<0.001
	no	23	13.7	90	38.1	
Mean A1c		10.20	1.94	9.62	1.93	0.003
Max a1c		11.37	2.42	10.52	2.13	<0.001
Min a1c		9.12	2.00	8.85	2.06	0.194
Abs A1c excursion*		2.71	1.80	2.31	1.67	0.059
Positive excursion**		2.37	1.79	2.19	1.51	0.561
Negative excursion**		-2.96	1.78	-2.46	1.78	0.095
*n=266, **N=117, ***N=147						

Binary logistic regression revealed that only the duration of diabetes is an independent factor for the development of DRP.
However, if we omit the duration of diabetes and the age from the equation (obviously they are strongly corelated r=0.31,p<0.001), then BMI and insulin usage appeared as independent factors.

Figure 2 percentage of maculopathy





P=0.018

P<0.001

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
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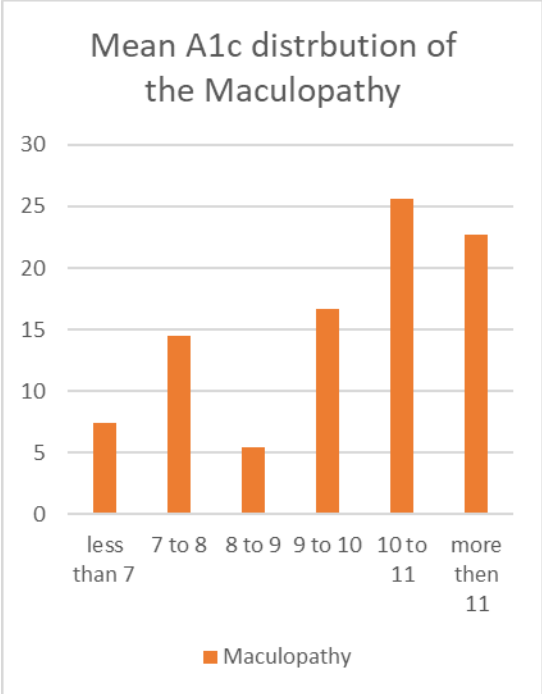
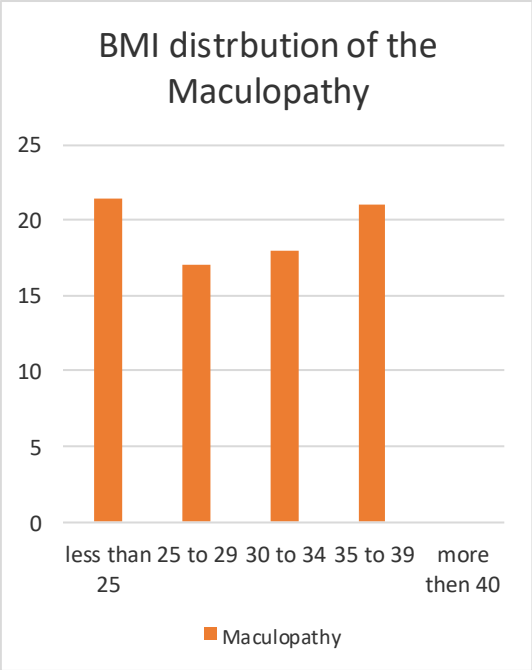




P=0.216

P=0.018

Table 3 general characteristics of the patients with Maculopathy
N=404

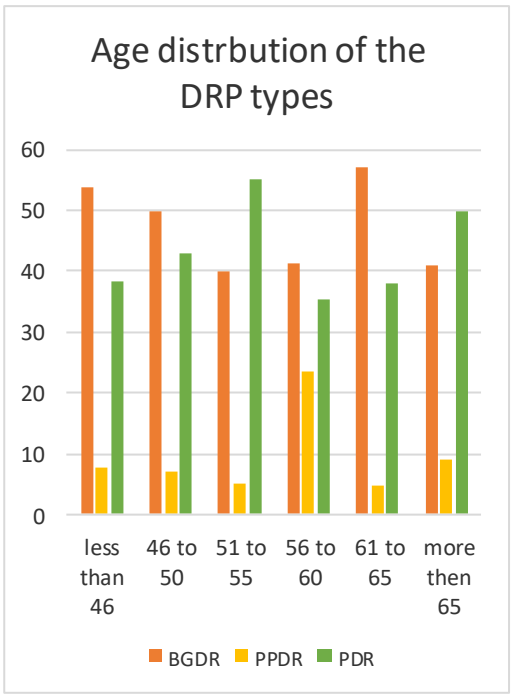
		Maculopathy				P
		Yes		No		
		N or mean	% or SD	N or mean	% or SD	
Age		58.66	8.30	55.58	9.76	0.014
Gender	Males	28	39.4	129	38.7	0.913
	Females	43	60.6	204	61.3	
Duration of Diabetes		13.68	5.50	10.54	6.85	<0.001
BMI		29.89	4.54	30.75	5.73	0.236
On insulin	yes	61	85.9	230	69.1	0.004
	no	10	14.1	103	30.9	
A1c		10.45	1.90	9.74	1.95	0.005
Max a1c		11.42	2.46	10.76	2.24	0.027
Min a1c		9.43	1.97	8.87	2.04	0.035
Abs A1c excursion*		2.68	2.00	2.45	1.70	0.420
Positive excursion**		2.26	1.60	2.27	1.65	0.992
Negative excursion***		-3.11	2.12	-2.62	1.72	0.239

*n=266, **n=117, ***n=147

Again, for maculopathy, binary logistic regression showed that only duration of diabetes is an independent factor, and with the exclusion of both the age and duration of diabetes from the equation, only insulin usage remains as an independent factor for then development for maculopathy.

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
Received 25 April 2021; Accepted 08 May 2021.

Figure 3 percentage of subtypes of diabetic retinopathy



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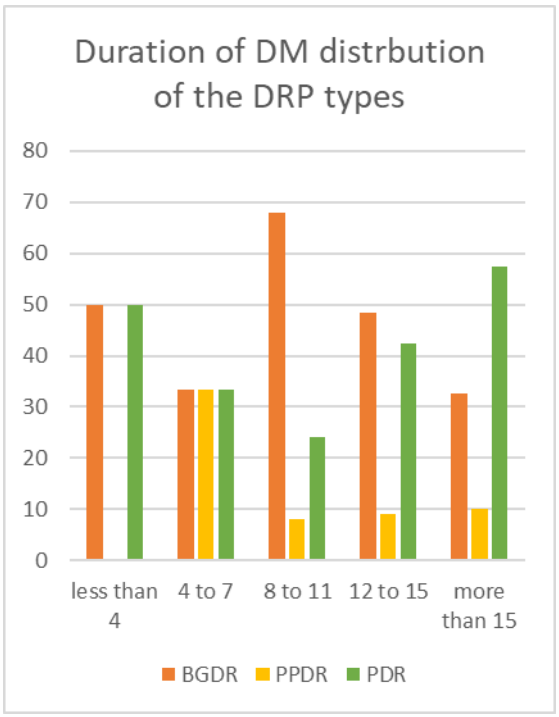

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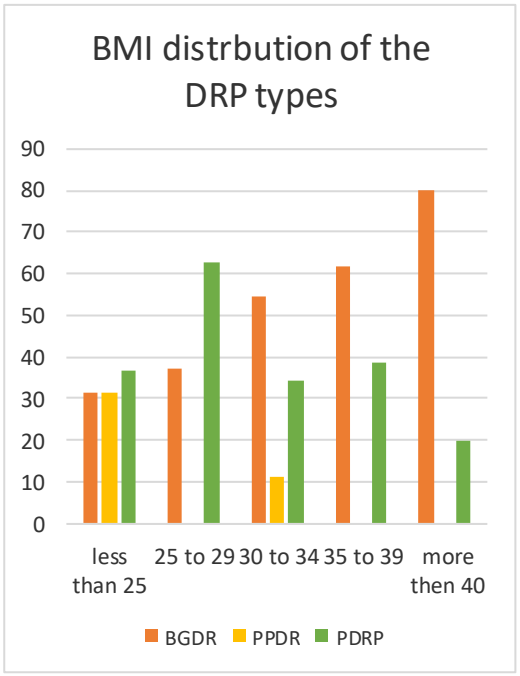

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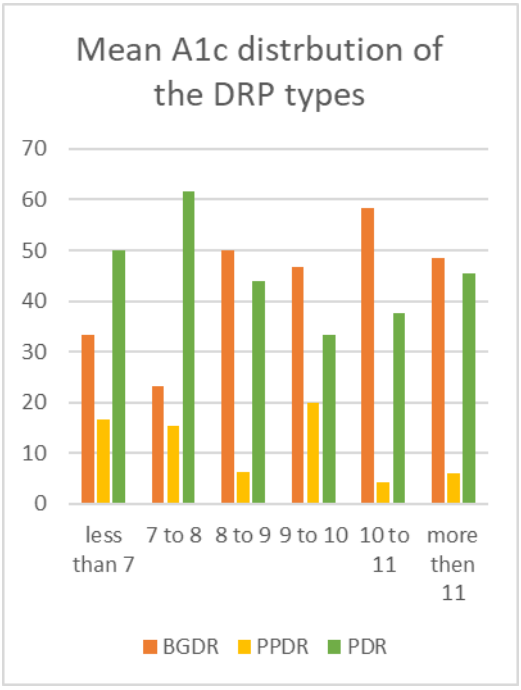


P=0.625

Table 4 general characteristics of the patients with types of DRP N=107				
	DRP			p
	BGDR	PPDR	PDR	

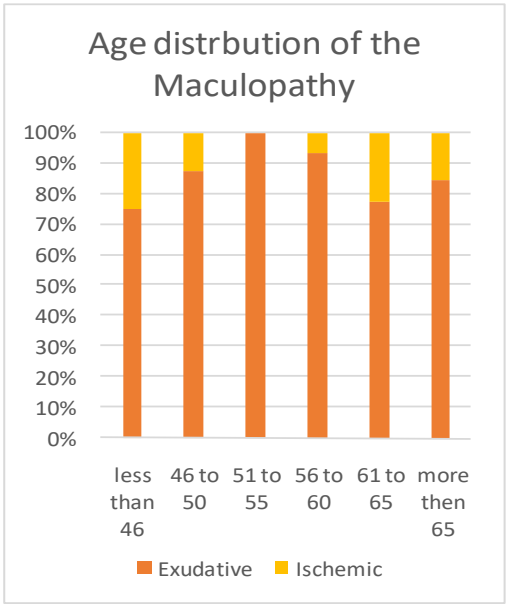
Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
Received 25 April 2021; Accepted 08 May 2021.

		n/Mean	%/SD	n/Mean	%/SD	n/Mean	%/SD	
Age		57.16	9.16	60.20	11.06	57.53	9.46	0.650
Gender[$]	Males	17	34.0	3	30.0	21	4.7	0.474
	Females	33	66.0	7	70.0	26	55.3	
Duration of Diabetes		13.30	5.98	13.90	5.04	16.85	8.16	0.042[a]
BMI		31.46	5.99	26.57	5.45	29.45	4.92	0.023[b]
On Insulin[$]	Yes	42	84.0	10	100.0	41	87.2	0.390
	No	8	16.0	0	0.0	6	12.8	
Mean A1c		10.25	1.67	9.27	1.69	10.01	2.11	0.337
Max A1c		11.72	2.19	10.13	2.37	11.25	2.56	0.148
Min A1c		8.86	1.70	9.00	1.86	8.97	2.25	0.959
Abs A1c excursion*		3.23	1.56	1.23	0.64	2.59	1.84	0.017[b]
Positive excursion**		2.97	1.80	1.00	0.50	2.34	2.01	0.249
Negative excursion***		-3.37	1.44	-1.47	0.78	-2.75	1.75	0.101

*n=80, **n=30, ***n=50, [a]: Significance between BGDR and PDR, [b]: Significance between BGDR and PPDR, [$]: Data expressed as n %.

Post Hoc multiple comparison analysis showed that the mean duration of diabetes in patients with PDR is significantly higher than that of patients with BGDR, and that a significantly higher BMI and a higher Positive HbA1c excursion was found in patients with BGDR than in patients with PPDR.
With multinomial logistic regression, it appears that only a higher absolute excursion of the HbA1c is significantly associated with BGDR.

Figure 4 percentage types of subtype of maculopathy.



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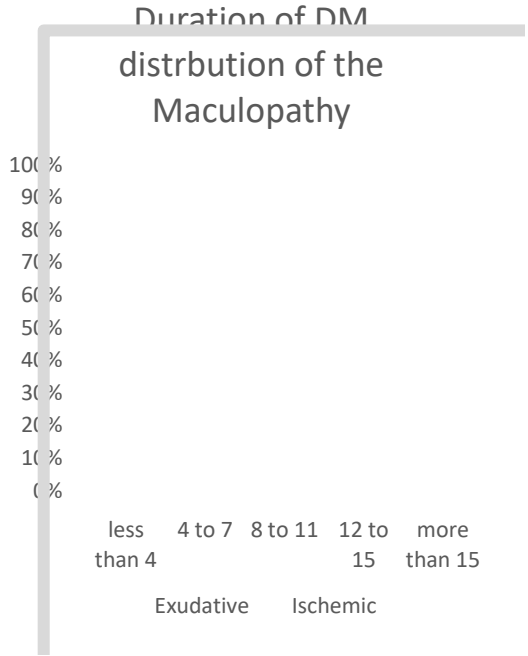

P<0.326

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
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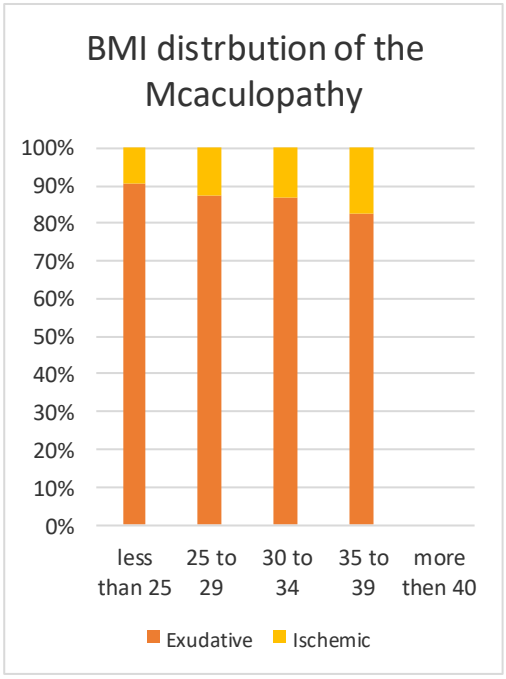
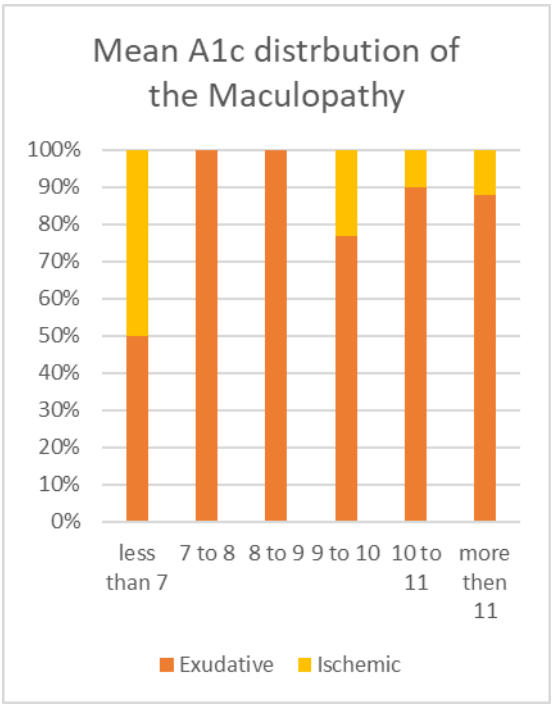


P=0.944



P=0.335

Table 5 general characteristics of the patients with types of Maculopathy N=71

		Maculopathy				P
		Exudative		Ischemic		
		N or mean	% or SD	N or mean	% or SD	
Age		58.44	8.33	60.22	8.41	0.550
Gender$	Males	25	40.3	3	33.3	0.494
	Females	37	59.7	6	66.7	
Duration of Diabetes		13.31	5.32	16.22	6.36	0.138
BMI		29.81	4.54	30.46	4.74	0.690
On insulin$	yes	53	85.5	8	88.9	0.628
	no	9	14.5	1	11.1	
A1c		10.45	1.86	10.43	2.25	0.976
Max a1c		11.39	2.31	11.64	3.49	0.770
Min a1c		9.47	2.01	9.14	1.72	0.649
Abs A1c excursion*		2.62	1.82	3.02	2.51	0.642
Positive excursion**		2.26	1.67	2.30	0.85	0.972
Negative excursion***		-3.05	1.94	-3.38	3.13	0.789
*N=45, **N=23, ***N=22,$:Data expressed as n %.						

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 14857 - 14875
Received 25 April 2021; Accepted 08 May 2021.

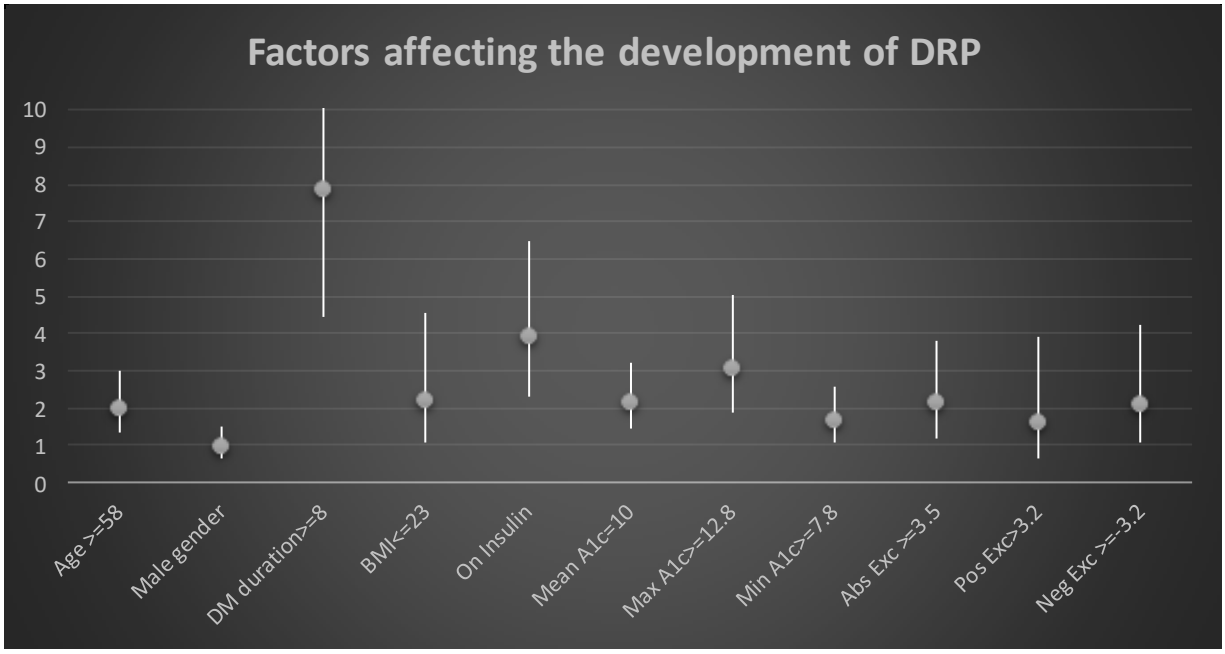


Figure 21 risk estimates for different factors affecting the development for DRP.

Table 6 Factors affecting the development of diabetic retinopathy

		Retinopathy				OR	95% CI		P
		Yes		no					
		n	%	n	%		lower	upper	
age	>=58	89	51.1	85	48.9	2.00	1.34	3.00	0.001
	<58	79	34.3	151	65.7				
gender	Males	65	41.4	92	58.6	0.99	0.66	1.48	0.953
	Females	103	41.7	144	58.3				
Duration	>=8	152	54.1	129	45.9	7.88	4.43	14.01	<0.001
	<8	16	13.0	107	87.0				
BMI	<=23	19	59.4	113	40.6	2.19	1.05	4.56	0.033
	>23	149	40.1	223	59.9				
insulin	Yes	145	49.8	146	50.2	3.89	2.33	6.49	<0.001
	No	23	20.4	90	79.6				
A1c	>=10	102	50.7	99	49.3	2.14	1.43	3.20	<0.001
	<10	66	32.5	137	67.5				
Max A1c	>=12.8	53	63.1	31	36.9	3.05	1.85	5.02	<0.001
	<12.8	115	35.9	205	64.1				
Min A1c	>=7.8	124	45.6	148	54.4	1.68	1.09	2.59	0.019
	<7.8	44	33.3	88	66.7				
Abs A1c excursion*	>=3.5	36	59.0	25	41.0	2.12	1.18	3.79	0.011
	<3.5	83	40.5	122	59.5				
Positive A1c excursion**	>=3.2	13	52.0	12	48.0	1.61	0.66	3.92	0.291
	<3.2	37	40.2	55	59.8				
Negative A1c excursion***	>=-3.2	29	59.2	20	40.8	2.10	1.05	4.22	0.035
	<-3.2	40	40.8	58	59.2				

*n=266, **N=117, ***N=147

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Binary logistic regression showed that: age equal or above 58, duration of diabetes for 8 years and above, and the mean of maximum HbA1c equal or above 12.8, all are independent factors associated with high risk of development of DRP

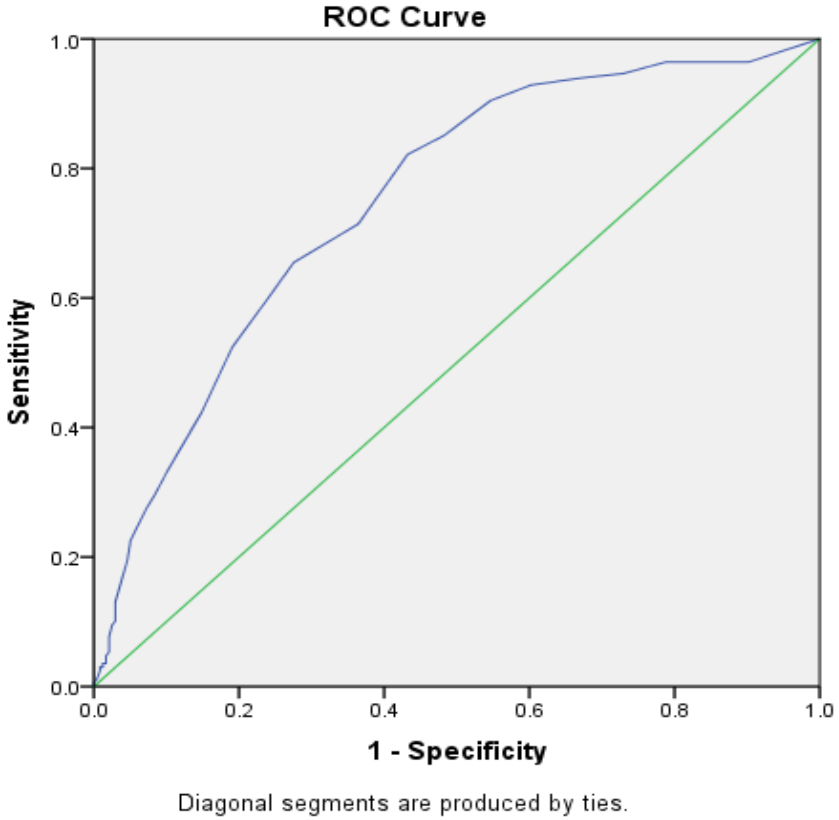

Figure 22 ROC curve for the duration of diabetes and diabetic retinopathy

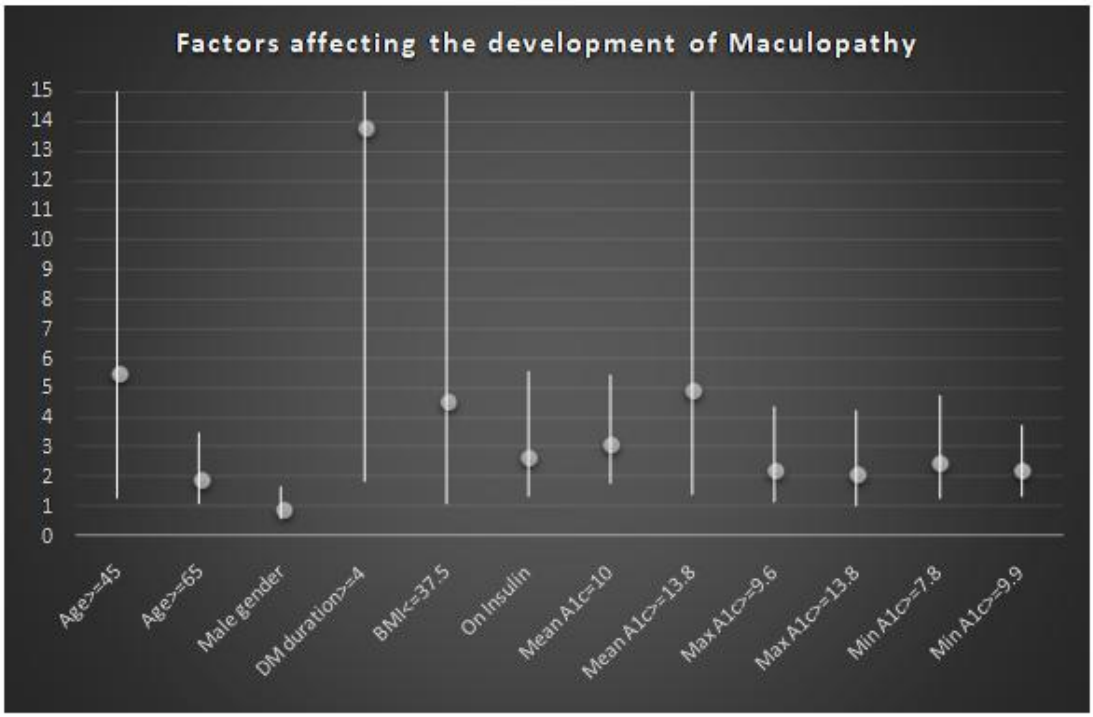

Figure 23 risk estimates for different factors affecting the development of maculopathy.

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Received 25 April 2021; Accepted 08 May 2021.

Table 7 Factors affecting the development of maculopathy									
		maculopathy				OR	95% CI		P
		yes		no					
		n	%	n	%		lower	upper	
age	>=45	69	19.4	287	80.6	5.53	1.31	23.34	0.009
	>=65	20	26.3	56	73.7	1.94	1.07	3.51	0.026
gender	Males	28	17.8	129	82.2	0.97	0.58	1.64	0.913
	Females	43	17.4	204	82.6				
Duration	>=4	70	20.1	278	79.9	13.85	1.88	101.82	0.001
	<4	1	1.8	55	98.2				
BMI	<=37.5	69	19.0	294	81.0	4.58	1.08	19.41	0.024
	>37.5	2	4.9	39	95.1				
insulin	Yes	61	21.0	230	79.0	2.73	1.35	5.55	0.004
	No	10	8.8	103	91.2				
A1c	>=10	51	25.4	150	74.6	3.11	1.78	5.45	<0.001
	>13.8	5	50.0	5	50.0	4.97	1.40	17.65	0.006
Max A1c	>=9.6	59	20.6	228	79.4	2.26	1.17	4.39	0.014
	>=13.6	13	28.9	32	71.1	2.11	1.04	4.26	0.034
Min A1c	>=7.8	58	21.3	214	78.7	2.48	1.31	4.71	0.004
	>=9.9	35	25.7	101	74.3	2.23	1.33	3.76	0.002

With binary logistic regression, Age equal or above 45, duration of diabetes for four years or more, BMI equal or above 37.5 and mean HbA1c of 10 or above, all were independently associated with a higher risk for the development of maculopathy.

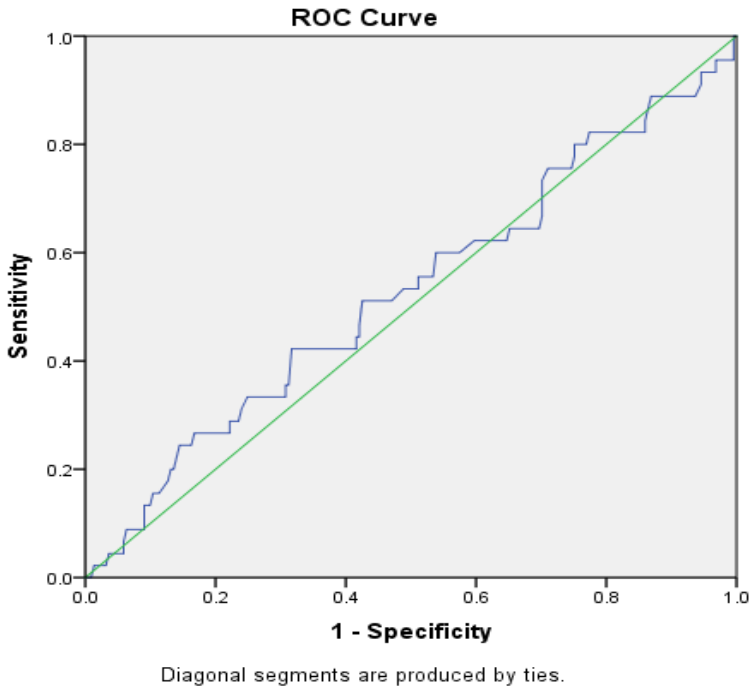

Figure 24 ROC curve for the absolute HbA1c excursion and maculopathy, revealed a very poor association. p=0.420