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Original Research Article

Effect of glycemic control on diabetic retinopathy and diabetic macular edema: a prospective observational study

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ABSTRACT

Background: The objective of the study was to examine the effect of long-term glycemic control, as measured by glycated hemoglobin levels (HbA_1C), on the onset and progression of diabetic retinopathy (DR) and diabetic macular edema (DME) over a period of 10 years.
Methods: Patients who were diagnosed to have type 2 diabetes mellitus participated in this cross-sectional observational study. Duration of onset of diabetes and the glycemic control status were analyzed. Fasting and postprandial blood sugar levels and HbA_1C levels were tested for every participant. Diabetic retinopathy was graded as per the ETDRS guidelines using stereoscopic fundus photographs. In addition to the clinical evaluation, optical coherence tomography was done to confirm the presence of DME.
Results: A total of 212 diabetic patients were enrolled in this study. One sixty-four patients (78.1%) had DR, out of which 71 patients (43.3%) had mild non proliferative diabetic retinopathy (NPDR), 42 patients (25.6%) had moderate NPDR, 31 patients (18.9%) had severe NPDR, and 20 (12.2%) had proliferative diabetic retinopathy (PDR). Fifty-nine patients with DR (36%) had DME. Duration of diabetes (14.62±6.18 vs 9.72±3.68 years, $p<0.001$), higher fasting blood glucose (176.79±59.13 vs 138.46±49.44 mg/dl, $p<0.001$) and higher HbA1c levels (8.21±1.38 vs 7.48±1.25 %, $p=0.002$) were significantly associated with DR.
Conclusions: The stage of diabetic retinopathy rather than metabolic status is a strong predictive factor for the development of diabetic macular edema.

Keywords: Diabetic retinopathy, Diabetic macular oedema, Glycaemic control, Glycated haemoglobin

INTRODUCTION

Diabetes mellitus have reached epidemic proportions in India as well as globally and it accounts for majority of visual impairment and blindness among adults worldwide. At present around 422 million people are estimated to be affected with diabetes mellitus, up from 171 million in 2000 as per WHO. The global prevalence of diabetes mellitus among adults has risen to 8.5 from 4.7% in 1980. This rise in prevalence is more rapid in low- and middle-income countries than in high income countries. The three countries with highest prevalence of diabetes are India, China and the United States. Diabetic retinopathy is an important cause of blindness and accounts for 2.6% of global blindness.[1] Various landmark randomised, multicentre clinical trials such as the diabetes control and complications trial (DCCT) and the UK prospective diabetes study (UKPDS) have demonstrated that an intensive glycaemic control regimen aimed at maintaining normal blood glucose levels markedly diminishes the risk of development and progression of diabetic retinopathy as well as other macrovascular and microvascular complications of diabetes mellitus as compared to the conventional treatment regimen.[2,3] The prevalence of diabetic retinopathy is estimated to be around 45.5% in patients with type 2 diabetes mellitus and 33.2% in patients with type 1 diabetes mellitus.[4,5] In patients with type 1 diabetes mellitus the prevalence of non-proliferative

diabetic retinopathy was 4.7% and 45.8% at 5 and 20 years respectively.[5] In type 2 diabetes mellitus theses prevalence were 18.7 and 60.6% at 5 and 20 years respectively.[4] These trials have identified numerous risk factors for the onset and progression of diabetic retinopathy including hyperglycaemia, duration of diabetes, hypertension, high body-mass index, smoking, nephropathy, genetic susceptibility and ethnicity.[6-17]

The objective of the study was to examine the effect of long-term glycemic control, as measured by glycated hemoglobin levels (HbA_1C), on the onset and progression of diabetic retinopathy (DR) and diabetic macular edema (DME) over a period of 10 years.

METHOD

The study was a cross sectional observational single center study conducted in a tertiary care center in South India (SUT academy of medical sciences) over a period of six months, from July 2018 to December 2018. Two hundred and twelve patients with type 2 diabetes mellitus diagnosed more than 5 years ago were enrolled in the study. Patients with other comorbidities such as hypertension, dyslipidemia, cardiovascular events, cerebrovascular diseases, thyroid diseases etc. were excluded from the study. Patients with ocular comorbidities such as cataract or other media opacities that interfere with fundus evaluation, glaucoma, other retinal pathologies such as retinal vascular occlusions, prior history of photocoagulation or intravitreal anti VEGF were excluded from the study. All patients who met the above criteria and presented to our outpatient department for screening and evaluation of diabetic retinopathy who have provided consent were included in the study. As it was an observational study Institutional Ethical Committee clearance was not required.

A questionnaire was prepared to include the following information: age, gender, weight, height, body mass index, family history of diabetes, history of smoking, hypertension, associated co morbidities, drug history and history of prior ophthalmic intervention. Ocular examination was done in all patients which included uncorrected distant visual acuity (UCDVA), best corrected distance visual acuity (BCDVA), anterior segment evaluation under slit lamp, intraocular pressure measurement with the Goldman applanation tonometer. Detailed fundoscopic evaluation was done after pupillary dilatation with 1% tropicamide and 5% phenylephrine eye drops using indirect ophthalmoscopy with +20D lens and stereoscopic slit lamp bio microscopy with +90D lens. Stereoscopic fundus photographs were taken of all retinal quadrants using Topcon fundus camera. The diagnosis and grading of diabetic retinopathy was done as per the ETDRS guidelines. The diagnosis of diabetic macular edema was done clinically and confirmed with an optical coherence tomography.

In our study the grading of diabetic retinopathy was done as per the classification of diabetic retinopathy in the early treatment of diabetic retinopathy study (ETDRS).[18] If at least one microaneurysm was detected and criteria were not met for more severe retinopathy it was classified as mild non proliferative diabetic retinopathy. Hemorrhages or microaneurysms more than standard photograph 2A; and/or cotton wool spots, venous beading, or intraretinal microvascular abnormalities (IRMA) definitely present; and criteria not met for more severe retinopathy. Severe NPDR was diagnosed if cotton wool spots, venous beading and IRMA were present in at least two of photographic fields 4-7 and hemorrhages/microaneurysms present in fields 4-7 ≥standard photograph 2A in at least one of them; or IRMA present in each of fields 4-7 and ≥ standard photograph 8A in at least one of them: and criteria not met for severe retinopathy. If new vessels were present and criteria did not meet for more severe retinopathy it was classified as early PDR. High risk PDR was diagnosed if new vessels were found on or within one-disc diameter of the optic disc (neovascularization of disc [NVD]) ≥ standard photograph 10A with or without vitreous or pre retinal hemorrhages; or vitreous and/or pre retinal hemorrhage accompanied by new vessels, either NVD < standard photograph 10A or new vessels elsewhere (NVE) ≥ ¼ disc area. Diabetic macular edema (DME) was graded according to the Disease Severity Scale for Diabetic Retinopathy.[19] The presence of DME was determined based on the presence of retinal thickening and hard exudates in the posterior pole. Mild DME was diagnosed when some retinal thickening or hard exudates are present in the posterior pole, distant from the center of the macula. If thickening and hard exudates are found near the center of macula but not involving the center it was graded as moderate DME. If retinal thickening and hard exudates are involving the center of macula kt was classified as severe DME.

Fasting blood sugar (FBS), postprandial blood sugar (PPBS), glycated hemoglobin (HbA_1C), total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), very low-density lipoprotein (VLDL) and triglycerides (TG) were assessed for each subject.

Statistical analysis

Continuous data is expressed as mean ± SD along with median with interquartile range. Kolmogorov-Smirnov test was used to test normality of the sample size. Categorical variables are expressed as number and proportion. Means of two groups of continuous variables with normal distribution was compared by independent sample t test and those with non-normal distribution by Mann-Whitney U test. Means of different categories of DR with normal distribution were compared using ANOVA and those with non-normal distribution by Kruskal Wallis test. Comparison of categorical variables was done using chi square test. All analysis was performed using SPSS version 20.0.

RESULTS

Demographic characteristics of the study population are given below (Table 1).

Figure 1 shows the prevalence of retinopathy in the study population. Figure 2 shows the distribution of the patients in different stages of diabetic retinopathy. Figure 3 gives the prevalence of DME in different stages of diabetic retinopathy.

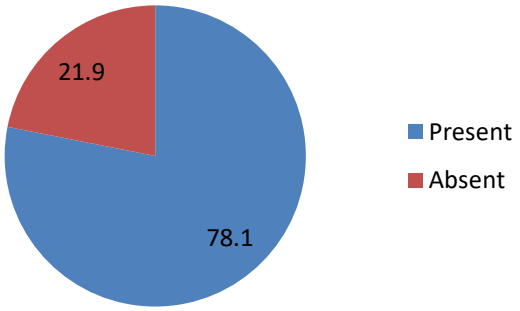

Figure 1: Prevalence of retinopathy in the study population.

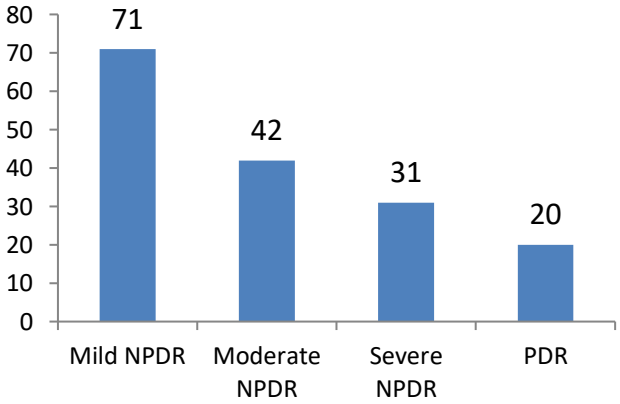

Figure 2: Stages of retinopathy in the study population.

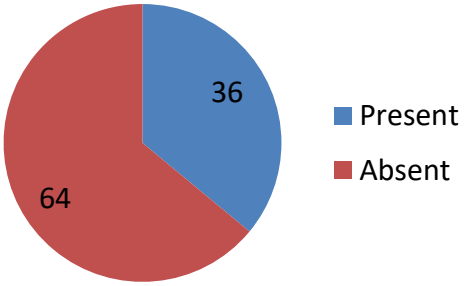

Figure 3: Prevalence of CSME in retinopathy.

Table 2 depicts the statistical analysis to assess the factors associated with diabetic retinopathy. The duration of onset of diabetes mellitus ($p<0.001$), the short-term glycaemic control as given by the fasting blood sugar levels ($p<0.001$) the glycated haemoglobin levels that depicts the long-term metabolic control and serum lipid levels are the parameters that shows a statistically significant relation with diabetic retinopathy.

Table 3 documents a statistically significant association of severity of DR with fasting blood glucose, HbA1c, total cholesterol, triglyceride and Low-density lipoprotein (LDL) cholesterol levels.

Table 4 gives the assessment of factors related to diabetic macular edema. Stage of diabetic retinopathy was the only factor that showed a strong statistical association to diabetic macular edema.

Table 1: Characteristics of study population.

Characteristics	
Age (years)	
Mean	63.93±9.52
Median	64 (57-71)
Sex (%)	
Male	108 (51.4)
Female	102 (48.6)
Smoking status (%)	
Yes	24 (11.4)
No	186 (88.6)
Duration of diabetes mellitus (years)	
Mean	13.54±6.07
Median	13.5 (8-17)
FBS (mg/dl)	
Mean	168.4±59.21
Median	156 (128-206)
HbA1c (%)	
Mean	8.05±1.38
Median	7.8 (7.1-8.9)
Total cholesterol (%)	
Desirable	102 (48.6)
Borderline high	57 (27.1)
High	51 (24.3)
Triglycerides (%)	
Normal	113 (53.8)
Borderline high	59 (28.1)
High	38 (18.1)
HDL (%)	
Low	62 (29.5)
High	148 (70.5)
LDL (%)	
Optimal	29 (13.8)
Near optimal	77 (36.7)
Borderline high	53 (25.2)
High	37 (17.6)
Very high	14 (6.7)

Table 2: Factors associated with retinopathy.

Factors	Retinopathy		P value
	Present (n=164)	Absent (n=46)	
Gender (%)			
Male	86 (79.6)	22 (20.4)	0.580
Female	78 (76.5)	24 (23.5)	
Smoking status (%)			
Yes	20 (83.3)	4 (16.7)	0.510
No	144 (77.4)	42 (22.6)	
Total cholesterol (%)			
Desirable	69 (67.6)	33 (32.4)	<0.001
Borderline high	44 (77.2)	13 (22.8)	
High	51 (100)	0 (0)	
Age (years)			
Mean	64.2±9.13	62.96±10.85	0.435
Duration of diabetes mellitus (years)			
Mean	14.62±6.18	9.72±3.68	<0.001
FBS (mg/dl)			
Mean	176.79±59.13	138.46±49.44	<0.001
HbA1c (%)			
Mean	8.21±1.38	7.48±1.25	0.002

Table 3: Factors associated with stages of retinopathy.

Factors	Retinopathy				P value
	Mild NPDR (n=71)	Moderate NPDR (n=42)	Severe NPDR (n=31)	PDR (n=20)	
Gender (%)					
Male	38 (44.2)	22 (25.6)	16 (18.6)	10 (11.6)	0.993
Female	33 (42.3)	20 (25.6)	15 (19.2)	10 (11.6)	
Smoking status (%)					
Yes	8 (40)	4 (20)	7 (35)	1 (5)	0.219
No	63 (43.8)	38 (26.4)	24 (16.7)	19 (13.2)	
Total cholesterol (%)					
Desirable	42 (60.9)	19 (27.5)	3 (4.3)	5 (7.2)	<0.001
Borderline high	21 (47.7)	14 (31.8)	7 (15.9)	2 (4.5)	
High	8 (15.7)	9 (17.6)	21 (41.2)	13 (25.5)	
Triglycerides (%)					
Normal	47 (59.5)	22 (27.8)	6 (7.6)	4 (5.1)	<0.001
Borderline high	21 (43.8)	13 (27.1)	8 (16.7)	6 (12.5)	
High	3 (8.1)	7 (18.9)	17 (45.9)	10 (27)	
HDL cholesterol (%)					
Low	15 (26.8)	15 (26.8)	15 (26.8)	11(19.6)	0.007
High	56 (51.9)	27 (25)	16 (14.8)	9 (8.3)	
LDL cholesterol (%)					
Optimal	15 (71.4)	4 (19)	1(4.8)	1 (4.8)	<0.001
Near optimal	32 (60.4)	15 (28.3)	2 (3.8)	4 (7.5)	
Borderline high	19 (43.2)	15 (34.1)	10 (22.7)	0 (0)	
High	4 (12.5)	5 (15.6)	12 (37.5)	11 (34.4)	
Very high	1 (7.1)	3 (21.4)	6 (42.9)	4 (28.6)	
Age (years)					
Mean	63.96±10.33	61.83±8.20	66.03±8.16	67.20±6.67	0.098
Duration of diabetes mellitus (years)					
Mean	11.66±5.17	14.79±4.84	17.06±6.42	20.95±5.40	<0.001
FBS (mg/dl)					
Mean	149.08±48.01	190.67±56.97	203.35±59.85	204.85±59.73	<0.001
HbA1c (%)					
Mean	7.60±1.17	8.45±1.32	8.83±1.45	8.87±1.28	<0.001

Table 4: Factors associated with CSME.

Factors	CSME		P value
	Present (n=59)	Absent (n=105)	
Gender (%)			
Male	26 (30.2)	60 (69.8)	0.108
Female	33 (42.3)	45 (57.7)	
Smoking status (%)			
Yes	5 (25)	15 (75)	0.275
No	54 (37.5)	90 (62.5)	
Total cholesterol (%)			
Desirable	16 (23.2)	53 (76.8)	0.010
Borderline high	18 (40.9)	26 (59.1)	
High	25 (49)	26 (51)	
Stages of retinopathy (%)			
Mild NPDR	12 (16.9)	59 (83.1)	<0.001
Moderate NPDR	15 (35.7)	27 (64.3)	
Severe NPDR	18 (58.1)	13 (41.9)	
PDR	14 (70)	6 (30)	
Age (years)			
Mean	64.27±9.07	64.16±9.21	0.942
Duration of diabetes mellitus (years)			
Mean	16.19±5.90	13.73±6.19	0.014
FBS (mg/dl)			
Mean	184.80±59.1	172.30±58.94	0.195
HbA1c (%)			
Mean	8.51±1.26	8.04±1.42	0.037

DISCUSSION

In our study we were able to establish a statistically significant association between glycemic control and diabetic retinopathy but not with diabetic macular edema. The short-term glycemic status was assessed by measuring the fasting and post prandial blood sugar levels. The long-term glycemic control status was assessed based on the glycated hemoglobin levels. If the metabolic control was poor and there was considerable variations in HbA1C then there is a higher risk of developing macrovascular and microvascular complications of diabetes mellitus.[20] Hence there understanding is crucial for the holistic management of a diabetic patient.[21,22] Duration of diabetes mellitus and long term metabolic control were the only significant independent risk factor for diabetic retinopathy and nephropathy.[23] When compared to patients who had all indicators of metabolic control under normal limits, patients with suboptimal glucose, lipid and blood pressure control were more likely to develop diabetic retinopathy. The risk of developing diabetic macular edema was similarly high in those with poor metabolic control.[24] These observations highlight the need of multifactorial systemic management plan in diabetic patients for the treatment of diabetic retinopathy and diabetic macular edema.

Systemic therapy in diabetic retinopathy and diabetic macular edema aims to decrease the risk of diabetic patients developing these conditions in the first place as well as to reduce the risk of progression of existing retinopathy or maculopathy to severe visually debilitating forms. The available systemic therapy targets the key modifiable risk factors such as metabolic control. The non-modifiable risk factors include duration of diabetes, residual functioning pancreatic β cells, insulin resistance and genetic predisposition. The DCCT and UKPDS have established the importance of metabolic control, and that this control should be achieved as early as possible and it should be maintained for as long as possible.[3,24] At the same time an extremely tight metabolic control has been found to increase the mortality in these patients.[25]

A thorough review of published literature shows a direct strong association between metabolic control and diabetic retinopathy, the same correlation has been established between DME and metabolic control as well. In our study we were able to establish the relation between diabetic retinopathy and short- and long-term metabolic control. Our study also depicted a strong association between stage of diabetic retinopathy and diabetic macular edema. Duration of diabetes mellitus-, short- and long-term glycemic control did not show any significant association with diabetic macular edema independently. Hence, we can conclude that local treatment of the retinopathy remains an important therapeutic measure in the control of diabetic macular edema.

The main limitation of the study is that here we have not assessed existing comorbidities of the patients in detail. Majority of diabetic patients present with coexisting illness such as hypertension, dyslipidemia, micronutrient deficiencies (vitamin D) etc. These parameters are potential confounding factors that may have affected the results of the study.

CONCLUSION

Metabolic control, both long term and short term had a significant impact on the development and progression of diabetic retinopathy. The stage of diabetic retinopathy rather than the metabolic status is a strong predictive factor for the development of diabetic macular edema. Long term and short-term glycemic control status do not have an independent association with DME.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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