ORIGINAL ARTICLE

Risk Factors Associated With Diabetic Retinopathy In Type II Diabetic Patients: A Cross-Sectional Study

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Abstract

A cross-sectional study was done on a total of 158 known cases of type II diabetes mellitus, with no history of ocular treatment to investigate the role of various risk factors associated with diabetic retinopathy. The patients were screened for presence or absence of retinopathy on the basis of dilated fundus examination. The patients showing retinopathy were graded for the type of retinopathy on the basis of Early Treatment Diabetic Retinopathy Study (ETDRS) classification system. The patients were divided into 2 groups: Group A composed of diabetic patients with no retinopathy and Group B comprised of diabetics with retinopathy. A detailed history was taken; physical examination and laboratory investigations were done in each case. Out of 158 patients with diabetes, 75(47.47%) had diabetic retinopathy. 23 patients (14.56%) had mild non-proliferative diabetic retinopathy (NPDR), 22(13.92%) moderate NPDR, 18(11.39%) severe to very severe NPDR and 12(7.59%) had proliferative diabetic retinopathy (PDR). The risk factors found to be significant for presence of retinopathy on univariate analysis were duration of diabetes ($p<0.0001$), glycated haemoglobin (HbA1c) ($p<0.0001$), proteinuria ($p<0.0001$), serum creatinine ($p<0.0001$), associated hypertension ($p=0.001$), hypomagnesaemia ($p= 0.0004$) and insulin use ($p= 0.009$). On multivariate analysis, only duration of diabetes ($p=0.000$), proteinuria ($p=0.022$) and hypomagnesaemia ($p=0.015$) were found to be significant. This study concludes that duration of diabetes, proteinuria and hypomagnesaemia are significantly associated with the risk of developing diabetic retinopathy.

Key Words

Glycated Haemoglobin, Hypertension, Hypomagnesaemia, Proteinuria

Introduction

Diabetes is a metabolic disorder, with environmental and hereditary factors playing an important role in its pathogenesis. Many systemic complications like neuropathy, nephropathy, retinopathy and cardiovascular complications are attributable to diabetes. With an estimated rise in population with diabetes from 69.2 million in 2015 to 123.5 million in 2040 in India (1); it is clear that the number of diabetics will increase tremendously in near future. With this rise, the complications will also increase proportionately.

Diabetic retinopathy (DR) is one of the most serious ocular complications of diabetes. The disease progresses from mild non-proliferative diabetic retinopathy to proliferative stage, which can ultimately lead to blindness if no measures are taken in time. DR is an important cause of blindness in the productive population all over the world. It is responsible for 3-7% blindness in major part of South-East Asia and the West Pacific Region (2). Financially, diabetes is an expensive disease. Depending upon the number of diabetics and the available health facilities, 7-15% of the yearly health care budget in a large number of countries goes for managing diabetes and its complications (1).

Presence and progression of diabetic retinopathy depends on certain factors. These risk factors can be either non-modifiable risk factors like age, gender, ethnicity, nephropathy, hypothyroidism, duration of diabetes, pregnancy, family history etc., or modifiable like glycaemic control, hypertension, hyperlipidaemia, smoking, obesity, anaemia, alcohol consumption, hypomagnesaemia, body mass index (BMI) etc.

The present study was undertaken to evaluate the role of various risk factors in the development of diabetic retinopathy.

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Materials and Methods

158 patients with type II diabetes mellitus having no previous history of treatment for diabetic retinopathy, clear ocular media, and with no contraindication for dilating the pupil were included in the study.The study was conducted over a period of 1-year. The patients were explained in detail the purpose of the study by the interviewer. No patient showed any reluctance in participation.

All the patients underwent visual acuity determination both unaided and aided. Intraocular pressure was documented. Slit-lamp bio-microscopy was done to assess anterior segment and posterior pole using +90 dioptre lens. Pupils of both eyes were dilated with a combination of 0.8% tropicamide and 5% phenylephrine hydrochloride eye drops to achieve maximum dilatation. Direct and indirect ophthalmoscopy was done in all patients. The findings were correlated with fundus photographs taken by fundus camera. Patients with diabetic retinopathy were graded according to ETDRS classification (3).

The patients were divided into 2 groups:

a) *Group A* consisted of participants with no signs of any retinopathy.

b) *Group B* consisted of participants with any grade of diabetic retinopathy.

Patients were questioned according to preformed proforma, which included details like age, age of onset of diabetes, duration of diabetes, history of hypertension, any other associated illness, family history, treatment history, personal history etc. Height in meters and weight in kilograms were recorded to calculate BMI. BMI>25 kg/m2 was taken as overweight.

Hypertension was defined as presence of systolic blood pressure (B.P.) >140mm Hg and /or diastolic B.P.> 90 mm Hg or if any person was being treated with antihypertensive drugs (JNC 7 guidelines) (4).

All the patients underwent required laboratory investigations. The reference values were taken according to analyser and the biochemical kit used. The following reference values were taken in our institution:

- Haemoglobin was estimated using cynmet haemoglobin method. (Normal values: males- 15 ± 1.5 g/dl and females- 13.5 ± 1.5 g/dl).
- Fasting blood sugar was estimated using hexokinase/ G6PDH enzymatic method. (Blood Sugar >126 mg/dl).
- Serum creatinine was estimated using kinetic alkaline picrate method. (Normal range: males- 0.6 - 1.2 mg/dl and females- 0.5 - 1.1mg/dl).
- Total serum cholesterol was estimated by using enzymatic principle (<200mg/dl).

Table 1. Univariate Analysis of Risk Factors Associated with Diabetic Retinopathy- Part 1

Variables	No DR (n=83) N (%)	DR (n=75) N (%)	OR	95% CI	p-value
Age in (years)					0.381
= 50	33(39.76)	22(29.33)	1(Ref.)	-	
51-60	24(28.92)	25(33.34)	1.56	0.72 - 3.40	
61-70	21(25.30)	19(25.33)	1.36	0.60 - 3.09	
= 71	5 (6.02)	9(12.00)	2.70	0.80 - 9.14	
Sex					0.573
Female	38(45.78)	31(41.33)	1(Ref.)	-	
Male	45(54.22)	44(58.67)	1.199	0.64 - 2.25	
Duration of diabetes (years)					<0.00 01
0-5	46(55.42)	16(21.33)	1(Ref.)	-	
6-10	29(34.94)	21(28.00)	2.08	0.94 - 4.63	
11-15	8(9.64)	19(25.34)	6.83	2.50 -	
16-20	-	10(13.33)	Undefined	18.62	
= 21	-	9(12.00)	Undefined	-	
				-	
Family history of diabetes					0.086
Absent	40(48.19)	26(34.67)	1(Ref.)	-	
Present	43(51.81)	49(65.33)	1.75	0.92 - 3.33	

No DR= No diabetic retinopathy; DR= Diabetic retinopathy; OR= Odds ratio; CI= Confidence interval; N= Number of patients; Ref. = Reference

Table 2. Univariate Analysis of Risk Factors Associated with Diabetic Retinopathy- Part 2

Variables	No DR (n=83) N (%)	DR (n=75) N (%)	OR	95% CI	p- value
Treatment					0.009
OHA	61(73.49)	40(53.33)	1(Ref.)	-	
Insulin	22(26.51)	35(46.67)	2.43	1.25 - 4.72	
Blood glucose (fasting, mg/dl)					0.149
<126	37(44.58)	25(33.33)	1(Ref.)	-	
> 126	46(55.42)	50(66.67)	1.61	0.84 - 3.07	
HbA1c (%)					<0.0001
<7	52(62.65)	21(28.00)	1(Ref.)	-	
> 7	31(37.35)	54(72.00)	4.31	2.20 - 8.45	
Associated hypertension					0.001
Absent	45(54.22)	21(28.00)	1(Ref.)	-	
Present	38(45.78)	54(72.00)	3.05	1.57 - 5.91	
Total serum cholesterol					0.415
< 200					
? 200	55(66.27)	45(60.00)	1(Ref.)	-	
	28(33.73)	30(40.00)	1.31	0.68 - 2.50	
Serum creatinine levels					<0.0001
Normal					
Deranged	77(92.77)	37(49.33)	1(Ref.)	-	
	6(7.23)	38(50.67)	13.18	5.12 - 33.95	
Type of albuminuria					<0.0001
Normoalbuminuria	61(73.50)	20(26.66)	1(Ref.)	-	
Microalbuminuria	17(20.48)	32(42.67)	5.74	2.64 - 12.47	
Macroalbuminuria	5(6.02)	23(30.67)	14.03	4.71 - 41.77	
Anaemia					0.143
Absent	44(53.01)	31(41.33)	1(Ref.)	-	
Present	39(46.99)	44(58.67)	1.60	0.85 - 3.01	
Hypomagnesaemia					0.0004
Absent	59(71.08)	32(42.67)	1(Ref.)	-	
Present	24(28.92)	43(57.33)	3.30	1.71 - 6.39	
BMI (kg/m^2)					0.106
< 25	45(54.22)	31(41.33)	1(Ref.)	-	
> 25	38(45.78)	44(58.67)	1.68	0.89 - 3.16	

OHA= Oral hypoglycaemic agents; HbA1c= Glycated haemoglobin; BMI= Body mass index

Table 3. Comparison of Univariate Vs Multivariate Analysis

Variables	Univariate analysis		Logistic regression analysis	
	p-value	Sig	p-value	Sig
Duration of diabetes	<0.0001	HS	0.000	HS
HbA1c	<0.0001	HS	0.177	NS
Proteinuria	<0.0001	HS	0.022	S
Serum creatinine	<0.0001	HS	0.054	NS
Hypomagnesaemia	0.0004	HS	0.015	S
Presence of hypertension	0.001	S	0.391	NS
Insulin users	0.009	S	0.984	NS

Sig= Significance; HS= Highly significant; S= Significant; NS= Non-significant

- Glycosylated haemoglobin (HbA1c) was estimated by enzymatic method measuring N-terminal fructosyl dipeptides of the beta chain of HbA1c (<7%).

- Serum magnesium levels were estimated by enzymatic method using enzyme isocitrate dehydrogenase. (Normal range: 1.7 - 2.4 mg/dl).

- Routine urine analysis- gross (pH, specific gravity, protein, sugar by urine reagent strips) and microscopic- was done on the first morning urine specimen.

- Urine dipsticks (Dirui H 11/MA, urine reagent testing strips) to estimate microalbuminuria and macroalbuminuria. The test strip is based on dye binding by albumin method. The principle is named as protein-error-of-indicator principle. It is a semi-quantitative method for protein estimation.

Stastical Analysis

Analysis of collected data was done using Statistical Package for the Social Sciences version 20.0 (SPSS 20.0). A p-value < 0.05 was taken as statistically significant.

Results

The total number of patients studied was 158. Out of these, 69(43.67%) were females. 75(47.47%) patients had diabetic retinopathy; 23(14.56%) had mild NPDR, 22(13.92%) moderate NPDR, 18(11.39%) severe to very severe NPDR and 12(7.59%) had PDR. Males were affected more by retinopathy (OR: 1.199; 95% CI: 0.64 - 2.25). Patients with longer duration of diabetes were at increased risk of developing retinopathy (OR: 2.08; CI: 0.94 - 4.63 and OR: 6.83; CI: 2.50 - 18.62 for 6 - 10 and 11 - 15 years, respectively). There were no patients in group A with duration of diabetes more than 15 years. Insulin users were more prone to develop retinopathy (OR: 2.43; CI: 1.25 - 4.72) as compared to diabetics on oral hypoglycaemic agents (OHAs). Patients with blood glucose fasting ?126 mg/dl were at 1.61 times more risk of developing retinopathy than patients with better control of blood sugar. Similarly, patients with HbA1c >7 % had increased chances of developing retinopathy (OR: 4.31; CI: 2.20 - 8.45). Diabetics who were hypertensives were at approximately 3 times more risk of developing retinopathy as compared to normotensives. Elevated total cholesterol, anaemia and BMI >25 also marginally increased the risk of developing the disease. Patients with deranged renal function tests (RFT's) were at 13 times and those with macroalbuminuria had 14 times more risk of developing retinopathy. Microalbuminuria also increased the risk to 5.74 times. Decreased serum magnesium levels also contributed towards development of disease (OR: 3.30; CI: 1.71 - 6.39) (*Table 1 & 2*).

Although the chances of developing diabetic retinopathy increased with all of the above mentioned factors, a significant association of retinopathy was seen only with increased duration of diabetes (p<0.0001), elevated HbA1c (p<0.0001), presence of proteinuria (p<0.0001), raised serum creatinine (p<0.0001), associated hypertension (p=0.001), hypomagnesaemia (p=0.0004) and use of insulin (p=0.009). After applying logistic regression analysis to these factors that have been found significant on univariate analysis, only duration of diabetes (p=0.000), proteinuria (p=0.022) and hypomagnesaemia (p=0.015) were found to be significantly associated with presence of diabetic retinopathy (*Table 3*). Whereas creatinine was found to be marginally significant (p=0.054); no association of diabetic retinopathy was seen with HbA1c, hypertension and insulin use on multivariate analysis.

Discussion

In this study, relationship of many factors was analysed with diabetic retinopathy. On univariate analysis, factors that were found to be significant were duration of diabetes, glycated haemoglobin (HbA1c), presence of proteinuria, elevated serum creatinine levels, associated hypertension, hypomagnesaemia and insulin use. However, after applying logistic regression analysis to these factors only duration of diabetes, presence of proteinuria and hypomagnesaemia came out to be significant in relation to diabetic retinopathy.Duration of diabetes has been significantly linked with diabetic retinopathy in many studies (5-13). With increasing duration, the chronicity of insult due to hyperglycaemia and other risk factors also increases. (13) Though duration of diabetes has generally been significantly linked with presence of diabetic retinopathy, but in a study conducted in Thailand no such association was found (14). Also in an Indian study about 10% newly diagnosed diabetics were already having retinopathy; the reason cited by author was that these diabetics remained undiagnosed or undetected, as a result the duration of hyperglycaemia did not corresponded with on record duration of diabetes (13).Association of albuminuria with diabetic retinopathy has been studied by many authors (15-19). Significant association has been reported between presence of microalbuminuria (15-19) and Macroalbuminuria (15-17), and development of diabetic retinopathy. In our study both the number of microalbuminurics and macroalbuminurics increased from group A to group B. The reason being there is concurrent microvascular damage to both kidney and retina caused by diabetes mellitus (15).Magnesium deficiency has long been linked with diabetes mellitus with hypomagnesaemia causing alteration in cellular glucose transportation, reduction in insulin secretion, defect in post-receptor

insulin signalling and alteration in insulin receptor interactions, and aggravation of insulin resistance (20). In the present study, hypomagnesaemia has been found to be associated with diabetic retinopathy. Similar findings have been reported by other authors (21-23). The limitation of present study was that it was a hospital based cross-sectional study so the relationship of diabetic retinopathy with various risk factors has been studied at one point of time only. That's why a causal relationship between these factors and retinopathy cannot be established. Secondly, risk factors like complete lipid profile, smoking, alcohol intake were not taken into account, which could have potential relation with retinopathy. Thirdly, the patients in retinopathy group were not equal for different grades of diabetic retinopathy which could have affected our results. Nevertheless, this study can be viewed as a small contribution to the ever expanding subject of diabetic retinopathy. Routine follow up of diabetic patients and control of various modifiable risk factors can delay development or at least slow down the progression of diabetic retinopathy.

Conclusion

This study concludes that duration of diabetes, proteinuria and hypomagnesaemia are significantly associated with the risk of developing diabetic retinopathy.

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