RETINOPATHY RISK FACTORS AMONG DIABETICS IN A TERTIARY CARE MILITARY HOSPITAL

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Abstract

Objective: To determine the frequency and risk factors for severity of retinopathy in diabetic patients referred to a tertiary military hospital.
Study Design: Cross-sectional study.
Place and duration of study: Armed Forces Institute of Ophthalmology, Rawalpindi from Jun 2008 to Dec 2009.
Patients and Methods: Diabetic patients aged 40 to 79, referred for suspected diabetic retinopathy (DR) on fundoscopy from medical outpatient clinic of Military Hospital Rawalpindi were randomly included in the study. Participants underwent a standardized interview and examination. Retinopathy was assessed through dilated pupils, and graded into absent retinopathy, mild to moderate, or advanced. Presence of clinically significant macular edema (CSME) was also recorded. To evaluate the simultaneous effect of significant risk factors on the different stages of DR, multivariate regression analysis was carried out.
Results: Out of five hundred and ten patients, DR was confirmed in 63% cases with advanced retinopathy in 21.3%. In univariate analysis, duration of diabetes, fasting blood glucose, and presence of macular oedema were significantly associated with retinopathy (P<0.005). On multivariate analysis, however, only duration of diabetes (Odds Ratio 6.15 for 5 to 10 years and 38.29 for more than 10 years) and macular oedema (OR 6.617 95% CI 3.95-11.07) remained significant. CSME was present in 173 (33%) patients and its frequency increased with the severity of DR (P <0.001).
Conclusion: The frequency of DR among military personnel and their dependants was high with strong association to duration of diabetes. This underscores the importance of regular retinal examination to detect DR in the early stages and timely intervention to prevent diabetes related blindness.

Keywords : Diabetic Retinopathy, Military Hospital, Macular Oedema.

Article

INTRODUCTION

Diabetic retinopathy (DR) is the most frequent microvascular complication of Diabetes Mellitus (DM), resulting in blindness for over 10,000 people with DM every year1. According to the latest World Health Organization (WHO) report, Pakistan has 5.2 million diabetic subjects, and the number is expected to increase to a staggering 13.9 million and 5th highest in the world by 20302. According to Pakistan national blindness survey the prevalence of blindness in adults more than 30 years of age is 2.7%, and out of these, 15.3% have diabetic retinopathy3.
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Several epidemiologic studies have provided valuable information on the prevalence of DR in Western countries along with the role of determinants for its development and progression, including type and duration of DM, age, gender, glycemic control, hypertension, body mass index (BMI), smoking, serum lipids and presence of microalbuminuria4. However, there is a paucity of data on the prevalence of diabetes-related eye diseases and the role of various risk factors in developing countries such as Pakistan5. Furthermore, diabetes in subcontinent differs from that in Europe in several aspects: The onset is at a younger age, obesity is less common, and genetic factors appear

to be stronger6. Recent studies on DR in our region have shown an increased incidence of retinopathy in newly diagnosed diabetics7. These clinical differences and the rising prevalence of diabetes warrant well-conducted epidemiologic surveys to assess and modify our approach in management of this globally alarming health issue.

The aim of this study was to determine the frequency of DR and associated risk factors in a tertiary care setup receiving referrals of military personnel and their dependants with clinical suspicion of DR.

Material and Methods

This was a cross-sectional study conducted on diabetics with clinical suspicion of DR based on direct ophthalmoscopy carried out in diabetic outdoor clinic of Military Hospital Rawalpindi and referred to our institute for confirmation or otherwise, from June 2008 to July 2009. Patients aged 40 years and older and who had not received any intervention for DR were randomly included in the study. All subjects in the study completed a questionnaire that included information on patient's age, gender, weight, height, type and duration of diabetes, and mode of diabetic control. After measurement of height and weight, the body mass index (BMI) was calculated using the formula: weight(kg)/height2 (m 2). Based on the BMI, individuals were classified into three categories; less than 25, between 25-30, and more than 308. Systolic blood pressure (SBP) was measured twice on the right arm to the nearest 2 mm of Hg after a 10 minute rest using a standard mercury sphygmomanometer, with the patient in the sitting position. Laboratory evaluations consisted of measuring blood HbA1C test, serum total cholesterol, and fasting blood glucose (FBG). HbA1C test was measured by high performance liquid chromatography system (reference range 4.7 - 6.0%; Merck-Hitachi 9100, Merck, Darmstadt, Germany). Fasting plasma glucose was measured by the glucose-peroxidase colorimetric enzymatic method. Serum total cholesterol was measured by enzymatic-colorimetric methods (Merck Diagnostics, Germany). The study protocol was approved by the Hospital Ethics Committees and an informed consent was obtained from all patients. Ophthalmoscopy was done after pupillary dilatation by 1% tropicamide and 10% phenylephrine eye drops. Classification of patient DR was based on the most severe degree of retinopathy in the worst affected eye. The binocular indirect ophthalmoscope (Keeler Instruments Inc. PA, USA) and slit lamp biomicroscope (Magnon SL-450, Japan) with fundus lens were used to examine the fundus. Any patient with corneal opacity or lenticular opacities which precluded proper fundus examination was rejected from the study. Diabetic retinopathy was clinically graded by an experienced retinal specialist as per the norms of the International Clinical Diabetic Retinopathy guidelines9. The cases were divided then as having no retinopathy, mild to moderate non proliferative retinopathy NPDR, and advanced retinopathy comprising severe non proliferative and proliferative retinopathy10. As regards diabetic maculopathy, only eyes with clinically significant macular oedema (CSME) were recorded, and it was defined as one or more of the following: Any retinal thickening within 500 mm of the center of the macula, with or without loss of retinal transparency; hard exudates associated with retinal thickening within 500 mm of the center of the macula; or one disc area of thickening within one disc diameter of the center of the macula.

A pre-tested form was used to collect the information for this study. The data was entered in SPSS version 15 (SPSS Inc, Chicago, Illinois, USA). For descriptive purposes, quantitative variables were presented as mean and standard deviation. Univariate analysis was carried out using Analysis of variance (ANOVA) for the comparison of quantitative variables between different stages of retinopathy. These variables were gender, type of diabetes, duration, BMI, SBP, hyperlipidemia, the type of glycemia control used, FBG, HbA1C and macular oedema. Qualitative variables were compared using chi-square test between the different stages of retinopathy. P-value less than 0.05 was considered significant. To evaluate the simultaneous effect of significant risk factors on univariate analysis on the different stages of DR (the response variable), multinomial multivariate regression model was used.

Results

A total of 510 patients were evaluated (65.7% males, 92.4% type II diabetics). Mean age was 60.97 + 9.30 years (95 % CI 60.16 to 61.78). Age distribution according to type of retinopathy is given in table-1.

Table 1 age characteristics of study patients with retinopathy.

Type of DR	No of cases	Mean age ± SD	95% Confidence Interval
No DR	185	60.94 ± 8.97	59.63 to 62.24
Mild to Moderate DR	206	61.26 ± 9.40	59.97 to 62.55
Advanced DR	119	60.53 ± 9.68	58.78 to 62.29
Total	510	60.97 ± 9.30	60.16 to 61.78

P value of 0.795 using ANOVA test

DR was confirmed in 63% cases (n = 325). 206 patients (40.3%) had mild to moderate NPDR and 119 patients (23.2%) were diagnosed with advanced DR. The demographic and clinical characteristics of patients are shown in table-2.

Table 2: Patients' characteristics according to different stages of diabetic retinopathy (n=510)

Risk Factors	Absent DR (n=185)	Mild to moderate DR (n=206)	Advanced DR (n=119)	P values
Gender				
Female	66 (35.7)	70 (34.0)	42 (35.3)	0.935
Male	119 (64.3)	136 (66.0)	77 (64.7)	
Type of DM				
Type –I	18 (9.7)	11 (5.3)	09 (7.6)	0.256
Type –II	167 (90.3)	195 (94.7)	110 (92.4)	
Duration of Diabetes				
Less than 5 yrs	57 (30.8)	41 (19.9)	16 (13.4)	< 0.001
5- 10 years	69 (37.3)	69 (33.5)	30 (25.2)	
More than 10 yr	59 (31.9)	96 (46.6)	73 (61.4)	
Body mass index				
Less than 25	113 (61.1)	121 (58.7)	78 (65.5)	0.208
From 25 to 30	58 (31.4)	70 (34.0)	27 (22.7)	
More than 30	14 (7.6)	15 (7.3)	14 (11.8)	
Systolic blood pressure				
More than 140 mm of Hg	81 (43.8)	109 (52.9)	52 (43.7)	0.127
Less than 140 mm of Hg	104 (56.2)	97 (47.1)	67 (56.3)	
Hyperlipidemia				
Total cholesterol more than 6.2 mmol/l	12 (6.5)	21 (10.2)	8 (6.7)	0.337
Total cholesterol of less than 6.2 mmol/l	173 (93.5)	185 (89.8)	111 (93.9)	
Control of diabetes				
Dietary control	0 (.0)	2 (1.0)	0 (.0)	0.001
Insulin Injection	32 (17.3)	20 (9.7)	4 (3.4)	
Oral medications	153 (82.7)	184 (89.3)	115 (96.6)	
Fasting Blood Glucose				
Less than 100 mg/dl	96 (51.9)	92 (44.7)	34 (28.6)	<0.001
From 100-150 mg/dl	70 (37.8)	87 (42.2)	48 (40.3)	
More than 150 mg/dl	19 (10.3)	27 (13.1)	37 (31.1)	
Glycosylated hemoglobin (HbA1c)				
Less than 7 %	125 (67.6)	101 (49.0)	40 (33.6)	<0.001
From 7 to 9 %	33 (17.8)	66 (32.0)	44 (37.0)	
More than 9 %	27 (14.6)	39 (18.9)	35 (29.4)	
Diabetic Macular Oedema				
Absent	146 (78.9)	148 (71.8)	43 (36.1)	<0.001
Present	39 (21.1)	58 (28.2)	76 (63.9)	

Data expressed as number of cases (percentage), DR= diabetic retinopathy

Overall, retinopathy was more prevalent in patients with type-2 DM compared with those with type-1 (38.2% v 2.2% for mild to moderate NPDR, and 21.5 % v 1.7 % for advanced DR respectively). During univariate analysis, patients with retinopathy showed statistically significant difference in duration of DM, FBG, HbA1c, and macular oedema compared to patients with no retinopathy ($p<0.001$). Insignificant differences were found in BMI ($p=0.208$), SBP ($p=0.127$), and hyperlipidemia ($p=0.337$). A multiple logistic regression model was then developed to identify which of the factors were related to each level of retinopathy.

Table -3 Multivariate analysis of risk factors for mild to moderate and advanced diabetic retinopathy (n = 510)

Risk factor	Mild to moderate retinopathy			Advanced retinopathy		
	Odds Ratio*	95% Confidence Interval	P value	Odds Ratio*	95% Confidence Interval	P value
Macular oedema	1.467	0.921 – 2.338	0.107	6.617	3.955 – 11.068	<0.001
Duration of Diabetes 05 to 10 years	6.150	3.293– 11.487	<0.001	2E008	2E008-2E008	<0.001
Duration of Diabetes more than 10 years	38.289	18.289 – 78.417	<0.001	2E009	1E009-3E009	<0.001

The results listed in Table-3 show that type of glycaemic control, HbA1C, and a high FBG were no longer significant. On the other hand, longer duration of diabetes and presence of macular oedema were still at risk of developing any grade of DR. When analysing these factors after considering mild to moderate NPDR and advanced retinopathy as separate dependent variables, it was found that as far as mild to moderate retinopathy was concerned, only duration of diabetes was a statistically significant risk factor (Odds Ratio 38.29 for more than 10 years and 6.15 to 5-10 years) and presence of CSME was not. In advanced DR both the variables were significant. During calculating the odds ratio the reference category was taken as no retinopathy. Similarly for duration of diabetes and its effect on retinopathy, the first category (duration less than five years) was taken as reference while absence of oedema was taken as the reference category.

DISCUSSION

With the improvement in the quality of health care in the various health institutes of the country in recent years, DM has emerged as one of the major health problems. Paralleling this high prevalence of diabetes is a concern that complications of diabetes, mainly diabetic retinopathy, in such subjects might also be high. In the present study diabetic retinopathy was present in 62.3% of the 510 patients considered for evaluation. Various studies give different figures for the prevalence of diabetic retinopathy. High prevalence rates of 50% or higher were found in UK11, near Australia and Sweden12. This could be a result of socioeconomic factors, which determine the access to and availability of medical care, the health care seeking behaviour of the specific group studied, as well as variation in the definitions used to define the presence of diabetes.

While the figure for mild retinopathy seems to be in line with other studies13 , the present study showed a higher prevalence of proliferative diabetic retinopathy which contrasted with most other reports that gave a maximum of 10% of prevalence of such a condition. However, in the study by Haddad14 and Jerneld15, the prevalence rate was similar to our study. A higher rate of DR could be explained by the fact that the microvascular complications of DR are higher in the subcontinent due to poorer diabetic control16.

Risk factors independently associated with any diabetic retinopathy, in order of importance, were, longer duration of diabetes, type of control, lean BMI, FBG, and macular oedema. Logistic regression analysis revealed certain independent risk factors associated with both the presence and severity of diabetic retinopathy; they were, longer duration of diabetes and macular oedema. Association of total cholesterol levels with DR has been clearly demonstrated, especially in type 2 DM patients17. However, this was not observed in the present study for any type of DR. This could be explained by low mean levels of total cholesterol (<200 mg/ dl) of our patients studied, and could reflect the major role of genetic factors in various stages of diabetic eye disease. On the other hand, method glycemic control was not associated with advanced DR in multivariate analyses. This absence of association could reflect improvement of glycemic control that results from medical advice, once diagnosis of microvascular chronic complication is established. However, the cross-sectional design adopted precludes confirmation of this hypothesis. Similarly the type of diabetes mellitus did not seem to be associated with the occurrence of diabetic retinopathy.

The duration of diabetes remained the strongest predictor for any diabetic retinopathy as well as its severity. Patients with duration 5-10 years had 6 times more chances to have mild to moderate retinopathy and 2E008 times more chances for advance retinopathy than patients with duration less than 5 years and no retinopathy. Similarly patients with duration more than 10 years had 38 times more chances to have mild to moderate retinopathy and 2E009 times more chance to have advance retinopathy than patients with duration less than 5 years and no retinopathy (table 3). Moreover, such an association has been observed by several other investigators as well18, and it was probably

related to the magnitude or prolonged exposure, or both, to hyperglycemia coupled with other risk factors.

The inverse relation between BMI and diabetic retinopathy was also observed in other similar studies10. As Asians with type 2 diabetes mellitus show lesser insulin secretion, as compared to Caucasian diabetic patients19, the catabolic effect of the lack of insulin over a long duration of hyperglycemia results in lean individuals.

The interesting aspect of this study, which is quite contrary to the published work in the international literature20, is the lack of significant association of blood pressure with the prevalence of retinopathy. This was also observed in a recent local study21, and it might be due to better awareness of hypertension then DR in general population. Reports in Asian developing countries8,22 have also observed an association of high levels of fasting plasma glucose and HbA1c with retinopathy. Our study also showed these factors to be significant in univariate analysis.

As regards to macular oedema, it was observed in 34% of patients, and its frequency increased with the severity of DR (7% in no DR group, 11.3% in mild to moderate group, and 15.9% in the group with advanced DR ($P < 0.001$). The frequency observed was slightly higher than a local study23, but that study involved rural population whereas our population was a mixed one, and rates of retinopathy and oedema are recognized to be higher in urban than rural population. Moreover CSME was defined on strict criterion as given in methodology. With multivariate analysis, however, significance of oedema was noticed only in the advanced retinopathy group wherein patients with macular edema had 6.6 times more chances to have advance retinopathy than patients with no macular edema and no retinopathy ($p < 0.001$)

The limitation of the present study was the target population and so the possibility of a selection bias. Another limitation was DR grading that was based on indirect ophthalmoscopy and not on fundus photography grading. This could have resulted in the underestimation of the prevalence of DR. It should be mentioned that our definition of hypertension differs from that of the American physician association from 2007, which defines appropriate blood pressure as less than 130/80 mmHg in diabetic patients; however, some of the major population-based surveys25 defined appropriate blood pressure in patients with diabetes as 140/90 mmHg.

Conclusion

In conclusion, presence of 62% of retinopathy in suspected DR patients attending a tertiary hospital shows that this condition continues to be a major public health problem despite current knowledge about advanced DR. Furthermore, prevalence of 24% of advanced DR stages is a warning sign. Those with a longer duration of diabetes, elevated fasting blood glucose and HbA1C levels, are at highest risk of presenting advanced DR forms. Finally, CSME should be suspected in presence of any degree of DR. This would minimize the occurrence of avoidable blindness in developing nations such as Pakistan.

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