Original Article

Prevalence of Diabetic Retinopathy among Type – 2 Diabetes Patients in Pakistan – Vision Registry

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Purpose: To estimate the prevalence of diabetic retinopathy (DR) among patients with type 2 diabetes mellitus (T2DM) in Pakistan.

Material and Methods: This is a cross-sectional study carried out in 25 centers across Pakistan between July 2009 to May 2010. Each centre recruited 9 consecutive patients meeting the eligibility criteria of age ≥ 18 years with known T2DM for ≥ 3 years and willing to provide written consent. Direct ophthalamoscopy to determine DR and blood tests for random blood sugar (RBS) and HbA_1c levels, were conducted. Descriptive statistics (frequency, proportion, and mean) were used to analyze the data.

Results: Of the 223 patients recruited, analysis was based on data gathered from 202 patients. The mean age of the patients was 52.9 ± 10.5 years, and their average RBS and HbA_1c levels were 219.2 ± 82.4 mg/dL and 8.9 ± 2.5%, respectively. Mean duration of diabetes was 8.8 ± 5.1 years. Over three-fourths (77.2%) of the patients had never been assessed for DR. The prevalence of DR was calculated at 56.9% (confidence interval: 50.1 – 63.3%). Factors associated with DR were systolic blood pressure (p = 0.009), diastolic blood pressure (p = 0.001) and duration of diabetes (p = 0.04).

Conclusions: The prevalence of DR in Pakistan is substantially high. Regular screening needs to be implemented for early diagnosis of DR.

Key Words: Diabetic Retinopathy, Prevalence, Type 2 diabetes mellitus.

Diabetes mellitus is a non-communicable medical disorder characterized by hyperglycaemia due to defective insulin secretion and is currently amongst the top ten causes of worldwide mortality.[1] The incidence of diabetes is on the rise, especially in developing nations like India and China,[2,3] and the estimated global burden for the year 2030 is 439 million people.[2] Pakistan currently ranks sixth amongst countries with the highest number of diabetes patients, and more than 11% of Pakistani adults have diabetes.[4] It is predicted that by 2030, Pakistan will rise to the 5th position with 13.9 million diabetic patients.[5]

Chronic hyperglycaemia in diabetes leads to various macrovascular (coronary heart disease, peripheral vascular disease, and stroke) and microvascular (retinopathy, neuropathy, and nephropathy) complications.[6] Given the observation that diabetes in most patients is diagnosed late, these micro- and macrovascular complications are already present in the patients at the time of diagnosis, and the frequency of their coexistence increases with the duration of diabetes.[7]

Diabetic retinopathy (DR) is the leading cause of visual impairment in adults worldwide[8]. In DR, the blood vessels in the eye become swollen and leaky and new abnormal vessels form on the retina. Eventually, DR causes irreversible blindness[9]. According to the American Diabetes Association (ADA), 21% of patients with diabetes have DR at diagnosis[10] and

more than 60% of patients with diabetes will have DR within two decades of diagnosis.[11] A recent meta-analysis of 35 population-based prevalence studies carried out in the US, Europe, Australia and Asia over a period of 28 years with data from 22,896 diabetes patients, revealed that the overall prevalence of DR is as high as 34.6% and more than 10% of the diabetes patients have vision – threatening DR.[12]

The findings of the two major diabetes trials, the Diabetes Control and Complications Trial [13] and the United Kingdom Prospective Diabetes Study,[14] have established the importance of tight glycaemic control (target HbA_1c levels under 7%) in reducing the risk of microvascular complications. This is especially beneficial in the early stages of DR and nephropathy. However, a vast majority of patients who develop DR do not display any symptoms till late stage. Since, early detection can prove beneficial in symptomatic amelioration and slowing the progression of DR, it is important to screen patients with diabetes for retinal disease on a regular basis[15]. According to ADA guidelines, ophthalmic examination should be conducted at the time of diabetes diagnosis[16], and repeated annually unless it is the ophthalmologist's clinical judgment to have the exam every 2 – 3 years.[17]

In Pakistan, there is insufficient data on the national prevalence and management of DR. A few community or hospital or region-based studies have been conducted, but the reported DR prevalence rates vary widely (15% – 33.3%).[18-22] It is also estimated that only about 33% to 44% of the patients with diabetes in Pakistan have accurate knowledge of their disease and its complications.[4,23] Cross-sectional studies play a vital role in determining the extent of the disease prevalence and can aid in implementation of effective strategies for early diagnosis, management, and patient education / awareness. Accordingly, we present the findings of the Prevalence of Diabetic Retinopathy amongst type – 2 diabetic population in Pakistan (VISION) registry that was designed to assess the prevalence of DR among diabetes patients in Pakistan and the association between DR and glycaemic control.

MATERIAL AND METHODS

The VISION registry was a national, multicentre, non-interventional, cross-sectional registry. It was designed to primarily estimate the prevalence of DR amongst patients with type 2 diabetes in Pakistan. The secondary objectives of this study were to 1) determine the distribution of DR across HbA_1c levels; 2) document patient profile of all patients willing to participate; and 3) document other diabetic complications based on clinical signs and symptoms and / or historical evidence. The study was conducted in 25 randomly selected centres from 9 cities across 4 provinces in Pakistan. The study was conducted in accordance with the principles laid by the 18th World Medical Assembly, the guidelines of Good Epidemiology Practice and all local laws and regulations. Written informed consent was obtained by the investigator from each patient enrolled in the study.

Study investigators were selected from a list of qualified general practitioners. Each centre was supported by services of qualified ophthalmologists. Each investigator recruited 9 consecutive patients who met the inclusion / exclusion criteria. Patients enrolled were of either gender, aged ≥ 18 years with type 2 diabetes for ≥ 3 years, provided an informed consent, and were willing to undergo ophthalmoscopic examination. Patients with known ophthalmic disorders other than DR were excluded.

On a scheduled day in the general practitioner's clinic, study patients were examined for evidence of DR by nine ophthalmologists. Fundoscopic examinations were conducted on dilated pupils using a direct ophthalmoscope (Welch Allyn Inc, Skaneateles Falls, NY, USA). Random blood sugar (RBS) levels were measured using OneTouch® blood glucose meter (Life Scan Inc., a Johnson & Johnson Company, Milpitas, CA). Diabetic neuropathy was determined by 10-g Semmes-Weinstein monofilament examination. Additionally, 2 consecutive seated blood pressure readings were recorded at 3 minutes interval. Patients also underwent the HbA_1c test by NGSP certified HbA_1c machine at a central laboratory (The Aga Khan University Hospital, Karachi).

Patient data was recorded on case report forms and included details on general and lifestyle information, diabetic history, RBS and HbA_1c levels, blood pressure, anthropometric measurements, ophthalmoscopic and microfilament findings and history of nephropathy, if present. Patients with DR findings were referred to specialized eye care centres for further consultation.

Given a reported prevalence of 26% of DR amongst a DM prevalence of 11% in Pakistan[24], 225 patients were planned to be recruited to give the study a precision of ± 6% at 95% confidence interval (CI)

after accounting for incomplete forms, withdrawal after consent, etc.

Being a descriptive cross-sectional study, categorical variables are reported as proportions and percentages while continuous variables are reported as mean with standard deviation (SD).

RESULTS

Of the 223 patients recruited, analysis was based on data gathered from 202 patients. The average age of patients evaluated was 52.9 ± 10.5 years (Table 1). There were more men (53.5%) than women (46.0%) enrolled. Average body mass index (BMI) was 28.6 ± 8.9 and the mean duration of diabetes in the patients was 8.8 ± 5.1 years. The average blood pressure was 133.5 ± 17.4 mm Hg systolic and 86.1 ± 9.6 mm Hg diastolic. Mean RBS was 219.2 ± 82.4 mg/dL while average HbA_1c was 8.9 ± 2.5%.

The most commonly observed risk factor was hypertension, reported in 125 (61.9%) patients, followed by sedentary lifestyle, reported in 90 (44.6%) patients (Table 1). Other risk factors reported in more than 20% of the patients included metabolic syndrome, past smoking, and family history of cardiovascular disorders.

Over three-fourths of the patients (n=163, 80.7%) were on oral antidiabetic (OAD) therapy (Table 1). The drug classes of choice were biguanide (76.7%) and sulphonylurea (74.8%). Only about one-third of the patients (35.6%) were on a single OAD agent while half the number of patients (50.0%) were on 2 OADs. Insulin monotherapy was reported in 4 (1.9%) patients while insulin in combination with OAD had been prescribed to 29 (14.4%) patients.

A total of 115 patients out of 202 (56.9%, CI: 50.1%-63.3%) had DR. As shown in Figure 1, the most common DR findings were haemorrhages (70/202, 34.7%), hard exudates (67/202, 33.2%), cotton wool spots (21/202, 10.4%) and neovascularization (15/202, 7.4%). A substantial number of patients (n = 157, 77.7%) had never been assessed for DR prior to enrolment in the reported study.

On 10-g monofilament examination, neuropathy was detected in 59.9% (121/201) patients and nephropathy was reported by 6.4% (13/202) patients.

A comparison of various parameters in patients with and without DR is presented in Table 2. Patients with DR had a higher systolic blood pressure than patients without DR (136.4 ± 17.9 mmHg versus 129.7 ± 16.0 mmHg; p = 0.009). Similarly, diastolic blood pressure in patients with DR was higher than patients without DR (88.1 ± 9.8 mmHg versus 83.5 ± 8.7 mm Hg; p = 0.001).

Moreover, patients with DR had had DM for a longer period than those without DR (average duration 9.4 ± 5.6 versus 7.9 ± 4.2 years, p = 0.04). There was no statistically significant difference in the association of DR with other risk factors. In addition, more percentage of patients without than with DR were on OAD monotherapy (34.9% versus 17.4%; p = 0.005).

Diabetic retinopathy was prevalent across all levels of HbA_1c values (Figure 2). The highest prevalence of DR was in patients with HbA_1c levels > 10% (41/115, 35.6%). Interestingly, the group with the next – highest prevalence was the one with HbA_1c levels < 7% where 45 (22.3%) patients had DR.

DISCUSSION

With a burgeoning epidemic of diabetes in South Asia and the significant impact of diabetic complications on patients and the healthcare system, the VISION registry aimed at estimating the prevalence of DR in Pakistan. The findings of this first attempt at understanding the pervasiveness of DR nationally did reveal some very significant results.

In comparison to the previously reported DR prevalence of 26% in patients with diabetes by Khan *et al* in 1991,[24] the current prevalence has doubled to 56.9%, which is substantially higher than any previously reported value worldwide[12]. While our study was not designed to identify the reasons for this dramatic increase, one can only speculate on subjective factors like lack of patient and physician education, glycaemic control, treatment adherence, and regular screening for DR. The latter holds especially true since we discovered that despite **Fig. 2:** Distribution of patients with diabetic retinopathy by their HbA_1c levels, N = 115 having diagnosed diabetes for an average duration of 8.8 ± 5.1 years, over three-fourths of the patients had never been assessed for presence of DR prior to enrolment in the VISION registry. Since DR progression can be slowed with early detection, this finding provides impetus to include retinal screening as a routine part of diabetes management, and general practitioners need to have a baseline assessment of their diabetic patients upon diagnosis. Moreover, comprehensive patient education programs on DR should be provided by the

Table 1: Patient characteristics, risk factors and antidiabetic therapy, N = 202

Patient Characteristics	No. of Patients n (%)
Age, in years, mean (SD)	52.9 (10.5)
Men	108 (53.5)
Women	93 (46.0)
BMI, kg/m^2, mean (SD)	28.6 (8.9)
Duration of diabetes in years, mean (SD)	8.8 (5.1)
SBP, mmHg, mean (SD)	133.5 (17.4)
DBP, mmHg, mean (SD)	86.1 (9.6)
RBS, mg/dl, mean (SD)	219.2 (82.4)
HbA1c, %, mean (SD)	8.9 (2.5)
Risk Factors	
Hypertension	125 (61.9)
Sedentary lifestyle	90 (44.6)
Metabolic syndrome	69 (34.2)
Past smoker	43 (21.3)
Family history of premature CVD	43 (21.3)
Coronary artery disease	25 (12.4)
Nephropathy	23 (11.4)
Current smoker	22 (10.9)
Peripheral artery disease	22 (10.9)
Myocardial infarction	13 (6.4)
Congestive heart failure	12 (5.9)
Stroke	2 (1.0)
Antidiabetic therapy	
OAD	163 (80.7)
Metformin	155 (76.7)
Sulphonylurea	151 (74.8)
TZD	27 (13.4)
Monotherapy	72 (35.6)
Two OADs	101 (50.0)
> two OADs	22 (1.9)
Insulin	4 (1.9)
Insulin + OAD	29 (14.4)

Values are n%, unless otherwise specified.
Abbreviations: SD - standard deviation, BMI - body mass index, SBP - systolic blood pressure, DBP - diastolic blood pressure, RBS - random blood sugar, CVD - cardiovascular disorder, OAD - oral antidiabetic, TZD - thiazolidinedione

Table 2: Comparison of parameters in patients with and without diabetic retinopathy, N = 202

	Retinopathy		p-value
	Yes N = 15	No N = 87	
Patient Characteristics			
Age, in years, mean (SD)	54.1 (10.5)	51.4 (10.4)	0.07
Men	56 (48.7)	51 (59.3)	0.15
Women	58 (50.4)	35 (38.4)	
BMI, kg/m^2, mean (SD)	29.8 (6.9)	29.9 (6.9)	0.80
Duration of diabetes in years, mean (SD)	9.4 (5.6)	7.9 (4.2)	0.04
SBP, mmHg mean (SD)	136.4 (17.9)	129.7 (16.0)	0.009
DBP, mmHg, mean (SD)	88.1 (9.8)	83.5 (8.7)	0.001
RBS, mg/dl, mean (SD)	225.2 (89.0)	213.6 (68.9)	0.32
HbA1c, %, mean (SD)	9.2 (2.6)	8.6 (2.2)	0.07
Risk Factors			
Hypertension	74 (64.3)	51 (60.7)	0.80
Sedentary lifestyle	52 (48.1)	38 (46.9)	0.58
Metabolic syndrome	39 (33.9)	30 (35.3)	0.32
Past smoker	28 (24.6)	15 (17.9)	0.23
Family history of premature CVD	22 (19.3)	21 (25.0)	0.52
Coronary artery disease	16 (13.9)	9 (10.3)	0.76
Nephropathy	17 (14.8)	6 (7.0)	0.22
Current smoker	16 (13.9)	6 (7.1)	0.21
Peripheral artery disease	17 (14.9)	4 (4.7)	0.05
Myocardial infarction	9 (7.8)	4 (4.7)	0.37
Congestion heart failure	10 (8.8)	2 (2.4)	0.28
Stroke	1 (0.9)	1 (1.2)	0.98
Antidiabetic Therapy			
OAD	91 (79.1)	72 (83.7)	0.41
Monotherapy	20 (17.4)	30 (34.9)	0.005
Two OADs	56 (48.7)	36 (41.9)	0.34
> two OADs	15 (13.0)	6 (6.9)	0.16
Insulin	3 (2.6)	1 (1.1)	0.47
Insulin + OAD	20 (17.4)	9 (10.5)	0.17

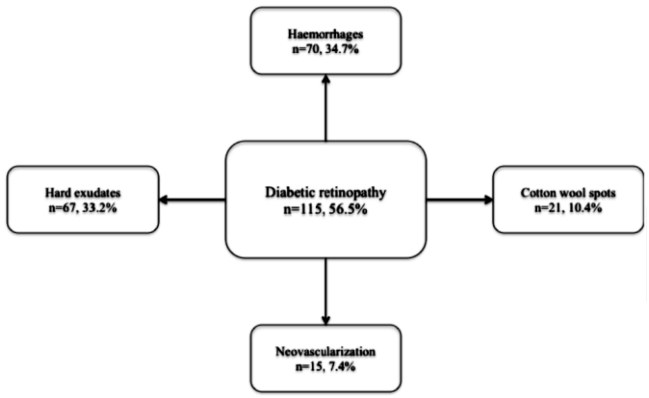
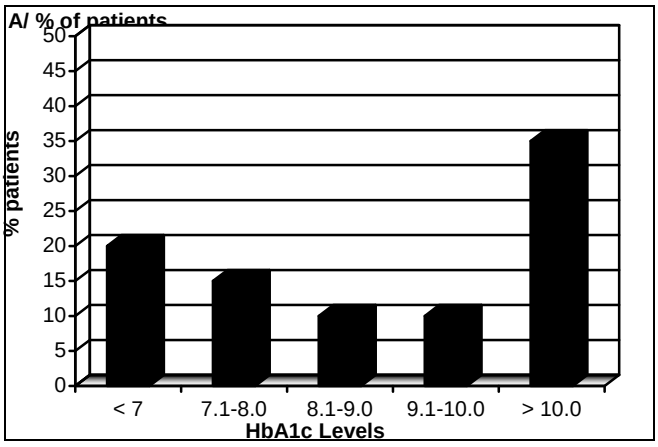
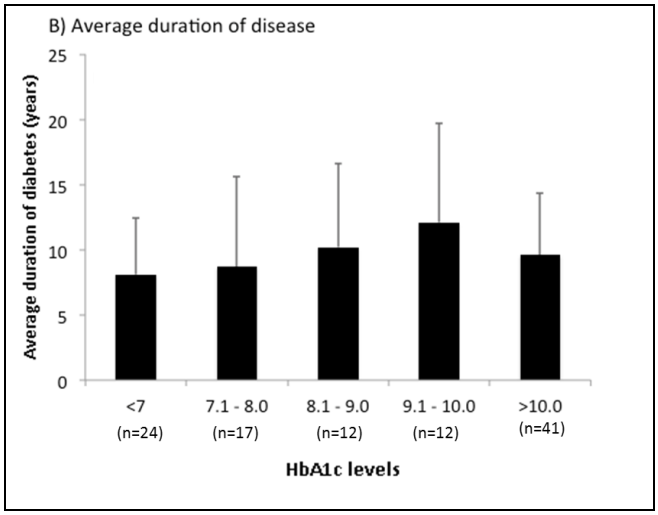


Fig. 1: The most common diabetic retinopathy findings noted in analysed patients (n=115)



Data was missing for 9 patients



Data was missing for 5 patients

physician/ophthalmologist at the time of diagnosis of diabetes.

The other major finding of the VISION registry is that it revealed the association of elevated blood pressure with DR. The systolic blood pressure in patients with DR was higher than that in patients without DR (136.4 ± 17.9 mm Hg versus 129.7 ± 16.0 mm Hg; p=0.009). Also, the diastolic blood pressure in patients with DR was higher than that in patients without DR (88.1 ± 9.8 mm Hg versus 83.5 ± 8.7 mm Hg; p = 0.001). We also discovered that average duration of diabetes was longer in patients with DR (9.4 ± 5.6 versus 7.9 ± 4.2 years; p=0.04) than that in patients without DR. The correlation between blood pressure and duration of diabetes with DR has been demonstrated in recent studies and our findings reiterate these.[25-27]

Hypertension and diabetes are usually co-morbid. Patients with diabetes are 1.5 – 2 times more susceptible to hypertension than patients without diabetes[28] and the co-existence of diabetes and hypertension is shown to accelerate microvascular complications[29]. A recent study to estimate the global prevalence of DR indicated hypertension as one of the major risk factors for DR.[12] In the VISION registry, we observed that the most common risk factor was hypertension, reported in 61.9% patients. The proportion of patients with hypertension was almost the same in patients with or without DR (64.3% vs. 60.7%, p = 0.8) However, patients with DR were relatively inadequately controlled for blood pressure compared to those without DR as described above. Better control of blood pressure in diabetic patients is likely to help impede the progression of DR.

Acetylated haemoglobin (HbA_1c) level is another major indicator of risk for DR. Diabetic patients with a tight glycaemic control of HbA_1c < 7% have slower progress of microvascular complications while those with poor glycaemic control tend to rapidly deteriorate.[12] The other major observation from the landmark Diabetes Control and Complication Trial is that even after regaining appropriate glycaemic control, a prolonged preceding hyperglycaemia does not halt the progression of DR.[30] This imprinted effect of high blood glucose even after normal levels have been attained is termed as "metabolic memory" and plays an important part in the development and progression of diabetic complications, especially DR.[31-33] The VISION registry revealed that patients with DR were present across the range of HbA_1c levels.

Expectedly, the rate of prevalence of DR (35.6%) was highest in patients whose HbA_1c levels were above 10%. However, the group with the next highest DR prevalence rate was the one in which the mean HbA_1c levels were < 7%. While this does not conform to the observations from other studies[34-35] could probably be attributed to the presence of other contributing risk factors – hypertension, peripheral artery disease, etc. It may also be postulated that these patients to begin with had an elevated HbA_1c and also developed DR but eventually managed to have a better glycaemic control without reversal of DR changes. This suggests that early diagnosis and good glycaemic control at initial stage of diabetes sets in a good metabolic memory and hence are critical in preventing or delaying onset of DR. Considering the limitation of cross sectional study it is suggested to follow the temporality of observations in such cohort of patients. Nonetheless, one can advocate early detection through regular blood check-ups and achievement of tight glycaemic control for delaying the progression of DR.

The other clinically significant complications of diabetes are neuropathy and nephropathy. Diabetic neuropathy usually results in foot ulceration, Charcot neuroarthropathy, and limb amputation;[36] while diabetic nephropathy leads to chronic renal failure.[37] Though there is a dearth of information on the global prevalence of these complications, certain regional studies indicate that the prevalence of neuropathy is between 22% and 29% amongst the diabetics in Europe,[38-40] and the prevalence of nephropathy is 5.5% in India and 22.3% in Asian Indians in the United Kingdom.[41] Given the seriousness of these diabetic complications it is equally necessary to monitor the prevalence of these in patients with diabetes.[42] In the VISION registry, a total of 6.4% of the diabetics had comorbid nephropathy. However, the prevalence of neuropathy was at a staggering 59.9%. This finding raises some critical questions on whether we are doing enough to increase awareness amongst patients and physicians, to ensure our physicians are compliant with international guidelines, to understand the gap between real-world practices and international recommendations, and to estimate the prevailing load of diabetic complications in our country. Once understood, we can implement effective strategies to positively influence public health and decrease the economic burden of diabetes in Pakistan.

Another observation from our study was the pharmacotherapy of Type 2 diabetes in Pakistan. More than 80% of the patients were prescribed OAD, a substantial number (n = 101; 50.0%) of these being prescribed a dual therapy, usually biguanide and sulphonylurea. Insulin usage was reported in a bit over 15% of the study patients. This is not entirely surprising given the ease of administration of OADs. Besides, most physicians and patients are hesitant to initiate insulin treatment due to the fear of injectable drug delivery, hypoglycaemia, weight gain and a "psychological insulin resistance".[43-44] Traditionally, management of diabetes progresses from lifestyle management to OAD to insulin.[45] However, keystone studies have demonstrated that insulin therapy reduces micro- and macrovascular complications in diabetics.[46,47] Currently, a new school of thought is emerging with its premise being early insulinization to elicit long-lasting glycaemic control.[45] In support, recent clinical trials have demonstrated the benefits of insulin therapy in new Type 2 diabetics in terms of glycaemic control, treatment satisfaction and quality of life.[48,49] The observation that over half of the patients in our study had DR but were still managed with OADs warrants the need for a well-monitored, better pharmacologic management of Type 2 diabetes.

VISION registry provides seminal insights on the burden DR in Pakistan despite few limitations. Being a cross-sectional study, it does not reveal the reasons for the surge in the prevalence of DR in Pakistan within a span of > 20 years. This apparent surge may yet be an underestimate of the disease burden as this study was conducted in the offices of the general practitioner, who is the primary contact for majority of the population. It is also known that for every patient seeking care at the grass root level there is at least an equal number who for different reason may not seek care.[50] Moreover, the patients in this study were only examined for the presence of DR and not classified for a particular kind or a particular stage of DR. Current statistical analysis was simple descriptive addressing study objectives. Rigorous data mining may generate more hypotheses for future perusal.

CONCLUSION

In conclusion, this first nationwide DR registry does indicate the gravity of the situation in Pakistan and serves as a stimulus to overhaul the current diabetes management practices and implement more appropriate and contemporary initiatives.

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