The prevalence of diabetic retinopathy in Faisalabad, Pakistan: a population-based study

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Aim: To determine the plasma prevalence and characteristics of diabetic retinopathy (DR) among Pakistani diabetic patients in the Faisalabad region. Diabetes mellitus (DM) is a major cause of avoidable blindness worldwide. People with DR are 25 times more likely to become blind than nondiabetics.

Materials and methods: The incidence of retinopathy was determined in 1524 people with diabetes during April 2008 and January 2009. Physician-diagnosed diabetic patients underwent an eye examination by ophthalmoscopy and fundus photography. Participants were also interviewed and examined in order to determine demographic characteristics and medical history.

Results: Of the 1524 patients screened, 183 (12%) had DR. Of these, 7% (106) had nonproliferative DR and 5% (77) had proliferative DR. Clinically significant macular edema was detected in 1.2% of patients. The prevalence of DR was higher in patients with type 1 diabetes than in those with type 2 diabetes. This difference was found to be statistically insignificant, however (P > 0.05). About 3% of the diabetic patients in our study had a family history of diabetes and only 6% had a history of regular eye examinations.

Conclusion: This study demonstrated a high prevalence of DR in Faisalabad. An organized approach is needed to ensure adequate prevention and treatment in patients with diabetes.

Key words: Retinopathy, diabetes mellitus, hyperglycemia

Introduction

Retinopathy, a potentially devastating microvascular complication in diabetes mellitus (DM), is a leading cause of acquired blindness. Diabetic retinopathy (DR) is known best in terms of epidemiology and natural history. Diabetic patients are 5 times more likely to experience a loss of vision than nondiabetics. Nearly 80% of the type 2 diabetic population experiences earlier clinical signs of DR. Patients with poor long-term glycemic control are more vulnerable to DR than to other secondary sequels of diabetes (1-3). Factors such as the duration of diabetes, age, gender, and glycemic control are associated with the development and progression of DR (3,4). The best empirical tool available to clinicians trying to delay the onset and progression of diabetic retinopathy is achieving near-normal levels of blood glucose (1). Nonetheless, DR remains a frightening prospect for patients and frustrates physicians.

In 2003, 6.2 million Pakistani people had diabetes, a number that is expected to reach 11.6 million by 2025. By then, Pakistan will rank fourth among countries most affected by diabetes.
Diabetic retinopathy in Faisalabad

(5). In Pakistan, reports project that casualties from diabetes will rise to 51% over the next 10 years. The growth of such an epidemic disease definitely burdens the economics of public and private sector health plans (6). Faisalabad is the third largest city in Pakistan, with an estimated population of 4 million. Existing studies (7-14) on DR prevalence are lacking in data from this area. This population-based study was therefore performed in order to determine the DR prevalence and clinical characteristics of the disease in the Faisalabad region.

**Materials and methods**

The incidence of retinopathy was determined in 1524 people with diabetes during April 2008 and January 2009. Before recruitment, ethical approval was granted by the institution's Advanced Studies and Research Board. The inclusion criteria for recruitment were based on disease duration (candidates should have been living with diabetes for more than 1 year) and age (candidates had to be between 20 and 70 years of age).

Our investigation was performed by 1 physician and 2 ophthalmologists who were experienced in treating DM and DR. After informed written consent, participants were interviewed and examined to determine their demographic, clinical characteristics, and medical history. Medical history included all medical conditions that had been and were presently being treated. Patient care was documented, from the first practitioner to the specialist. Baseline demographic characteristics such as age, gender, type of diabetes, and diabetes duration were also documented. A detailed ophthalmic examination was given, which included visual acuity, slit-lamp biomicroscopy, intraocular pressure, gonioscopy, dilated funduscopy including stereoscopic examination of the posterior pole, and an examination of the peripheral retina and vitreous (15,16).

Initial retinal examinations are recommended for patients with type 1 diabetes 3-5 years after diagnosis and for type 2 diabetes patients at the time of diagnosis. Follow-up screenings for both types of DM should be performed annually, although abnormal findings may necessitate more frequent eye examinations (17,18). All of our participants were examined only once, at the start of the study, but they were informed about the recommended examination schedule.

Retinopathy was diagnosed using direct and indirect ophthalmoscopy, with results divided into 2 categories, nonproliferative (NPDR) and proliferative diabetic retinopathy (PDR). The criteria for each category were as follows.

**NPDR:** Presence of microaneurysms (less than in severe NPDR); the presence of any of the following: >20 intraretinal hemorrhages in each of the 4 quadrants, definite venous beading in 2+ quadrants, prominent intraretinal microvascular abnormalities in 1+ quadrant, and no signs of proliferative retinopathy.

**PDR:** Presence of one or more indicators of neovascularization, vitreous/preretinal hemorrhage, or diabetic macular edema (DME). DME was identified by apparent retinal thickening or hard exudates in the posterior pole, retinal thickening or hard exudates in the posterior pole but distant from the center of the macula, retinal thickening or hard exudates approaching but not involving the center of the macula, or retinal thickening or hard exudates involving the center of the macula (18,19).

For the biochemical assay, 5-mL blood samples were collected in EDTA-coated tubes from all study participants. Blood plasma samples, separated by centrifugation at 4500 rpm for 20 min, were stored in vials at −20 °C until further analysis was possible. Postprandial glucose and A1c were measured with a glucose oxidase and A1c kit (Biosystem, Spain). The thiobarbituric acid (TBA) colorimetric technique was used for the determination of plasma protein nonenzymatic glycation (NEG) (20). All measurements were performed in triplicate in our clinical-medical biochemistry laboratory with adherence to quality control procedures. Descriptive statistics were expressed as a number (n), a mean ± SD, or a percentage (%) ± SD, as appropriate. For analytic purposes, the chi-square test was utilized with SPSS 14 with the level of significance set at P ≤ 0.05.
Results

Baseline demographic and clinical characteristics of the participants are outlined in the Table. Case participants were further stratified into 3 groups: diabetic patients with NPDR, diabetic patients with PDR, and diabetic patients without DR. Of the 1524 patients examined, 183 (12%) had DR. Of these, 7% and 5% had nonproliferative DR and proliferative DR, respectively. Clinically significant macular edema was detected in 1.2% of patients. The prevalence of DR was higher in type 1 diabetes patients when compared to type 2 diabetics. About 3% of our diabetic patients had a family history of diabetes and only 6% had a history of regular eye examination. Differences in mean postprandial glucose, HbA1c, total proteins, and NEG levels among the 3 groups were insignificant (P > 0.05).

Discussion

Retinopathy, a potentially devastating microvascular complication that occurs with diabetes, is a leading cause of acquired blindness. Little research has been performed on the incidence of DR and its clinical characteristics among the Pakistani population. To our knowledge, none of the previous studies from Pakistan (7-14) describe the incidence of DR in Faisalabad. The current study demonstrates that the prevalence of DR was 12% in a representative sample of diabetic patients in Faisalabad, Pakistan in 2008-2009. This prevalence is analogous to the rates previously reported (15% to 19.9%) in the literature (14,21-24).

A study of chronic complications by the Diabetic Association of Pakistan (8) reported that eye damage (retinopathy) affected 43% of the 500 diabetic patients examined. Pilot studies performed by Kayani et al. (9) and by Khan (10) suggested a higher prevalence of DR (26.1% and 33.3%) among diabetic Pakistanis. Wong et al. observed a 35% prevalence of DR in Singapore (25), while Ossama et al. observed a 42.4% DR incidence among the Omani population (26). Regarding the prevalence of NPDR (7%) and PDR (5%) observed in our study, ambiguous results exist

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Diabetic Patients with NPDR</th>
<th>Diabetic Patients with PDR</th>
<th>Diabetic Patients without DR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic subjects (n)</td>
<td>106</td>
<td>77</td>
<td>1341</td>
</tr>
<tr>
<td>Sex (male/female)</td>
<td>65/41</td>
<td>43/34</td>
<td>833/508</td>
</tr>
<tr>
<td>Diabetes type (1/2)</td>
<td>62/44</td>
<td>45/32</td>
<td>714/627</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>8.3 ± 2.41</td>
<td>9.66 ± 1.31</td>
<td>8.1 ± 2.92</td>
</tr>
<tr>
<td>Family history of diabetes (n)</td>
<td>17</td>
<td>10</td>
<td>15</td>
</tr>
<tr>
<td>History of regular eye examination (n)</td>
<td>29</td>
<td>47</td>
<td>15</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>11.78 ± 1.36</td>
<td>12.4 ± 2.41</td>
<td>11.44 ± 1.89</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>11 ± 0.5</td>
<td>10 ± 1.1</td>
<td>10 ± 0.87</td>
</tr>
<tr>
<td>Total plasma proteins (g/dL)</td>
<td>12.89 ± 0.75</td>
<td>13.61 ± 1.7</td>
<td>13.01 ± 1.97</td>
</tr>
<tr>
<td>NEG (mol/mol)</td>
<td>1.27 ± 0.55</td>
<td>1.35 ± 0.35</td>
<td>1.33 ± 0.77</td>
</tr>
</tbody>
</table>

Data as number (n), mean ± SD, or percentage (%) ± SD
NPDR: Nonproliferative diabetic retinopathy, PDR: proliferative diabetic retinopathy, NEG: nonenzymatic glycation
In the literature. Among Omani diabetics, NPDR and PDR were discovered in 4% and 12.8% patients (26). In contrast, 2 studies from Shanghai indicated 19.4%-21.6% and 0.5%-1.3% prevalence of NPDR and PDR, respectively (24,27). The comparison of prevalence rates using different methodologies requires caution. In the multiethnic population of Mauritius, the prevalence of NPDR and PDR was 42% and 2.3%, respectively, among known diabetics (28). Collins et al. observed a 38.7% and 4.5% incidence of NPDR and PDR in the Polynesian population (29). The Wisconsin Epidemiologic Study of DR indicated prevalence rates of 35.5% for NPDR and 2.9% for PDR in Caucasians (2). A direct comparison of rates between studies indicates variation in prevalence among various ethnic groups. Haffner et al. proposed that insulin resistance might explain these apparent differences (30).

In our study, the prevalence of DR was higher in type 1 diabetic patients when compared with type 2 diabetics. Hietala et al. (31) found a familial clustering of proliferative retinopathy in patients with type 1 diabetes. This observation suggests a genetic component in the pathogenesis of proliferative retinopathy in type 1 diabetes. After living with diabetes for 20 years, nearly all patients with type 1 diabetes were found to have some degree of retinopathy (32). Type 2 diabetes involves islet dysfunction and insulin resistance, which may improve with treatment. Type 2 diabetes is often associated with genetic and environmental factors, but the nature of the interactions is complex and not clearly defined (33,34). Such factors may justify the high prevalence of DR among type 1 diabetic patients found in our study.

Contrary to these observations, several studies (35-37) suggest the presence of retinopathy and proteinuria (indicating renal damage) in approximately one-third of type 2 diabetics at the time of diagnosis. Generally, patients have type 2 diabetes mellitus for about a decade before the diagnosis is made, and it is estimated that about half of the cases are undiagnosed (38). A direct association between retinopathy and diabetes duration has been shown to exist (39). Variations in average diabetes duration was not found to be significant (P > 0.05) among diabetics with NPDR, PDR, and those without DR, and the established male preponderance in DR prevalence (21,40) was not shown by our study population. A consistent gender pattern in the DR prevalence of the Faisalabad region (P > 0.05) is supported by another study (25). Genetic predisposition to DR (41) was also not prominent in our data analysis, as only 3% of patients had a family history of DR.

The precise relevance of postprandial glucose is not exactly comprehensible or quantifiable in DM. Evidence shows that, after mean daily blood glucose, the postprandial glucose level is the major determinant of the HbA1c level (42-45), and a reduction in postprandial hyperglycemia significantly reduces the HbA1c level in diabetics. Postprandial excursions of blood glucose may be involved in the development of diabetes complications (46-48).

In our research, the difference in postprandial blood glucose levels among diabetic subjects with NPDR, those with PDR, and those who showed no signs of DR was determined to be insignificant. Elevated 2-h plasma glucose measurements (16.6 mmol/L) among diabetics with retinopathy were observed by Dowse et al (28).

Many lines of evidence attest to the fact that the direct deleterious action of glucose and other sugars on proteins, known as glycation or the nonenzymatic glycosylation process, attenuates the development of a range of diabetes-related complications. Postprandial glucose levels were measured because intensive blood glucose monitoring during both fasting and postprandial states is important for glycemic control (49). Postprandial glucose and HbA1c were analogous (P > 0.05) among diabetics with NPDR, those with PDR, and those with no such ocular complications. Effective glycemic control has been demonstrated to reduce both the incidence and progression of DR (50,51).

The nonsignificant difference in blood glucose and HbA1c values among all 3 study groups may be due to the fact that plasma hemoglobin A1c (HbA1c) reflects ambient mean glycemia over a period of 2 to 3 months (51). Although glycemic goals should be individualized based on several clinical factors, most diabetic patients would probably benefit from glucose being lowered to a hemoglobin A1c level between 7% and 8% (52). Factors such as disease severity, health status, and poorer quality of care are often associated
with differences in glycemic levels, but these factors did not fully explain the higher HbA1c levels in all races (53,54).

Metabolic derangements lead to a breaking down of tissue protein in DM. Anabolic processes like protein synthesis are sacrificed to catabolic activity such as gluconeogenesis (55,56). All of the case groups in our study had a negligible difference (P > 0.05) in total plasma proteins levels. These results are justifiable when considering that the enhanced protein degradation associated with diabetes and starvation is fundamentally different from normal protein catabolism. In normal eukaryotic cells, large molecular weight proteins tend to be degraded more rapidly than small proteins. Acidic proteins tend to be degraded more rapidly than neutral or basic proteins, and glycoproteins tend to be degraded more rapidly than nonglycoproteins. All 3 of these general correlations are thought to be absent or markedly reduced in the liver and muscle of diabetic and starved rats. These results suggest that diabetes alters the general characteristics of intracellular protein degradation in the target tissues of insulin. The degradation of serum proteins is also affected in cases of diabetes. Under normal conditions, a general correlation exists between the isoelectric points of serum proteins and their degradative rates; this relationship is abolished in diabetes (57).

Nonenzymatic glycation (NEG) is the covalent binding of reducing sugars to α- or ε-amino groups on protein (58). Glucose and protein initially form a labile glycosylamine or Schiff base, the concentration of which varies with hourly changes in the glucose concentration. Over time, this intermediate product undergoes an irreversible Amadori rearrangement to produce a more stable glycated protein (59,60). High concentrations of Amadori product indicate poor diabetic control and are associated with an increased risk of developing some of the longer-term complications of the disease (61-63). Quantitative analysis of these end products could provide a tissue measure of integrated glycemia over several years and an estimate of the consequent risk of developing the above complications. Advanced glycation end products (AGEs) are found in the retinal vessels of diabetic patients and their levels correlate with that in serum as well as with the severity of retinopathy. It is also known that AGEs accumulate in the peripheral nerves of diabetic patients and that the use of anti-AGE agents improves nerve conduction velocities and neuronal blood flow abnormalities (64-67).

Averaged NEG plasma concentrations in diabetics with PDR were higher than those in patients with NPDR or those without DR, but the difference was insignificant (P > 0.05). In 2002 and 2004, Tan et al. (68,69) indicated that diabetic patients had higher plasma glycation than that of normal subjects (4.24 ± 0.88 compared to 3.15 ± 0.81 unit/mL [2002]; 4.6 ± 0.7 compared to 3.1 ± 0.8 unit/mL [2004]). Our results support the findings of Anitha et al. (70), who investigated the association of the advanced glycation index (AGI), a simple assay to detect AGEs in serum, with the severity of DR in type 2 diabetic subjects. Their findings showed that AGI values increased with the severity of DR. Among diabetic subjects, AGI (mean ± SE) was higher among subjects with nonproliferative diabetic retinopathy (6.7 ± 0.1 U) and proliferative diabetic retinopathy (9.1 ± 0.3 U) than among subjects without DR.

These results support the description of diabetes as a disease characterized by accelerated ocular complications. Protein glycation may be implicated in the development of diabetic retinopathy. Intensive glycemic control by multiple insulin injection therapy can delay the onset and progression of this complication, however.

Conclusion

This study demonstrated a high prevalence of DR in Faisalabad. An organized approach is needed for adequate prevention and treatment in patients with diabetes.
References


