ABSTRACT
INTRODUCTION: Diabetic Retinopathy (DR) is a chronic eye concern for developing blindness in the patients of T2DM in low and middle income countries. Globally, the prevalence of DR was reported to be around 75% among type 2 diabetic patients (T2DM) patients. However, in Pakistan the figure is approximately 28.7%. Clinically there are three stages of DR depends upon the severity of the disease known as non-proliferative (NPDR), proliferative DR (PDR) and diabetic macular edema (DME).

OBJECTIVE: Thus, this study aims to investigate the prevalence of DR with respect to its categorized types and associated risk factors in T2DM patients localized in Nawab Shah District. METHODOLOGY: It is a cross-sectional study comprised of ins=381 subjects of DR ethical approval and informed consent was taken for volunteer participation. Detailed questionnaire was filled out for the collection of sociodemographic data. Anthropometric and biochemical measures were estimated for all study participants. Data analysis is performed by SPSS v 22.0. RESULTS: In this study, the prevalence of DR was found to be 44.4%. However, 36.5% prevalence rate is obtained for NPDR and 41.4% for PDR patients. Though, smoking, hypertension, higher BMI and positive family history of diabetes found to be more abundant and showed an association with the pathogenesis of higher PDR diagnosis as compared to NPDR. Therefore, this study provides the first report on prevalence of DR in Nawab Shah District. Moreover, more studies are required to evaluate the association of this higher prevalence rate DR with the environmental and genetic aspects.

KEYWORDS: Diabetic retinopathy, prevalence, proliferative, socio-demographic

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INTRODUCTION
Type 2 diabetes mellitus (T2DM) is a well-known metabolic syndrome in which individuals suffered from hyperglycaemia due to impaired insulin levels in the body. The prevalence of diabetes has been multiplied over the last few decades. According to the report of World Health Organization, type 2 diabetes accounts for 8.5% prevalence comprised of 422 million affected individuals globally.1 International Diabetes Federation Atlas has reported that this figure is expected to increase up to 10.4% prevalence mark till 2040.2 However, in Pakistan, the current status of prevalence is round 1.77% DM.3 It is one of the most chronic disorder that becomes complicated with the process of aging. Its pathophysiology modulates the diabetic complications which affects several parts of the body.4 One of most prevalent complication is diabetic retinopathy (DR). DR is a major eye concern for visual impairment in the patients of T2DM in most of the low and middle income regions of developing countries.5 It was reported that the prevalence rate for the development of DR is approximately 75% in the patients of T2DM which develops within the period of 15-20 years of duration after the onset.6,7 However, in Pakistan, the prevalence rate of DR was estimated to be around 28.7%.8 In DR, the altered hyperglycaemic blood flow induces dilatation and disruption in the basement membrane of vascular structures and endothelial lining cells (pericytes) of the retina by means of insulin and other biochemical and physiological mechanisms.9 The major biochemical mechanisms included protein kinase C (PKC), hexosamine, advanced glycation end products (AGEs) and polyol pathways which shows active involvement in the modulation of the pathogenesis of retinopathy in diabetic patients due to uncontrolled hyperglycaemia.10 Clinically there are three stages of DR depends upon the severity of the disease known as non-proliferative (NPDR), proliferative DR (PDR) and diabetic macular edema (DME). NPDR pathogenesis is usually characterized by the formation of microaneurysm and flame-shaped haemorrhages found to occur in all four fundus quadrants.11 PDR develops by the condition of hypoxia that stimulates the production of vasoproliferative factors which are responsible to initiate the formation of new supply of vascular structures to promote oxygenation in retina.
These new blood vessels might produce haemorrhage into the retinal fluid which causes swelling in the macula and leads to develop macular edema in DR patients.12 There are several risk factors that might initiate and accelerate the progression of DR haemorrhage such as duration of T2DM, alterations in the homeostasis of blood glucose levels, hypertension, hyperlipidaemia, hormonal changes during pregnancy and addictions for alcohol and smoking.13 DR is a serious health concern equally for both gender in later age groups of rural and urban regions of the developing countries worldwide. Although studies have been conducted on investigation of prevalence rate and demographic risk factors particularly for DR with several limitations due to occurrence of variations among populations residing in different geographical localities.14-16 To the best of our knowledge, no study has been conducted for the evaluation of prevalence of DR particularly in the areas of interior Sindh, Pakistan. Thus, present study aims to assess the prevalence of diabetic retinopathy and its related demographic risk factors in Nawab Shah District of Pakistan.

**METHODOLOGY**

It is a cross-sectional study comprised of approximately n=381 T2DM individuals after their confirmed diagnosis. This study was conducted in the duration of six months from July 1, 2016 – December 31, 2017. The patients were recruited from outpatient department of Ophthalmology Department of PMC Hospital, Nawabshah. Ethical approval and informed consent were also taken from all the study participants after confirming their volunteer participation. Blood samples were collected in EDTA vacitainer for the estimation of HbA1c levels and in flouride vacitainer for fasting blood glucose testing.

**Inclusion/exclusion criteria**

The study participants included in this study have confirmed diagnosed T2DM of more than 5 years, above 30 years of age and HbA1c level of greater than 6.5%. However, the patients suffering from type 1 diabetic patients, gestational diabetes, media opacities, Sickle cell retinopathy, proliferative vitreoretinopathies including retinal vein & artery occlusion, Eale’s disease, and retinal vasculitis were excluded from this research study.

**Data collection**

Structured questionnaire was filled out for the purpose of data collection of socio demographic risk factors including age, sex, smoking, hypertension, duration of diabetes, mild, moderate, heavy physical health activity and family history of diabetes. The study subjects were screened through detailed ophthalmological examination using eye drops of 10% phentolamine and 1% tropicamide and fundal examination by intraocular pressure (IOP) using slit lamp bio microscopy with 90D lens and indirect ophthalmoscopy with 20D and measurement of visual acuity by Snellen chart.

**Anthropometric and biochemical measurements**

Anthropometric parameters such as weight (kg) and height (m²) were measured by following the standard methods. Body mass index (BMI) was calculated using height and weight for each of the study participant to evaluate the grading for obesity. For biochemical analysis, FBG and HbA1c test were carried out for the evaluation of blood glucose status to confirm the accurate diagnosis of type 2 diabetes mellitis in all the study participants according to the standards of WHO. Though, total cholesterol levels were recorded from the patient’s clinical history.

**Data analysis**

Data analysis was done using statistical software SPSS version 22.0 and Microsoft Excel 365. The prevalence of DR and the sociodemographic risk factors were indicated as frequencies.

**RESULTS**

The data obtained from this research study was compiled and represented in the form of estimated frequencies. Total n=381 T2DM subjects were screened for the prevalence of DR. Figure 1.1. represented that approximately n=169 individuals were diagnosed with DR accounts for 44.4% prevalence among type 2 diabetic patients as compared to non DR patients in this study.

**Figure 1.1. Represents the prevalence of diabetic retinopathy among the study subjects of type 2 diabetic patients.**

Figure 1.2. represents the prevalence of grading of NPDR classified according to the types of NPDR. Total 36.5% patients were diagnosed with NPDR. It consists of very mild (5.3%), mild (7.1%), moderate (9.4%), severe (6.5%) and very severe (8.2%) grades. However, it is observed that moderate type of NPDR was found to be most prevalent and significantly higher in study subjects among others (p<0.001).
Figure 1.2. Represents the prevalence of NPDR found in different grades among study subjects of DR.

Figure 1.3. represents the prevalence of proliferative diabetic retinopathy (PDR) which is found to be approximately 41.4% graded by mild to moderate (27.2%) and severe/ vitreous haemorrhages (14.2%). While in most of PDR cases; macular edema was found in (21.8%) patients.

Figure 1.4. represents the prevalence rate in different age groups of non-proliferative diabetic retinopathy. It is observed that highest frequency of NPDR was found in the age group of 41–50 years of patients which is approximately equal to 33.8%. However, the lowest frequency of 14.5% was detected in the 30–40 years age group of NPDR patients.

Figure 1.5. represents the prevalence rate in different age groups of proliferative diabetic retinopathy. It is suggested that highest frequency of PDR was 41.1% observed in the age group of 61–70 years of patients. However, the lowest frequency of 4.67% is observed in the age group of 30–40 years in NPDR patients.

Figure 1.6. shows that among all the subjects it is observed that n=256 patients were categorized as males and n=125 patients were categorized as females. Therefore, it is suggested that the frequency of males (67%) was greater than females (33%) among the individuals of this study group.
Table 1.1. reflects the distribution of major risk factors among DR patients of Nawab Shah District in this study. Smoking is found to be one of the major factor which might contributes to the progression of DR. It is observed that high frequency of smoking habit was found in PDR (67.1%) and Macular edema patients (67.6%) as compared to NPDR patients (46.7%). Though, hypertension also shows an association with the susceptibility of DR group. It is revealed that highest distribution of hypertension was observed in PDR patients (81.9%) in contrast to other groups. Among the duration of diabetes, period of 21-30 years is most prevalent in NPDR (13.5%) and Macular edema patients (43.2%) while period of greater than 30 years is found to be more abundant in PDR patients (32.8%). The biochemical parameters included estimations of FBG, HbA1c and total cholesterol levels. It is observed that FBG level of greater than 126mg/dl is prevalent in all three study groups. While, HbA1c level of greater than 10% is found in PDR (71.4%) and Macular edema patients (78.4%). However, total cholesterol levels are found to be less than 200mg/dl in NPDR patients (16.4%) and greater than 200mg/dl in PDR (85.7%) and Macular edema (83.8%) patients.

Table 1.1. Distribution of sociodemographic risk factors found in the patients of DR.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>NPDR (%)</th>
<th>PDR (%)</th>
<th>Macular Edema</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smokers</td>
<td>128 (46.7%)</td>
<td>47 (67.1%)</td>
<td>25 (67.6%)</td>
</tr>
<tr>
<td>Non-Smokers</td>
<td>146 (53.3%)</td>
<td>23 (32.9%)</td>
<td>12 (32.4%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>34 (12.4%)</td>
<td>57 (81.9%)</td>
<td>30 (81.1%)</td>
</tr>
<tr>
<td>No</td>
<td>240 (87.6%)</td>
<td>13 (18.1%)</td>
<td>7 (18.9%)</td>
</tr>
<tr>
<td>Duration of Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11-20</td>
<td>24 (8.8%)</td>
<td>15 (21.4%)</td>
<td>5 (13.6%)</td>
</tr>
<tr>
<td>21-30</td>
<td>37 (13.5%)</td>
<td>21 (30%)</td>
<td>16 (43.2%)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>23 (8.4%)</td>
<td>23 (32.8%)</td>
<td>10 (27%)</td>
</tr>
<tr>
<td>FBS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;126</td>
<td>250 (91.2%)</td>
<td>59 (84.2%)</td>
<td>32 (86.4%)</td>
</tr>
<tr>
<td>&gt;126</td>
<td>24 (8.8%)</td>
<td>11 (15.8%)</td>
<td>5 (13.6%)</td>
</tr>
<tr>
<td>HbA1c</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6.5</td>
<td>260 (94.8%)</td>
<td>7 (10%)</td>
<td>3 (8.1%)</td>
</tr>
<tr>
<td>6.5-10</td>
<td>10 (3.7%)</td>
<td>13 (18.6%)</td>
<td>5 (13.5%)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>4 (1.5%)</td>
<td>50 (71.4%)</td>
<td>29 (78.4%)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 200mg/dl</td>
<td>45 (16.4%)</td>
<td>15 (21.4%)</td>
<td>6 (16.2%)</td>
</tr>
<tr>
<td>&gt;200mg/dl</td>
<td>9 (3.3%)</td>
<td>60 (85.7%)</td>
<td>31 (83.8%)</td>
</tr>
</tbody>
</table>

Table 1.2. depicts the distribution of frequencies of BMI among the two groups of NPDR and PDR. There are three basically categories of BMI. It is found that normal range of BMI is higher in NPDR patients while obese category of BMI is more prevalent in PDR patients.

Table 1.2. Distribution of body mass index (BMI) among all the patients of DR.

<table>
<thead>
<tr>
<th>BMI (kg/m²)</th>
<th>NPDR (N=274)</th>
<th>PDR (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal &lt; 18.5-24.9</td>
<td>124 (45.2%)</td>
<td>17 (15.8%)</td>
</tr>
<tr>
<td>Overweight 25-29.9</td>
<td>97 (35.4%)</td>
<td>37 (34.6%)</td>
</tr>
<tr>
<td>Obese 30</td>
<td>53 (19.3%)</td>
<td>53 (49.6%)</td>
</tr>
</tbody>
</table>

Table 1.3. represents the distribution of family history of T2DM and types of physical activity found in patients lifestyle routine. It is observed that higher frequency of diagnosed PDR patients (60.7%) suffer from prior history of T2DM as compared to NPDR patients (52%). However, most of study subjects of both NPDR and PDR groups undertakes mild physical activity in their daily life routine.

Table 1.3. Distribution of family history of diabetes and physical activity among the patients of NPDR and PDR.

<table>
<thead>
<tr>
<th>Family history of Diabetes</th>
<th>NPDR (n=274)</th>
<th>PDR (n=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ve</td>
<td>250 (52%)</td>
<td>65 (60.7%)</td>
</tr>
<tr>
<td>-ve</td>
<td>24 (48%)</td>
<td>42 (39.3%)</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>130 (47.4%)</td>
<td>63 (58.8%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>89 (33.18%)</td>
<td>29 (27.1%)</td>
</tr>
<tr>
<td>Heavy</td>
<td>55 (19.39%)</td>
<td>15 (14.1%)</td>
</tr>
</tbody>
</table>
DISCUSSION
In this study, the prevalence of diabetic retinopathy in the District of Nawab Shah was reported to be around 44.4% (n=169/381) Among T2DM patients which is found to be much higher in comparison to other studies conducted in different regions of Pakistan. Our findings are supported by few global surveys reports which states that the prevalence of DR accounts for 45.8% in a Los Angeles, 37% to 43% in a cross-sectional study conducted in China, 50.6% in Bangladesh and 30.06% in India. However, the counteracting studies found the prevalence range of 21-60 % for the pathogenesis of DR among diagnosed T2DM patients collected from different cities of Pakistan. However, another study reported the prevalence of DR around 24.4% as one of the major diabetic microvascular complication in Pakistan. A research survey carried out by the Diabetic Association of Pakistan has reported that retinopathies related to diabetes overall affects around 15% of people in Pakistan, 43% of type II diabetes patients. The current study also provides data related to different categories of DR which includes NPDR, PDR and Macular edema. Our findings suggests 36.5% prevalence for NDPR and 41.4% prevalence for PDR patients. While among PDR group, almost 21.8% patients were diagnosed with Macular edema. According to a study, the prevalence of NPDR was reported to be around 79.1% in Karachi, Pakistan. Contrasting reports suggests that the prevalence of NPDR accounts for 92% in Australia, 89.3-94.0% in India and 69.8% in Oman. However, the prior studies have reported that the prevalence rate of PDR was found to be around 42.8% in Larkana, Pakistan and 57% in India. In addition, a meta-analysis for eye diseases conducted on global prevalence of DR revealed nearly 6.96% frequency for the proliferative DR and 6.81% frequency for diabetic macular edema worldwide. The severity of progression caused by the pathogenesis of diabetic retinopathy is primarily related to the exposure of some external risk factors. In this study, smoking and hypertension were found to be more prevalent in PDR group. While 21-30 years duration of diabetes was abundantly observed in NPDR and Macular edema patients. In a previous study, age group of 51-75 years was found to show highest frequency of DR in T2DM patients among both the genders. However, a significant association of BMI and impaired glucose level was revealed in a study conducted on urban population of Panjab, Pakistan which shows correlation with our findings. Saudi population report suggests that BMI and hypertension confers higher risk for the development of early diabetic complications in females. Our study supports the relationship with family history of diabetes in most of the diagnosed DR patients. Although, Prior study suggests the positive correlation of family history of diabetes and impaired glucose levels in posing the higher risk with the susceptibility of diabetes and its related complications. Some studies also reports that the positive correlation of a higher level of BMI and waist to hip ratio (WHR) serves as a significant factor in elevating the risk of DR. Therefore, the higher distribution of demographic risk ifactors observed in diagnosed iDR patients stimulates the progression of diabetes. It may be due to several reasons, such as severity of idiopathic progression, immunity, ihealth status, ipoor quality ifood, isedentary iife style, ilonger exposure iperiods, iuse iof icorticosteroid idrugs and others.  

CONCLUSION
This study has demonstrated the prevalence of DR among T2DM patients in Nawab Shah District. Distinctively, the prevalence of PDR was found to be substantially higher in our studied group as compared to overall Pakistan’s prevalence. However, the presence of higher BMI, smoking and hypertension shows an association with the risk of higher incidence of diabetic retinopathy. Proper screening for the status of retinopathy and its progressive invasion is required to control the increasing prevalence and treat this eye complication among T2DM patients. An organized screening program and public awareness is needed for the proper management and adequate control of progression of DR in T2DM patients.  

ETHICS APPROVAL: The ERC gave ethical review approval  
CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin  
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AUTHORS’ CONTRIBUTIONS: All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated in the work to take public responsibility of this manuscript. All authors read and approved the final manuscript.  
CONFLICT OF INTEREST: No competing interest declared.

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