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Correlation Between HbA1c Levels and Severity of Diabetic Retinopathy: A Cross-Sectional Evaluation

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ABSTRACT

Background: Diabetic retinopathy (DR) is a frequent microvascular complication of type 2 diabetes mellitus and the major cause of visual impairment. The most important factors affecting the development of DR are glycemic control and duration of diabetes. The purpose of this study was to determine the correlation between glycemic indices and the extent of DR in patients with type 2 diabetes mellitus. **Methods:** This cross-sectional study (November 2022 to April 2023) included 150 patients with type 2 diabetes and was divided into three groups according to the severity of DR, which included No DR (n=60), Non-Proliferative DR (NPDR, n=58), and Proliferative DR (PDR, n=32). The ophthalmic examination was carried out in detail, and HbA1c and glucose levels were assessed with fasting blood samples. Demographic and clinical information were recorded. ANOVA, Pearson correlation, and multivariate logistic regression were used to analyze associations between glycemic indices, diabetes duration, and DR severity. **Results:** NPDR and PDR patients reported greater levels of HbA1c, longer duration of diabetes and elevated fasting glucose than patients with no DR. HbA1c had the most significant positive correlation with the severity of DR ($r = 0.72$, $p < 0.001$). Multivariate logistic regression found HbA1c (OR=1.92, 95% CI=1.48-2.51) and length of diabetes (OR=1.15, 95% CI=1.07-1.25) as independent predictors of DR. **Conclusion:** DR severity is highly linked with poor long-term glycemic control and increased duration of diabetes. HbA1c monitoring and early ophthalmic examination is critical to prevent further development of the disease and minimize the risk of developing vision loss in patients.

Keywords: Diabetic Retinopathy, HbA1c, Glycaemic Control, Diabetes Duration.

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INTRODUCTION

Diabetic retinopathy (DR) is a frequent and potentially vision-limiting microvascular complication of type 2 diabetes mellitus (T2DM), and it impacts one-third of all persons living with diabetes globally [1]. Continuous hyperglycemia causes structural and functional changes in the retinal microvasculature, which cause capillary leakage, ischemia, and pathological neovascularization [2]. The most common biomarker, which is widely accepted to gauge long-term glycemic control, is glycated hemoglobin (HbA1c), which indicates the average level of blood glucose during the last 8-12 weeks [3]. Some clinical trials have shown elevated levels of HbA1c to be linked to the onset and the progression of DR, and hence, it is a decisive measure of early screening and risk profiling [4].

Although there is an extensive literature indicating hyperglycemia as an important determinant of DR, there are wide disparities in the intensity and uniformity of the relationship between the HbA1c level and the severity of DR among different populations and clinical contexts [5]. Ethnicity, duration of diabetes, comorbidities, and access to ophthalmic care are the factors that lead to heterogeneous findings [6]. Furthermore, numerous researches have centered on general risk factors instead of directly determining the direct relationship between HbA1c levels and particular stages of the DR through standardized grading scales such as the Early Treatment Diabetic Retinopathy Study (ETDRS) scale [7,8]. Some studies of methodological differences explain the stages of DR, which further reduce the ability to compare results across studies [9]. Also, the absence of the regional-specific evidence that is up-to-date also limits the chance to customize the screening plans to the local disease trends [10].

The purpose of the study was to assess the relationship between the level of HbA1c and the stage of diabetic retinopathy in adults with type 2 diabetes mellitus based on the standardized ETDRS grading.

METHODS

This cross-sectional (November 2022 to April 2023) was carried out at the Department of Pathology at NHU FMH Lahore **(Ref: 114/23)** after informed consent. The size of the sample was determined using the OpenEpi version 3.0.0 (Atlanta, GA, USA) with a 95 % confidence level with power of 80 % and margin of error of five % based on the prevalence rates of diabetic retinopathy reported previously among type 2 diabetes patients[11]. The total number of participants analyzed is 150. A consecutive non-probability sampling method was used to recruit the participants by including all eligible patients attending the ophthalmology outpatient clinic at any time of the study period.

Inclusion criteria involved adults aged above 30 years with a known diagnosis of type 2 diabetes mellitus of at least one year. Exclusion criteria involved patients who have ocular trauma within six months, have undergone any retinal laser therapy, intraocular surgery within six months, other retinal

diseases, severe media opacities or systemic disorders that would influence HbA1c outcome (e.g. hemoglobinopathies). Every participant was screened first, where a comprehensive review of the medical history and confirmation of past eye examination records were done.

The ETDR was used to classify the participants according to the severity of diabetic retinopathy. These groups were: No-DR, NPDR and PDR. The assessment was done by a certified ophthalmologist who was blinded to the HbA1c of the participants to minimize observer biasness. Each participant was given a standardized ophthalmic assessment that was comprised of the best-corrected visual acuity, slit-lamp bio-microscopy, and dilated fundus examination. Fasting Venous blood samples of 0.5 ml were assessed in the laboratory to determine the level of HbA1c and fasting glucose.

The high-performance liquid chromatography (HPLC) on an automated analyzer (Bio-Rad D-10, Hercules, CA, USA) was used to measure the level of HbA1c. The assays were all done twice and internal standards of quality control were used to assure that it was accurate and reproducible. The standardized enzyme method (hexokinase method, Abbott Architect c8000, IL, USA) was used to measure fasting glucose.

All laboratory and clinical data were authenticated and recorded in a standardized electronic database. HbA1c values were tabulated as percentages (percent or percentage), fasting glucose in mg/dL and DR severity was coded numerically (No-DR = 0, NPDR = 1, PDR = 2).

The argument of the data was done in SPSS 26.0 (IBM Corp., Armonk, NY, USA). The continuous variables were done in the form of Mean + SD and compared to one-way ANOVA. Categorical variables were analyzed by use of chi-square or Fisher exact test. The HbA1c, fasting glucose, duration of diabetes, and the severity of DR were correlated with each other using Pearson correlation. The predictors that are not dependent on DR have been made into a multivariate logistic regression model with the adjusted odds ratios (OR) given with a 95 percent confidence interval (CI). The p-value of below 0.05 was observed to be significant.

RESULTS

Table 1: Baseline Characteristics of Study Participants across DR Severity

Variable	No-DR (n=60)	NPDR (n=58)	PDR (n=32)	p-value
Age (years, Mean ± SD)	54.1 ± 9.8	57.9 ± 10.6	60.3 ± 9.4	0.012*
Male Gender, n (%)	30 (50.0)	34 (58.6)	18 (56.3)	0.612

Duration of Diabetes (years)	6.8 ± 3.1	9.4 ± 4.2	12.1 ± 4.5	<0.001*
Fasting Blood Glucose (mg/dL)	138.5 ± 26.7	159.3 ± 31.8	178.9 ± 34.2	<0.001*
HbA1c	6.9 ± 0.8	8.1 ± 0.9	9.4 ± 1.1	<0.001*
BMI (kg/m²)	27.8 ± 3.5	28.6 ± 3.1	28.9 ± 3.7	0.274
Hypertension, n (%)	22 (36.7)	27 (46.6)	19 (59.4)	0.083
Dyslipidemia, n (%)	18 (30.0)	31 (53.4)	21 (65.6)	0.003*

**Significant at $p < 0.05$.*

One hundred and fifty patients with type 2 diabetes mellitus were involved in the analysis. The average age was 56.8 ± 10.4, of which 82 (54.7%) were males and 68 (45.3%) females. The participants were divided into three groups as per detailed ophthalmic examination: No-DR = 60 (40%), NPDR = 58 (38.7%), and PDR = 32 (21.3). The three groups were compared in terms of demographic and clinical variables such as age, gender, duration of diabetes, BMI, blood pressure and metabolic indices. The patients with NPDR and PDR exhibited increasingly higher levels of HbA1c (8.1 ± 0.9 and 9.4 ± 1.1 respectively), duration of diabetes (9.4 ± 4.2 and 12.1 ± 4.5 years, respectively) and fasting glucose (159.3 ± 31.8 and 178.9 ± 34.2 mg/dL respectively), which increased with the progression of DR. **Table 1** shows the distribution of these characteristics based on the severity of DR.

Table 2: Correlation between HbA1c and DR Severity

Variable	Correlation Coefficient (r)	p-value
HbA1c vs DR Severity Score	0.72	<0.001*
Duration of Diabetes vs DR Severity	0.65	<0.001*
Fasting Glucose vs DR Severity	0.58	<0.001*

To assess the relationship between HbA1c, fasting glucose, length of diabetes, and the severity of DR, Pearson correlation analysis was conducted. The correlation coefficients are presented in **Table 2.** The positive correlation with the severity of DR was observed with HbA1c ($r = 0.72$, $p < 0.001$), then duration of diabetes ($r = 0.65$), following fasting glucose ($r = 0.58$), which constituted a significant disease progression marker.

Table 3: Logistic Regression for Predictors of Any DR

Predictor	Adjusted OR (95% CI)	p-value
HbA1c	1.92 (1.48–2.51)	<0.001*
Duration of Diabetes (years)	1.15 (1.07–1.25)	<0.001*
Hypertension	1.42 (0.79–2.56)	0.236
Dyslipidemia	1.87 (1.02–3.41)	0.041*

Multivariate logistic regression analysis was conducted to predict independent predictors of DR. The important ones were HbA1c and diabetes duration, whereas hypertension and dyslipidemia had weaker correlations. The adjusted odds ratios of these predictors are given in **Table 3**. The independent factors that had significant predictive value on DR were higher HbA1c (OR =1.92, 95% CI= 1.48-2.51, $p < 0.001$) and longer duration of diabetes (OR =1.15, 95% CI= 1.07-1.25, $p < 0.001$).

DISCUSSION

This study evaluated the correlation between the severity of diabetic retinopathy and glycemic control. Patients who had more advanced DR had lower glycemic control, and their period of diabetes and fasting glucose levels were worse than of patients who did not have DR. Correlation analysis demonstrated that HbA1c was the best predictor of the severity of DR and multivariate regression revealed that both high levels of HbA1c and the duration of the disease were significant independent variables. These results highlight the importance of long-term glycemic control and monitoring of the disease in the prevention of the development of DR.

The prior studies that have established that poor glycemic regulation is a major contributor to the occurrence of microvascular complications [12]. Previous research has demonstrated that an increase in HbA1c is constantly associated with NPDR and PDR and the higher are the levels, the more advanced is the retinal change [13]. The findings are consistent with the idea that sustained hyperglycemia enhances the damage of the capillaries, which are the main processes underlying the development of DR [14]. Moreover, population-based studies have also observed such correlations between fasting glucose, HbA1c, and DR severity, and hence both long-term and short-term glycemic control are significant in retinal health [15,16].

The relationship between diabetes duration and DR severity is also observed to be in agreement with the available literature. Increased prevalence and progression of DR is always related to longer disease duration [17]. According to previous longitudinal studies, cumulative exposure to hyperglycemia over the years leads to endothelial dysfunction and retinal ischemia, enhancing the

progression of NPDR into PDR [18,19]. Remarkably, this study confirms that the patients with PDR had average diabetes duration of more than 12 years, which is much higher when compared to patients without DR. Further, the intermediate relationship between fasting glucose and the severity of DR in this study is consistent with the previous literature showing that the changes in glucose levels, along with chronic hyperglycemia, can increase the rate of retinal micro-vascular damage [20,21]. The combined effect of the length of diabetes and GCC on the retinal disease progression is indicated by these findings.

The clinical significance of the results is that HbA1c and diabetes duration are major predictors of DR and can be used to notify early intervention strategies. Mechanistically, chronic hyperglycemia causes oxidative stress and inflammation as well as advanced glycation end-products, which cause microvascular injury and retinal neovascularization [22]. The predictive ability of HbA1c relative to fasting glucose is stronger which implies that long-term glycemic regulation is more determinant in the development of DR than short-term changes [23]. The implications of these findings on clinical practice are significant as continuous monitoring of HbA1c and early ophthalmic screening can be advocated, especially in those with a longer disease history [24]. Moreover, the specific lifestyle intervention and pharmacologic treatment to ensure the HbA1c stays within the suggested levels can help decrease the prevalence of severe DR and associated visual impairment [25].

There are a number of limitations of the study. Its cross-sectional design does not allow the determination of cause and effect between glycemic indices and the development of DR. This sample was selected in one tertiary care facility and this does not necessarily guarantee generalization to the larger population. The other possible confounding factors, including genetic predisposition, medication adherence, and comorbidities, were also not fully examined. Future studies must incorporate prospective longitudinal research studies to test relationships in changes over time between glycemic control and progression of DR, and multi-center research to enhance external validity. The risk stratification can be enhanced by including new methods of retinal imaging and molecular biomarkers to tailor the risk and implement changes in the management approach.

CONCLUSION

The level of diabetic retinopathy in type 2 diabetes mellitus patients closely correlates with a lack of glycemic control and an extended period of diabetes. HbA1c became the most significant predictor of DR, and it is important to note that glucose can be managed at long-term management and thus help to avoid retinal complications. The metabolic profile of patients with NPDR and PDR was progressively deteriorating, which underlines the importance of early diagnosis and frequent

ophthalmic examination. These results can be used to favor the introduction of specific interventions, such as rigorous glycemic regulation, patient education, and regular retinal screening, to minimize the risk of DR development and subsequent visual loss.

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None.

CONFLICT OF INTEREST

None.

ETHICAL APPROVAL

This cross-sectional (November 2022 to April 2023) was carried out at the Department of Pathology at NHU FMH Lahore **(Ref: 114/23)** after an informed consent.

AUTHORS' CONTRIBUTION

All authors contributed equally as per ICMJE.

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