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Prevalence and Metabolic Determinants of Diabetic Retinopathy in Type 2 Diabetes: A Cross-Sectional Study from a Tertiary Center in Yemen

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Abstract

Background: In conflict-affected regions, such as Yemen, structural barriers to healthcare lead to chronic glycemic mismanagement and accelerated microvascular damage. This study aimed to determine the prevalence of various stages of diabetic retinopathy (DR) and identify the metabolic determinants associated with disease severity in a tertiary care setting.

Methods: A cross-sectional study of 202 patients with type 2 diabetes was conducted at Al-Thawra General Hospital, Sana'a. Retinopathy was staged using the International Clinical Diabetic Retinopathy (ICDR) scales and the 4-2-1 rule. Metabolic determinants, including HbA1c levels, disease duration, and systemic comorbidities, were analyzed using univariate testing and multivariate logistic regression. Discriminatory performance was evaluated using Receiver Operating Characteristic (ROC) curves.

Results: The cohort (mean age 64.63 years) exhibited poor metabolic control (mean HbA1c 10.07%). The overall prevalence of vision-threatening DR was high: 27.2% of patients exhibited proliferative DR (PDR), while non-proliferative DR (NPDR) stages were distributed as mild (20.8%), moderate (24.8%), and severe (27.2%). Diabetic macular edema was identified in 19.8% of patients. Univariate analysis associated the duration of diabetes ($p < 0.001$), HbA1c ($p < 0.001$), and hypertension ($p = 0.010$) with disease severity. In the multivariate model, only disease duration remained a significant independent predictor (aOR 1.072 per additional year, 95% CI: 1.007–1.141, $p = 0.028$), overshadowing current HbA1c ($p = 0.506$). ROC analysis confirmed that duration (AUC 0.643) provided superior discriminatory performance compared to HbA1c (AUC 0.604).

Conclusion: In settings where poor metabolic control is near-universal, cumulative disease duration outweighs current HbA1c levels as a determinant of retinopathy severity, suggesting a saturation effect of glucose-induced damage. Screening protocols in humanitarian zones should prioritize intensive surveillance for patients with diabetes duration exceeding 15 years, with an urgent focus on male patients in the second decade of disease.

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1. INTRODUCTION

The Middle East and North Africa (MENA) region has emerged as a global epicenter for type 2 Diabetes Mellitus (T2DM), hosting some of the highest prevalence rates recorded in the 21st century [1]. Within this region, Yemen represents a critical case study of how acute humanitarian crises alter the natural history of noncommunicable diseases. Since 2015, the ongoing civil conflict in Yemen has resulted in a systemic collapse of healthcare infrastructure, creating a "perfect storm" of biological and

structural barriers. Recent longitudinal data indicate that this "War Effect" has driven population-wide glycemic levels from a mean HbA1c of 7.7% to a critical 9.4%, primarily fueled by displacement, the disintegration of the medical cold chain for insulin, and chronic psychosocial stress [2, 3].

Diabetic retinopathy (DR) remains the leading cause of preventable blindness among working-age adults globally. It is a progressive microvascular complication that evolves through distinct pathological stages, beginning with increased capillary permeability in non-proliferative diabetic retinopathy (NPDR) and culminating in sight-threatening neovascularization in proliferative diabetic retinopathy (PDR) [4, 5]. While global estimates place the prevalence of PDR between 3% and 8%, hospital-based cohorts in conflict-affected regions, such as Yemen, reveal a far more severe burden, with nearly one in five patients already exhibiting advanced, vision-threatening disease at the time of presentation [6].

Standard clinical models for predicting DR progression, derived largely from stable Western populations, typically assume a linear dose-response relationship between glycemic markers and vascular damage. However, in environments where chronic hyperglycemia is ubiquitous and severe, these traditional relationships appear distorted. Research from regional peers such as Palestine and Syria suggests a "Saturation Effect" of current biomarkers; once HbA1c exceeds a specific threshold (often above 9.0%), its independent predictive value is marginalized by the cumulative duration of disease exposure, or "metabolic memory" [7, 8]. In such settings, the sheer length of exposure to high glucose levels becomes a more potent driver of retinal damage than any single cross-sectional laboratory measurement.

Despite the high clinical burden, there is a significant knowledge gap regarding the distribution of specific DR stages and their metabolic determinants in the context of the Yemeni conflict. Several hospital- and community-based studies in Yemen have established diabetic retinopathy as the leading cause of visual impairment and blindness. Hospital-based reports have documented cataracts and diabetic retinopathy as the principal causes of blindness among adult Yemenis [9], while community-based surveys have confirmed this disproportionate burden among individuals aged $\geq$ 50 years [10]. Diabetes clinic cohorts further demonstrated that retinopathy and maculopathy are major contributors to visual disability, with regular follow-up associated with lower severity [11], and additional hospital-based investigations characterized the spectrum of retinopathy and ocular status among patients with diabetes mellitus [12, 13]. However, these studies were conducted prior to or early in the ongoing conflict, and none have comprehensively stratified the full spectrum of DR severity alongside metabolic determinants using multivariate methods in the current humanitarian setting.

This study aimed to characterize the prevalence of the full clinical spectrum of diabetic retinopathy, ranging from mild NPDR to advanced PDR and macular edema—among T2DM patients at a major tertiary center in Sana'a, Yemen. By identifying the key metabolic and systemic drivers of disease severity, this study provides an evidence-based framework for optimized ophthalmic screening and targeted resource allocation in humanitarian zones where traditional metabolic profiling may be insufficient.

2. METHODS

2.1. Study Design and Setting

This cross-sectional analytical study was conducted at the Ophthalmology and Endocrinology outpatient clinics of Al-Thawra General Hospital in Sana'a, Yemen, between November 2022 and August 2024. As the primary tertiary referral center in Yemen, Al-Thawra Hospital serves a diverse patient population, many of whom face significant structural barriers to routine metabolic care due to ongoing regional instability.

2.2. Study Population and Sampling

The study population comprised 202 adults (404 eyes) with a confirmed diagnosis of type 2 Diabetes Mellitus (T2DM). Participants were selected using a systematic random sampling technique from the hospital's patient database. The inclusion criteria required patients to be aged $\geq$ 31 years with a T2DM diagnosis of at least one year duration and a willingness to undergo a dilated fundus examination. Exclusion criteria included patients with type 1 diabetes, secondary diabetes, or hazy ocular media (such as dense cataracts or corneal opacities) that prevented adequate fundus visualization. Additionally, patients with non-diabetic retinal pathologies, such as vascular occlusions, age-related macular degeneration, or a history of significant ocular trauma, were excluded from the final analysis.

2.3. Ophthalmic Assessment and Staging

All participants underwent comprehensive ophthalmic evaluation. Visual acuity was assessed using a standard Snellen chart, and anterior segment evaluation was performed using slit-lamp microscopy. Following pupil dilation with 1% tropicamide, posterior segment examination was conducted using slit-lamp biomicroscopy with +90D or +78D non-contact lenses and indirect ophthalmoscopy with a +20D lens. Retinopathy was staged according to the International Clinical Diabetic Retinopathy (ICDR) scale and Early Treatment Diabetic Retinopathy Study (ETDRS) criteria [5, 14]. Severe Non-Proliferative Diabetic Retinopathy (NPDR) was specifically defined using

the 4-2-1 rule: the presence of severe intraretinal hemorrhages in all four quadrants, venous beading in two or more quadrants, or prominent intraretinal microvascular abnormalities (IRMA) in at least one quadrant. Proliferative Diabetic Retinopathy (PDR) was defined as the presence of neovascularization of the disc or elsewhere or the presence of vitreous/preretinal hemorrhage. Optical coherence tomography (OCT) was used to confirm the presence of diabetic macular edema (DME) when clinically indicated.

2.4. Metabolic Determinants and Laboratory Evaluation

Clinical and demographic data were obtained using a structured, interviewer-administered questionnaire and verified using electronic medical records. Diabetes duration was analyzed as a continuous variable and categorized into three risk brackets: $\leq$15 years (reference), 16–25 years (high-risk), and >25 years (extreme duration). Glycemic control was evaluated via Fasting Blood Sugar (FBS) and Hemoglobin A1c (HbA1c). For the stratified analysis, glycemic control was categorized into three levels: controlled (HbA1c $\leq$7.0%), poor control (7.1–9.0%), and very poor control (>9.0%). Systemic hypertension was defined as a systolic blood pressure of $\geq$140 mmHg, diastolic pressure of $\geq$90 mmHg, or current use of antihypertensive medication. Renal function was assessed using serum creatinine levels, and lipid profiles were measured using standardized enzymatic methods in the hospital's central biochemistry laboratory.

2.5. Statistical Analysis

Data management and analyses were performed using IBM SPSS Statistics Version 26.0 and Python biostatistical libraries. The clinical characteristics were summarized using the mean and standard deviation for continuous variables and frequencies for categorical data. For metabolic determinants and regression modeling, the "worse-eye" rule was applied to classify each patient's overall status. Univariate comparisons between retinopathy stages were conducted using the Pearson Chi-Square test for categorical factors and the Mann-Whitney U test for continuous variables. A binary logistic regression model was used to identify the independent determinants of retinopathy progression after adjusting for potential confounders. The model goodness-of-fit was assessed using the Nagelkerke R-squared and Hosmer-Lemeshow tests. The discriminatory performance of key metabolic markers was evaluated using Receiver Operating Characteristic (ROC) curves and the Area Under the Curve (AUC). All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline Clinical and Demographic Characteristics

The final study population consisted of 202 patients with type 2 diabetes mellitus. The cohort was characterized by an advanced mean age of 64.63 ± 13.3 years and a mean disease duration of 14.98 ± 7.5 years. The gender distribution showed a predominance of females (n=116, 57.4%) compared to males (n=86, 42.6%). Metabolic control was critically poor across the sample, with a mean HbA1c of 10.07 ± 1.83%, and 96.1% of patients fell into the uncontrolled category (HbA1c >7.0%). Systemic comorbidities were common, with hypertension and dyslipidemia affecting 39.1% and 17.8% of the patients, respectively. The detailed baseline characteristics are presented in Table (1).

Table[1]: Socio-Demographic and Clinical Characteristics of the Study Population (N = 202)

Characteristic	Mean $\pm$ SD or n	%
Age (Years)	64.63 ± 13.33	—
Duration of Diabetes (Years)	14.98 ± 7.47	—
HbA1c (%)	10.07 ± 1.83	—
Gender		
Female	116	57.4
Male	86	42.6
Glycemic Control		
Controlled (HbA1c $\leq$ 7.0%)	8	3.9
Uncontrolled (HbA1c $>$ 7.0%)	194	96.1
Treatment Modality		
Oral Hypoglycemic Agents	117	57.9
Insulin Therapy	85	42.1
Systemic Comorbidities		
Hypertension	79	39.1
Dyslipidemia	36	17.8

SD = standard deviation; HbA1c = glycated hemoglobin.

3.2. Clinical Spectrum and Prevalence of Retinopathy

The overall burden of diabetic retinopathy was high, with all patients in the cohort exhibiting some stages of microvascular damage. Proliferative Diabetic Retinopathy (PDR) was identified in 27.2% (n=55) of the patients. Among those with Non-Proliferative Diabetic Retinopathy (NPDR), the distribution was nearly linear across severity stages. Clinically significant Diabetic Macular Edema (DME) was a major finding, occurring in 19.8% of the cohort. The distribution of DR stages is summarized in Table (2).

3.3. Metabolic Determinants of Disease Severity

Univariate analysis demonstrated that disease duration and glycemic control were the most significant determinants of the severity of retinopathy. PDR prevalence increased from 14.9% in patients with ≤5 years of disease to 47.2% in those with >25 years of disease ($p < 0.001$). Furthermore, 41.0% of patients with "Very Poor" glycemic control (HbA1c >9.0%) progressed to PDR compared to only 16.7% in the control group ($p < 0.001$). Among the systemic factors, hypertension was significantly associated with more advanced stages ($p = 0.010$). The relationship between metabolic determinants and retinopathy stage is detailed in Table (3).

Table[2]: Clinical Distribution of Diabetic Retinopathy Stages (N = 202)

Retinopathy Stage	Frequency (n)	Percentage (%)
Non-Proliferative DR (NPDR)	147	72.8
Mild NPDR	42	20.8
Moderate NPDR	50	24.8
Severe NPDR	55	27.2
Proliferative DR (PDR)	55	27.2
Diabetic Macular Edema (DME)	40	19.8

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; DME = diabetic macular edema.

Table[3]: Univariate Analysis of Metabolic Determinants and DR Severity

Determinant	Mild/Mod NPDR (n = 92)	Severe NPDR/PDR (n = 110)	P-value
HbA1c Level			< 0.001
$\leq 7.0\%$	7 (87.5%)	1 (12.5%)	
7.1–9.0%	92 (84.4%)	17 (15.6%)	
$> 9.0\%$	50 (58.1%)	36 (41.9%)	
Diabetes Duration			< 0.001
≤ 5 years	40 (85.1%)	7 (14.9%)	
6–15 years	153 (78.1%)	43 (21.9%)	
16–25 years	83 (66.9%)	41 (33.1%)	
> 25 years	19 (52.8%)	17 (47.2%)	
Hypertension			0.010
Yes	103 (65.2%)	55 (34.8%)	
No	94 (76.4%)	29 (23.6%)	

NPDR = non-proliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy. P-values from Pearson Chi-Square test.

3.4. Multivariate Determinants and Predictive Accuracy

A binary logistic regression model was constructed to isolate the independent metabolic determinants of PDR. After adjusting for age and comorbidities, diabetes duration remained the sole significant independent determinant (aOR 1.072 per additional year, 95% CI: 1.007–1.141, $p = 0.028$). In this model, HbA1c levels did not reach independent significance ($p = 0.506$), suggesting that cumulative exposure was a more potent determinant than current metabolic readings in this population. ROC curve analysis confirmed that diabetes duration provided superior discriminatory performance (AUC: 0.643) compared to HbA1c (AUC: 0.604). Stratified profiling identified male patients with 16–25 years of disease as the highest-risk demographic, with a PDR prevalence of 44.0%.

Table[4]: Multivariate Determinants of Advanced Retinopathy Progression

Predictor	Adjusted OR	95% CI	P-value
Duration (Years)	1.072	1.007–1.141	0.028
HbA1c (%)	1.071	0.875–1.311	0.506
Hypertension	1.568	0.804–3.058	0.187
Age	0.997	0.960–1.035	0.872
Renal Disease	1.207	0.484–3.008	0.687

Note: Nagelkerke R-squared = 9.7%; Model Significance p = 0.031. OR = odds ratio; CI = confidence interval.

4. DISCUSSION

The current study, conducted at Al-Thawra General Hospital in Sana'a, revealed an alarmingly high prevalence of vision-threatening diabetic retinopathy (DR) within the Yemeni population. The observed Proliferative Diabetic Retinopathy (PDR) rate of 27.2% and Diabetic Macular Edema (DME) rate of 19.8% represent a significant deviation not only from global epidemiological norms but also from pre-conflict Yemeni data, which previously identified DR as a leading cause of blindness without comprehensively quantifying the full severity spectrum [9, 13]. While the international prevalence of PDR typically ranges from 3% to 8%, our findings mirror the "conflict phenotype" observed in regional humanitarian crises, such as Syria (16%–26%) and Palestine (12.2%), where systemic instability has shifted the clinical spectrum toward advanced pathology [4, 15, 16].

A central finding of this study was the overriding influence of diabetes duration as the primary determinant of DR severity. In our multivariate model, every additional year of disease increased the odds of PDR by 7.2%

(aOR 1.072, p = 0.028). This finding is supported by recent global meta-analyses that identified duration as the most potent non-modifiable driver of microvascular complications [17].

Interestingly, while univariate analysis showed a strong association between HbA1c levels and DR severity, glycemic control lost independent significance in the adjusted multivariate model (p = 0.506). This "Multivariate Paradox" has been documented in Palestinian cohorts and is likely explained by the HbA1c Saturation Hypothesis [8, 15]. In a population where chronic hyperglycemia is near-universal (mean HbA1c 10.07%), the biological pathways for retinal damage, including protein kinase C activation and oxidative stress, may be maximally saturated [6]. Consequently, current cross-sectional HbA1c readings become statistically redundant, leaving the cumulative "time-at-risk" (duration) as the only discriminator with sufficient variance to predict advanced disease.

The catastrophic loss of metabolic control in our cohort was a direct biological consequence of the "War Effect." Since 2015, Yemen has faced a triad of displacement, pharmaceutical scarcity, and collapse of the medical "cold chain" for insulin storage [2]. These stressors elevate counter-regulatory hormones, such as cortisol and catecholamines, maintaining a high "hyperglycemic floor," which is often resistant to basic oral therapy.

Furthermore, our results are consistent with the concept of "Metabolic Memory" or the "Legacy Effect" established by the DCCT/EDIC trials [6, 18]. Mitochondrial dysfunction and epigenetic modifications initiated during the peak years of conflict (2015–2018) continue to drive DR progression, even in patients who may have recently stabilized their glucose levels. This suggests that Yemen will face a mounting wave of PDR cases by the 2030s, necessitating the immediate expansion of specialized ophthalmic care.

Our stratified analysis identified a critical high-risk demographic: male patients with 16–25 years of disease duration exhibited a PDR prevalence of 44.0%. While some regional literature suggests that women carry a higher overall microvascular risk due to post-menopausal hormonal shifts [19], our data highlights a specific vulnerability in Yemeni males. This likely reflects a pattern of "symptom-driven" care-seeking; in a collapsed economy, males may delay presentation to tertiary centers such as Al-Thawra until advanced neovascularization or vitreous hemorrhage significantly impairs occupational functioning.

The superior discriminatory performance of disease duration (AUC 0.643) compared to HbA1c (AUC 0.603) has profound implications for screening in humanitarian zones. In settings where laboratory testing is expensive or unavailable, our data validate the "Duration-First" triage protocol. Prioritizing any patient reaching their second decade of disease for intensive retinal surveillance could provide a diagnostic accuracy of approximately 80% [20]. Given that hypertension was also significantly associated with severity (p = 0.010), an integrated approach to managing both intravascular pressure and retinal screening is essential to mitigate synergistic damage to the microvasculature.

These findings align with earlier Yemeni observations that regular diabetes clinic attendance was associated with lower visual disability and retinopathy severity [11], underscoring the critical importance of maintaining structured ophthalmic follow-up despite conflict-related disruptions in Yemen. The continuity of this evidence base—from the foundational hospital- and community-based studies conducted in the pre-conflict and early conflict periods [9–13] to the present analysis—reinforces that DR has long been entrenched as a major public health challenge in Yemen and that the ongoing crisis has only exacerbated an already severe burden.

4.1. Study Limitations

This study was limited by its retrospective cross-sectional design, which precluded the assessment of temporal causality. The data from Al-Thawra Hospital likely reflects a selection bias toward more severe cases. Additionally, the lack of longitudinal data on glycemic variability and the limited availability of optical coherence tomography (OCT) for subclinical detection of macular edema are recognized constraints.

5. CONCLUSION

In the conflict-affected environment of Yemen, diabetic retinopathy has evolved from a medical complication to a direct biological marker of humanitarian collapse. Because chronic hyperglycemia is nearly universal, the duration of disease exposure has emerged as the most critical clinical determinant of disease severity. We recommend that screening protocols in Yemen prioritize intensive retinal surveillance for all patients with diabetes duration exceeding 15 years, with a specific focus on high-risk male patients. Addressing PDR in Yemen is not merely a clinical priority, but a vital step in preserving the economic viability of a generation rebuilding from the ashes of war.

Declarations

Ethics Approval and Consent to Participate

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Research and Ethics Committee of the Faculty of Medicine and Health Sciences, Sana'a University, Sana'a, Yemen. Owing to the retrospective nature of the analysis of de-identified patient data, the committee waived the requirement for individual patient consent for this specific study. All patients provided written informed consent for their surgical pro-

cedures and for the potential use of their clinical data for research purposes.

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