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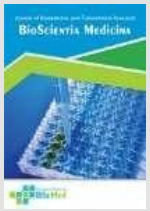

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Impact of Glycemic Control on Amsler Grid Findings in Patients with Diabetic Retinopathy in Palembang, Indonesia

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A B S T R A C T

Background: Diabetic retinopathy (DR) remains a principal cause of vision impairment globally, frequently affecting the macula and central vision. This study aimed to investigate the association between glycemic control status and the presence of Amsler grid abnormalities in patients diagnosed with diabetic retinopathy in Palembang. **Methods:** This cross-sectional study was conducted at the outpatient ophthalmology and internal medicine clinics of a tertiary referral hospital in Palembang between January 2023 and December 2024. Patients aged 18 years or older with a confirmed diagnosis of type 1 or type 2 diabetes mellitus and any stage of diabetic retinopathy, capable of performing Amsler grid testing, were included after providing informed consent. Patients with other significant ocular pathologies affecting the macula or media opacities precluding fundus examination were excluded. Data collected included demographics, diabetes history, comprehensive ophthalmic examination findings, standardized Amsler grid testing results, and recent HbA1c levels. Glycemic control was categorized as good (<7.0%), fair (7.0-9.0%), and poor (>9.0%). Statistical analysis involved descriptive statistics, chi-square tests, t-tests/Mann-Whitney U tests, and multivariable logistic regression to assess the association between HbA1c levels and abnormal Amsler grid findings, adjusting for potential confounders. **Results:** A total of 385 patients with DR (mean age 58.2 ± 9.5 years; 53.8% female) were included. The mean duration of diabetes was 12.4 ± 6.8 years, and the mean HbA1c was 8.9% ± 2.1%. Abnormal Amsler grid findings were reported by 161 participants (41.8%). Patients with abnormal Amsler grid findings had significantly higher mean HbA1c levels compared to those with normal findings (9.8% ± 1.9% vs. 8.3% ± 1.8%, $p < 0.001$). In the multivariable logistic regression analysis, after adjusting for age, diabetes duration, DR severity, and hypertension, poor glycemic control (HbA1c >9.0%) was independently associated with significantly higher odds of having abnormal Amsler grid findings compared to good glycemic control (HbA1c <7.0%) (Adjusted Odds Ratio [aOR] = 3.45, 95% CI: 1.98-6.01, $p < 0.001$). Fair glycemic control (HbA1c 7.0-9.0%) also showed increased odds, although to a lesser extent (aOR = 1.82, 95% CI: 1.05-3.15, $p = 0.032$). Each 1% increase in HbA1c was associated with a 35% increased odds of abnormal Amsler findings. **Conclusion:** This study demonstrated a significant association between poorer glycemic control, as indicated by higher HbA1c levels, and the presence of abnormal Amsler grid findings among diabetic retinopathy patients in Palembang. These findings underscore the critical role of meticulous glycemic management in preserving not only retinal structure but also central visual function detectable through simple psychophysical tests. The Amsler grid serves as a valuable, accessible tool for functional monitoring in this patient population.

1. Introduction

Diabetes mellitus (DM) is rapidly becoming a global health issue, with increasing prevalence in developed and developing countries, including Indonesia. The International Diabetes Federation (IDF) predicts a continued rise in the number of individuals affected

by this disease worldwide. In Indonesia, Palembang, the capital of South Sumatra province, is experiencing a significant burden of diabetes and its related complications, which presents challenges for the local healthcare system. One of the most serious chronic complications of DM is diabetic retinopathy (DR), a microvascular disease that affects the retina. DR is a leading cause of preventable blindness and visual impairment among working-age adults across the globe. The development of DR is closely linked to chronic hyperglycemia, which triggers a series of metabolic and vascular abnormalities in the retinal microenvironment. These abnormalities include the activation of the polyol pathway, the formation of advanced glycation end-products (AGEs), the activation of protein kinase C (PKC), and increased flux through the hexosamine pathway. These processes collectively lead to oxidative stress, chronic low-grade inflammation, thickening of the basement membrane, loss of pericytes, endothelial dysfunction, increased vascular permeability, and ultimately, retinal ischemia and neovascularization. DR progresses through several clinical stages, starting with non-proliferative diabetic retinopathy (NPDR), characterized by microaneurysms, hemorrhages, and cotton wool spots, and advancing to proliferative diabetic retinopathy (PDR), marked by the growth of abnormal new blood vessels that can cause vitreous hemorrhage and tractional retinal detachment. Vision loss in DR often results from damage to the macula, the central part of the retina responsible for sharp, detailed, high-acuity vision needed for tasks such as reading, driving, and facial recognition. Diabetic macular edema (DME), the accumulation of fluid and thickening in the macular layers due to the breakdown of the blood-retinal barrier (BRB), is the most common cause of central vision loss in DR patients and can occur at any stage of the disease. Macular ischemia, caused by capillary non-perfusion in the foveal avascular zone (FAZ), can also lead to irreversible central vision loss, even without significant edema. Subclinical changes, including neuroretinal degeneration and Müller cell dysfunction, can impair macular function before any structural changes are visible through clinical examination or standard imaging.[1-3]

Given the significant impact of macular dysfunction on a patient's quality of life, early detection and monitoring are crucial. While advanced imaging techniques like Optical Coherence Tomography (OCT) can provide detailed anatomical information about the macula, including retinal thickness and the presence of fluid or traction, they may not always capture the subtle functional deficits that patients experience. Additionally, the availability and cost of OCT can be limiting factors, especially in resource-limited settings. The Amsler grid, developed in the 1940s, is a simple, inexpensive, and widely accessible test used to evaluate the central 20 degrees of the visual field, primarily reflecting macular function. The test requires the patient to focus on a central dot on a grid of straight lines and report any perceived distortions (metamorphopsia), missing areas (scotomas), or blurring. Metamorphopsia, an early symptom of macular pathology, is thought to result from the displacement or disruption of photoreceptor alignment caused by edema, traction, or subretinal fluid, which makes straight lines appear wavy or bent. Scotomas are areas of reduced or absent vision within the central field, potentially caused by edema, ischemia, or atrophic changes. Although the Amsler grid test is subjective and relies on patient cooperation and interpretation, it is a valuable tool for patient self-monitoring and clinical screening to detect functional changes suggestive of macular involvement, prompting further evaluation. The Amsler grid's usefulness in detecting changes in various macular conditions, including age-related macular degeneration (AMD) and DME, has been well documented. Systemic glycemic control, typically assessed by measuring glycated hemoglobin (HbA1c), is fundamental in diabetes management and plays a critical role in the onset and progression of diabetic microvascular complications, including DR. Landmark clinical trials like the Diabetes Control and Complications Trial (DCCT) in type 1 diabetes and the

United Kingdom Prospective Diabetes Study (UKPDS) in type 2 diabetes have definitively shown that intensive glycemic control significantly reduces the risk of developing DR and slows its progression. HbA1c reflects average blood glucose levels over the past 2-3 months and is a crucial biomarker for assessing long-term glycemic status and treatment effectiveness. Higher HbA1c levels are strongly associated with an increased risk and severity of DR and DME. Tight glycemic control has been shown to decrease the need for interventions such as laser photocoagulation and vitrectomy.[4-7]

Despite the well-established link between poor glycemic control (high HbA1c) and the structural progression of DR and DME, as observed through funduscopy or OCT, there is limited research on the direct relationship between HbA1c levels and functional macular deficits detected by the Amsler grid in DR patients. Understanding this correlation is important because Amsler grid abnormalities may indicate early functional consequences of hyperglycemia-induced macular changes, potentially preceding significant structural alterations or a decline in visual acuity. Furthermore, documenting this association reinforces the importance of glycemic control not only for preventing anatomical disease progression but also for preserving the subjective quality of central vision. This study is particularly relevant in Palembang, Indonesia, where local data on the prevalence and characteristics of DR and its functional impact are essential for developing effective public health strategies and clinical management protocols. In many Indonesian healthcare settings, resource limitations highlight the potential value of simple, low-cost diagnostic tools like the Amsler grid. Investigating the association between glycemic control and Amsler grid findings in this specific population can provide valuable insights for local healthcare providers and policymakers.[8-10] Therefore, this study aimed to evaluate the impact of systemic glycemic control, measured by HbA1c levels, on the presence of Amsler grid abnormalities (metamorphopsia or scotoma) in patients with diabetic retinopathy attending tertiary care clinics in Palembang, South Sumatra, Indonesia.

2. Methods

This investigation was designed as a hospital-based, cross-sectional study. Participants were recruited consecutively from the outpatient Ophthalmology Clinic at Dr. Mohammad Hoesin General Hospital, a tertiary referral center and teaching hospital affiliated with the Faculty of Medicine, Universitas Sriwijaya, in Palembang, South Sumatra, Indonesia. The study period spanned from January 1st, 2023, to December 31st, 2024. This setting was selected due to its role in serving a large and diverse population from Palembang and surrounding areas, which facilitates access to a substantial number of patients with diabetes and its complications. The study's target population consisted of adult patients with a pre-existing diagnosis of either type 1 or type 2 diabetes mellitus who also had a confirmed diagnosis of diabetic retinopathy in at least one eye. Inclusion criteria; Age ≥ 18 years; Established diagnosis of type 1 or type 2 diabetes mellitus based on American Diabetes Association (ADA) or Indonesian Society of Endocrinology (PERKENI) criteria; Confirmed diagnosis of diabetic retinopathy (any stage, from mild NPDR to PDR, with or without DME) in at least one eye, determined via dilated funduscopic examination by an experienced ophthalmologist; Ability to understand and perform the Amsler grid test reliably, as judged by the examining ophthalmologist or trained research assistant; Availability of an HbA1c measurement performed within the three months preceding or on the day of the ophthalmic assessment; Willingness and ability to provide written informed consent to participate in the study. Exclusion criteria; Presence of other significant ocular diseases that could independently affect macular function or confound Amsler grid results, such as advanced age-related macular degeneration (geographic atrophy or choroidal neovascularization), macular holes, epiretinal membranes unrelated to DR, pathological

myopia (spherical equivalent > -6.0 D or axial length > 26.5 mm), hereditary retinal dystrophies, or uveitis involving the posterior segment; Significant media opacities (dense cataracts, severe corneal scarring, significant vitreous hemorrhage) precluding adequate visualization of the macula during fundus examination or reliable Amsler grid testing; History of intraocular surgery (other than uncomplicated cataract surgery performed > 6 months prior) or intravitreal injections within the past 3 months; Neurological or cognitive impairment significantly limiting the patient's ability to cooperate with testing procedures or provide reliable responses; Pregnancy. The study protocol was designed and conducted in strict accordance with the ethical principles outlined in the Declaration of Helsinki and its subsequent amendments. Prior to commencement, the study protocol, informed consent forms, and data collection instruments received formal approval from the Institutional Review Board (IRB) / Health Research Ethics Committee of the Faculty of Medicine, Universitas Sriwijaya and Dr. Mohammad Hoesin General Hospital, Palembang. All potential participants were approached by trained research personnel who explained the study's purpose, procedures, potential risks and benefits, confidentiality measures, and their right to withdraw at any time without penalty or impact on their standard clinical care. Written informed consent was obtained from every participant before any study-specific procedures or data collection commenced. Patient anonymity and data confidentiality were maintained throughout the study using unique identification codes. Data were stored securely in password-protected electronic databases accessible only to authorized study personnel. Data for enrolled participants were collected through a combination of patient interviews, review of existing medical records, comprehensive ophthalmic examinations, standardized Amsler grid testing, and recent laboratory results. A standardized case report form (CRF) was used for data collection to ensure consistency.

Information collected included; Demographics: Age (years), gender; Diabetes History: Type of diabetes (Type 1 or Type 2), duration of diagnosed diabetes (years), current diabetes medications (oral hypoglycemic agents, insulin therapy); Comorbidities: Presence of systemic hypertension (defined as documented diagnosis, use of antihypertensive medication, or measured blood pressure ≥ 140/90 mmHg on at least two occasions), dyslipidemia (documented diagnosis or use of lipid-lowering medication), chronic kidney disease, cardiovascular disease history; Smoking Status: Current smoker, former smoker, never smoker.

Each participant underwent a comprehensive ophthalmic evaluation performed by an experienced ophthalmologist or a supervised ophthalmology resident, following a standardized protocol. This included; Best-Corrected Visual Acuity (BCVA): Measured monocularly using a Snellen chart at 6 meters or an ETDRS chart, converted to LogMAR (Logarithm of the Minimum Angle of Resolution) for statistical analysis; Intraocular Pressure (IOP): Measured using Goldmann applanation tonometry or a calibrated non-contact tonometer; Slit-Lamp Biomicroscopy: Examination of the anterior segment (cornea, lens status including cataract grading using LOCS III system) and posterior segment after pupillary dilation (using tropicamide 1% and phenylephrine 2.5% eye drops); Dilated Fundus Examination: Detailed examination of the retina and macula using indirect ophthalmoscopy with a 20D or 28D lens and slit-lamp biomicroscopy with a 78D or 90D non-contact fundus lens; Diabetic Retinopathy Grading: The severity of DR was graded based on the findings in the fundus examination according to the international clinical classification system based on the Early Treatment Diabetic Retinopathy Study (ETDRS) criteria. Patients were categorized into: No apparent DR (excluded by definition), Mild NPDR, Moderate NPDR, Severe NPDR, or PDR. The presence or absence of clinically significant macular edema (CSME), as defined by ETDRS criteria, or DME identified on slit-lamp biomicroscopy was also

recorded. For analysis, the eye with the more severe grade of DR was used if grades differed between eyes. If Amsler grid findings differed, the result from the eye with worse DR or worse Amsler finding was considered for primary analysis, with sensitivity analyses performed using data from both eyes where appropriate; Optional Ancillary Testing: While not mandated for inclusion, results from OCT imaging, if performed as part of standard care around the time of enrollment, were noted (central macular thickness, presence of subretinal/intraretinal fluid). Standardized Amsler grid testing was performed monocularly for each eye under appropriate room lighting conditions. Patients wore their usual near correction (reading glasses). The standard Amsler grid chart (a 10x10 cm square containing a grid of black lines on a white background with a central fixation dot) was presented at a consistent reading distance of approximately 30-33 cm (12-13 inches). The untested eye was occluded completely. Patients were instructed to fixate steadily on the central dot and report their observations based on specific questions asked by the examiner: "Can you see the central dot?", "While looking at the dot, can you see all four corners/sides of the large square grid?", "Are all the lines within the grid straight and parallel, or do any lines appear wavy, distorted, bent, or curved (metamorphopsia)?", "Are all the small squares within the grid visible and of equal size, or are any areas blurred, missing, blank, or dark (scotoma)?" The Amsler grid finding for each eye was recorded as either 'Normal' (patient reported seeing the central dot, all grid lines were straight and parallel, and no areas were missing or distorted) or 'Abnormal' (patient reported the presence of metamorphopsia on any part of the grid OR the presence of a scotoma/missing area within the grid). The specific type of abnormality (metamorphopsia, scotoma, or both) was also noted. For patients with bilateral DR, if one eye had normal findings and the other abnormal, the patient was categorized into the 'Abnormal Amsler Grid' group for the primary analysis correlating with systemic HbA1c. The primary measure of systemic glycemic control was the HbA1c level. The HbA1c value used was the most recent measurement obtained within a 3-month window (before or on the day of) the ophthalmic assessment. Results were obtained from the hospital's central laboratory records or patient-provided official reports. The laboratory utilized a standardized assay method, typically High-Performance Liquid Chromatography (HPLC), certified by the National Glycohemoglobin Standardization Program (NGSP). HbA1c values were recorded as percentages (%).

Dependent Variable: Amsler Grid Finding (binary): Categorized as 'Normal' or 'Abnormal' (presence of metamorphopsia and/or scotoma in at least one eye meeting inclusion criteria); Primary Independent Variable: Glycemic Control (HbA1c): Treated both as a continuous variable (percentage) and a categorical variable based on established thresholds relevant to diabetes management guidelines: Good Control: HbA1c < 7.0% (53 mmol/mol), Fair Control: HbA1c 7.0% to 9.0% (53-75 mmol/mol), Poor Control: HbA1c > 9.0% (75 mmol/mol); Covariates (Potential Confounders): Age (continuous, years), Gender (categorical: male/female), Duration of Diabetes (continuous, years), Type of Diabetes (categorical: Type 1/Type 2); Severity of Diabetic Retinopathy (categorical: Mild NPDR, Moderate NPDR, Severe NPDR, PDR) - based on the worse eye; Presence of Clinically Significant Macular Edema (CSME) or DME (binary: yes/no) - based on the worse eye; Best-Corrected Visual Acuity (BCVA) in LogMAR (continuous) - from the eye tested with Amsler or the worse eye; Presence of Systemic Hypertension (binary: yes/no); Presence of Dyslipidemia (binary: yes/no); Smoking Status (categorical: never/former/current); Type of Diabetes Treatment (categorical: diet/oral agents only/insulin ± oral agents). All collected data were entered into a secure electronic database using Microsoft Excel software and subsequently imported into IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp., Armonk, NY, USA) for analysis. A two-sided p-value < 0.05 was considered statistically significant for all analyses. Continuous variables (age, diabetes duration, HbA1c, BCVA LogMAR) were

summarized using means and standard deviations (SD) if normally distributed (assessed using histograms and Shapiro-Wilk test) or medians and interquartile ranges (IQR) if non-normally distributed. Categorical variables (gender, DR severity, Amsler grid outcome, glycemic control categories, comorbidities) were summarized using frequencies and percentages (n, %).

To compare characteristics between patients with normal Amsler grid findings and those with abnormal findings, appropriate statistical tests were used; Independent samples t-test (for normally distributed continuous variables) or Mann-Whitney U test (for non-normally distributed continuous variables) to compare means/medians of variables like age, diabetes duration, and HbA1c; Chi-square (x^2) test or Fisher's exact test (when expected cell counts were < 5) to compare proportions of categorical variables like gender, DR severity categories, glycemic control categories, hypertension.

To assess the independent association between glycemic control (HbA1c) and the likelihood of having abnormal Amsler grid findings, while controlling for potential confounding factors, binary multivariable logistic regression analysis was performed. The dependent variable was the Amsler grid outcome (Abnormal=1, Normal=0); Model 1: Included HbA1c as a continuous variable. The Odds Ratio (OR) represents the change in odds of having an abnormal Amsler grid for each 1% increase in HbA1c; Model 2: Included HbA1c as a categorical variable (using 'Good Control' <7.0% as the reference category). ORs were calculated for 'Fair Control' (7.0-9.0%) and 'Poor Control' (>9.0%) relative to the reference group. Confounders included in the models were selected based on clinical relevance and findings from bivariate analyses (variables with p < 0.10 in bivariate comparison or known strong confounders like age, diabetes duration, DR severity). Variables included were: Age, duration of diabetes, DR severity category, presence of hypertension, and presence of DME. Results were presented as Adjusted Odds Ratios (aORs) with their corresponding 95% Confidence Intervals (CIs) and p-values. Model diagnostics, including assessment of multicollinearity (using Variance Inflation Factor, VIF) and goodness-of-fit (using Hosmer-Lemeshow test), were performed. A sensitivity analysis considering the Amsler grid result from only the right eye, or only the left eye, was planned to assess the robustness of the findings. Another sensitivity analysis was planned excluding patients with PDR to see if the association held primarily within the NPDR stages.

3. Results

Table 1 presents the baseline characteristics of the 385 participants included in the study, categorized into the total cohort, those with normal Amsler grid findings, and those with abnormal Amsler grid findings. It also provides p-values to indicate the statistical significance of differences observed between the normal and abnormal Amsler groups; Demographic Characteristics: The mean age of the total cohort was 58.2 years, with a standard deviation of 9.5 years. The mean age was similar between the Normal Amsler group (57.5 years) and the Abnormal Amsler group (59.2 years), and this difference was not statistically significant. The total cohort had a slightly higher proportion of females (53.8%) compared to males (46.2%). The distribution of gender was not significantly different between the Normal and Abnormal Amsler groups; Diabetes Characteristics: The majority of participants in the total cohort had Type 2 diabetes (95.1%), with a small proportion having Type 1 diabetes (4.9%). The distribution of diabetes type was similar across the Normal and Abnormal Amsler groups, showing no significant difference. The mean duration of diabetes in the total cohort was 12.4 years, with a standard deviation of 6.8 years. Notably, the Abnormal Amsler group had a significantly longer mean duration of diabetes (14.2 years) compared to the Normal Amsler group (11.1 years). The most common treatment modality in the total cohort was insulin, either alone or in combination with oral agents (66.0%). There was a difference in treatment distribution between the groups, with a higher proportion of patients in the

Abnormal Amsler group using insulin compared to the Normal Amsler group. The mean HbA1c for the total cohort was 8.9%, with a standard deviation of 2.1%. A significant difference was observed in HbA1c levels between the groups. The Abnormal Amsler group had a higher mean HbA1c (9.8%) compared to the Normal Amsler group (8.3%). When categorized, the Abnormal Amsler group had a lower proportion of patients with "Good" glycemic control and a higher proportion with "Poor" glycemic control compared to the Normal Amsler group; Ophthalmic Characteristics: The mean BCVA for the total cohort was 0.48 LogMAR, with a standard deviation of 0.35. The Abnormal Amsler group exhibited significantly worse mean BCVA (0.59 LogMAR) compared to the Normal Amsler group (0.40 LogMAR). The distribution of diabetic retinopathy (DR) severity varied significantly between the groups. The Abnormal Amsler group had a higher proportion of patients with more severe DR (Severe NPDR and PDR) compared to the Normal Amsler group. Diabetic macular edema (DME) or clinically significant macular edema (CSME) was present in 40.0% of the total cohort. A significantly higher proportion of patients in the Abnormal Amsler group had DME/CSME (58.4%) compared to the Normal Amsler group (26.8%); Comorbidities: Hypertension was present in 61.0% of the total cohort. While there was a trend towards a higher proportion of hypertension in the Abnormal Amsler group, this difference did not reach statistical significance. Dyslipidemia was present in 47.0% of the total cohort. There was no significant difference in the prevalence of dyslipidemia between the Normal and Abnormal Amsler groups; Smoking Status: Smoking status was categorized as Never, Former, or Current. The distribution of smoking status was similar across the total cohort and the Normal and Abnormal Amsler groups, with no significant differences observed.

Table 1. Baseline demographic and clinical characteristics of study participants (N=385).

Characteristic	Total Cohort (N=385)	Normal Amsler (n=224)	Abnormal Amsler (n=161)	p-value
Demographics				
Age (years), mean ± SD	58.2 ± 9.5	57.5 ± 9.8	59.2 ± 9.0	0.105
Gender, n (%)				0.688
Male	178 (46.2)	102 (45.5)	76 (47.2)	
Female	207 (53.8)	122 (54.5)	85 (52.8)	
Diabetes Characteristics				
Type of Diabetes, n (%)				0.753†
Type 1	19 (4.9)	10 (4.5)	9 (5.6)	
Type 2	366 (95.1)	214 (95.5)	152 (94.4)	
Duration of Diabetes (years), mean ± SD	12.4 ± 6.8	11.1 ± 6.5	14.2 ± 6.9	<0.001
Diabetes Treatment, n (%)				0.008
Diet/Lifestyle only	18 (4.7)	14 (6.3)	4 (2.5)	
Oral Agents only	113 (29.4)	78 (34.8)	35 (21.7)	
Insulin ± Oral Agents	254 (66.0)	132 (58.9)	122 (75.8)	
Glycemic Control				
HbA1c (%), mean ± SD	8.9 ± 2.1	8.3 ± 1.8	9.8 ± 1.9	<0.001
HbA1c Category, n (%)				<0.001
Good (<7.0%)	68 (17.7)	55 (24.6)	13 (8.1)	
Fair (7.0-9.0%)	139 (36.1)	98 (43.8)	41 (25.5)	
Poor (>9.0%)	178 (46.2)	71 (31.7)	107 (66.5)	
Ophthalmic Characteristics				
BCVA (LogMAR), mean ± SD	0.48 ± 0.35	0.40 ± 0.29	0.59 ± 0.38	<0.001
DR Severity (Worse Eye), n (%)				<0.001
Mild NPDR	75 (19.5)	58 (25.9)	17 (10.6)	
Moderate NPDR	128 (33.2)	80 (35.7)	48 (29.8)	
Severe NPDR	92 (23.9)	46 (20.5)	46 (28.6)	
PDR	90 (23.4)	40 (17.9)	50 (31.1)	
Presence of DME/CSME, n (%)	154 (40.0)	60 (26.8)	94 (58.4)	<0.001
Comorbidities				
Hypertension, n (%)	235 (61.0)	129 (57.6)	106 (65.8)	0.098
Dyslipidemia, n (%)	181 (47.0)	100 (44.6)	81 (50.3)	0.243
Smoking Status, n (%)				0.451
Never	298 (77.4)	175 (78.1)	123 (76.4)	
Former	45 (11.7)	25 (11.2)	20 (12.4)	
Current	42 (10.9)	24 (10.7)	18 (11.2)	

Notes: SD: Standard Deviation; BCVA: Best-Corrected Visual Acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; DR: Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy; DME: Diabetic Macular Edema; CSME: Clinically Significant Macular Edema. †Fisher's exact test.

Table 2 presents the results of two multivariable logistic regression models that predict the likelihood of abnormal Amsler grid findings in the study participants. The table shows the Adjusted Odds Ratios (aOR), 95% Confidence Intervals (CI), and p-values for each predictor variable in both models; Model 1 (HbA1c Continuous): This model examines the effect of HbA1c as a continuous variable on the odds of abnormal Amsler grid findings, while adjusting for other potential confounding factors. The aOR is 1.35, with a 95% CI of 1.20 - 1.52 and a p-value of <0.001. This indicates that for every 1% increase in HbA1c level, the odds of having abnormal Amsler grid findings increase by 35%, and this association is statistically significant. The aOR is 1.01, with a 95% CI of 0.98 - 1.04 and a p-value of 0.450. This suggests that age is not significantly associated with the odds of abnormal Amsler grid findings when other factors are controlled. The aOR is 1.06, with a 95% CI of 1.02 - 1.10 and a p-value of 0.003. This indicates that for each additional year of diabetes duration, the odds of having abnormal Amsler grid findings increase by 6%, which is a statistically significant finding. DR Severity (Ref: Mild NPDR) section examines the impact of different stages of diabetic retinopathy (DR) severity, using Mild NPDR as the reference category; Moderate NPDR: The aOR is 1.40, with a 95% CI of 0.78 - 2.50 and a p-value of 0.265. This result is not statistically significant, suggesting that Moderate NPDR is not independently associated with increased odds of abnormal Amsler grid findings compared to Mild NPDR; Severe NPDR: The aOR is 1.98, with a 95% CI of 1.08 - 3.63 and a p-value of 0.027. This is statistically significant, indicating that patients with Severe NPDR have approximately 1.98 times higher odds of abnormal Amsler grid findings compared to those with Mild NPDR; PDR: The aOR is 2.55, with a 95% CI of 1.30 - 4.99 and a p-value of 0.006. This is also statistically significant, showing that patients with Proliferative DR (PDR) have 2.55 times higher odds of abnormal Amsler grid findings compared to those with Mild NPDR. The aOR is 2.89, with a 95% CI of 1.80 - 4.64 and a p-value of <0.001. This demonstrates that the presence of diabetic macular edema (DME) or clinically significant macular edema (CSME) is strongly associated with abnormal Amsler grid findings, with affected patients having 2.89 times higher odds compared to those without DME/CSME. The aOR is 1.35, with a 95% CI of 0.85 - 2.15 and a p-value of 0.201. This result is not statistically significant, indicating that hypertension is not independently associated with the odds of abnormal Amsler grid findings; Model 2 (HbA1c Categorical): This model examines the effect of HbA1c when categorized into clinically relevant groups, using "Good (<7.0%)" as the reference category. HbA1c Category (Ref: Good <7.0%) section compares the odds of abnormal Amsler grid findings for different HbA1c categories, relative to the "Good" control group; Fair (7.0-9.0%): The aOR is 1.82, with a 95% CI of 1.05 - 3.15 and a p-value of 0.032. This statistically significant result indicates that patients with "Fair" glycemic control have 1.82 times higher odds of abnormal Amsler grid findings compared to those with "Good" control; Poor (>9.0%): The aOR is 3.45, with a 95% CI of 1.98 - 6.01 and a p-value of <0.001. This highly significant finding shows that patients with "Poor" glycemic control have 3.45 times higher odds of abnormal Amsler grid findings compared to those with "Good" control. The aOR is 1.01, with a 95% CI of 0.98 - 1.04 and a p-value of 0.488. Similar to Model 1, age is not a significant predictor in this model. The aOR is 1.05, with a 95% CI of 1.01 - 1.09 and a p-value of 0.010. This result confirms that longer diabetes duration is associated with increased odds of abnormal Amsler grid findings. DR Severity (Ref: Mild NPDR); Moderate NPDR: The aOR is 1.35, with a 95% CI of 0.75 - 2.43 and a p-value of 0.318. This is not statistically significant; Severe NPDR: The aOR is 1.85, with a 95% CI of 1.01 - 3.40 and a p-value of 0.047. This is statistically significant; PDR: The aOR is 2.30, with a 95% CI of 1.17 - 4.52 and a p-value of 0.016. This is statistically significant. The aOR is 2.75, with a 95% CI of 1.71 - 4.43 and a p-value of <0.001. The

presence of macular edema remains a strong predictor in this model. The aOR is 1.38, with a 95% CI of 0.87 - 2.20 and a p-value of 0.175. Hypertension is not a significant predictor.

Table 2. Multivariable logistic regression analysis predicting abnormal Amsler grid findings (N=385).

Variable	Adjusted Odds Ratio (aOR)	95% Confidence Interval (CI)	p-value
Model 1 (HbA1c Continuous)			
HbA1c (per 1% increase)	1.35	1.20 – 1.52	<0.001
Age (per year)	1.01	0.98 – 1.04	0.450
Duration of Diabetes (per year)	1.06	1.02 – 1.10	0.003
DR Severity (Ref: Mild NPDR)			
Moderate NPDR	1.40	0.78 – 2.50	0.265
Severe NPDR	1.98	1.08 – 3.63	0.027
PDR	2.55	1.30 – 4.99	0.006
Presence of DME/CSME (Yes vs No)	2.89	1.80 – 4.64	<0.001
Hypertension (Yes vs No)	1.35	0.85 – 2.15	0.201
Model 2 (HbA1c Categorical)			
HbA1c Category (Ref: Good <7.0%)			
Fair (7.0-9.0%)	1.82	1.05 – 3.15	0.032
Poor (>9.0%)	3.45	1.98 – 6.01	<0.001
Age (per year)	1.01	0.98 – 1.04	0.488
Duration of Diabetes (per year)	1.05	1.01 – 1.09	0.010
DR Severity (Ref: Mild NPDR)			
Moderate NPDR	1.35	0.75 – 2.43	0.318
Severe NPDR	1.85	1.01 – 3.40	0.047
PDR	2.30	1.17 – 4.52	0.016
Presence of DME/CSME (Yes vs No)	2.75	1.71 – 4.43	<0.001
Hypertension (Yes vs No)	1.38	0.87 – 2.20	0.175

Notes: DR: Diabetic Retinopathy; NPDR: Non-Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy; DME: Diabetic Macular Edema; CSME: Clinically Significant Macular Edema; DR Severity = Mild NPDR; HbA1c Category = Good (<7.0%); DME/CSME = No; Hypertension = No.

4. Discussion

The study's primary revelation of a strong link between elevated HbA1c levels and Amsler grid abnormalities carries substantial weight in the context of diabetic retinopathy management. This significance is underscored by the fact that this association remained robust even after rigorous adjustment for a range of potential confounding variables. These confounders included age, duration of diabetes, the severity of diabetic retinopathy, the presence of macular edema, and systemic hypertension, all of which are known to influence both glycemic control and the development or progression of diabetic retinopathy. The observation that individuals exhibiting poor glycemic control, defined as HbA1c levels exceeding 9.0%, demonstrated over three times the odds of experiencing Amsler grid abnormalities compared to their counterparts with good glycemic control (HbA1c < 7.0%) is particularly striking. This finding underscores the clinical importance of maintaining strict glycemic control to not only mitigate the progression of structural retinal damage but also to preserve optimal central visual function. Furthermore, the study's quantification of the impact of incremental changes in HbA1c, revealing a 35% increase in the odds of Amsler grid abnormalities for each 1% elevation in HbA1c, reinforces the concept of a dose-response relationship. This dose-response relationship suggests that even relatively small improvements in glycemic control may translate to tangible benefits in terms of preserving macular function and preventing or reducing visual distortions or blind spots perceived by patients.[11,12]

The study also revealed a substantial prevalence of abnormal Amsler grid findings within the cohort of patients diagnosed with diabetic retinopathy, with

41.8% of participants reporting some form of visual distortion or defect on the Amsler grid test. This significant proportion highlights the frequency with which individuals with diabetic retinopathy experience subjective disturbances in their central vision. These disturbances can manifest as metamorphopsia, characterized by the perception of distorted or wavy lines, scotoma, representing blind spots or areas of reduced vision, or a combination of both symptoms. Metamorphopsia emerged as the most commonly reported symptom among those with Amsler grid abnormalities, a finding consistent with its established association with macular edema and the disruption of the precise alignment of photoreceptor cells within the macula. Macular edema, a frequent complication of diabetic retinopathy, involves the accumulation of fluid within the retinal layers of the macula, leading to swelling and distortion of the retinal architecture, which in turn affects the orderly arrangement of photoreceptors responsible for accurate visual perception. The notable prevalence of Amsler grid abnormalities observed in this study underscores the potential clinical utility of the Amsler grid as a simple, rapid, and cost-effective screening tool for identifying patients who may require more detailed ophthalmological evaluation or closer monitoring of their macular function. This is particularly relevant in resource-limited settings, such as Palembang, Indonesia, where access to advanced imaging technologies like Optical Coherence Tomography (OCT) may be constrained due to cost or availability. In such contexts, the Amsler grid can serve as a valuable initial assessment to detect subtle functional changes indicative of macular involvement, prompting timely referral and intervention to prevent or mitigate further vision loss.[13-15]

The study's central finding, which establishes a clear link between higher HbA1c levels and the presence of Amsler grid abnormalities, aligns with the fundamental understanding of the pathophysiology of diabetic retinopathy and the well-documented benefits of maintaining strict glycemic control in preventing or slowing its progression. Chronic hyperglycemia, the hallmark of diabetes mellitus, is the primary driving force behind the microvascular damage that underlies both diabetic retinopathy and diabetic macular edema. Elevated blood glucose levels trigger a complex cascade of metabolic and biochemical derangements within the retinal microenvironment, leading to increased vascular permeability, a breakdown of the blood-retinal barrier, and subsequent fluid leakage into the macular tissue. Key pathways implicated in this process include the activation of the polyol pathway, the formation of advanced glycation end-products (AGEs), the activation of protein kinase C (PKC), and increased flux through the hexosamine pathway. These metabolic abnormalities collectively promote oxidative stress, chronic low-grade inflammation, basement membrane thickening, pericyte loss, and endothelial dysfunction, all of which contribute to the increased permeability of retinal blood vessels and the development of macular edema. Diabetic macular edema (DME) is a well-recognized and frequent cause of metamorphopsia and blurred central vision in individuals with diabetic retinopathy. The accumulation of intraretinal fluid disrupts the normal architecture of the macula, leading to distortion of the photoreceptor layer and impaired visual function. In this study, the strong and independent association observed between the presence of DME/CSME (clinically significant macular edema) and abnormal Amsler grid findings (with adjusted odds ratios of approximately 2.8-2.9) further supports the established link between macular edema and visual distortions or defects detected by the Amsler grid.[16,17]

However, a crucial and novel observation arising from the multivariable analysis in this study is that poor glycemic control, as reflected by elevated HbA1c levels, remained significantly associated with Amsler grid abnormalities even after accounting for the presence of clinically detected DME/CSME. This finding suggests that hyperglycemia may exert its detrimental effects on macular function, leading to metamorphopsia or scotoma, through mechanisms

that extend beyond the development of overt, clinically apparent macular edema. In other words, functional macular deficits, detectable by the Amsler grid, may occur even in the absence of clinically evident swelling or thickening of the macula. Several potential mechanisms could explain this observation. Firstly, chronic hyperglycemia induces oxidative stress and inflammation within the retina, leading to damage and dysfunction of retinal neurons, including photoreceptors and Müller cells. Photoreceptors are the specialized light-sensing cells responsible for converting light into electrical signals that are transmitted to the brain for visual processing, while Müller cells are glial cells that play a crucial role in maintaining retinal homeostasis and supporting neuronal function. Damage to these cells can disrupt the normal transmission and processing of visual information, resulting in metamorphopsia or scotoma. Müller cell dysfunction, in particular, can disrupt retinal homeostasis and fluid balance, potentially leading to subtle intracellular swelling or functional changes that affect the precise alignment of photoreceptors within the macula. Even minor alterations in photoreceptor alignment can result in the perception of distorted lines or shapes, characteristic of metamorphopsia. Secondly, macular ischemia, resulting from capillary non-perfusion and reduced blood flow to the macula, is another potential consequence of poor glycemic control that can lead to functional deficits and the development of scotomas, even in the absence of significant macular edema. Chronic hyperglycemia can damage the small blood vessels of the retina, leading to their occlusion and reduced delivery of oxygen and nutrients to the macular tissue. This ischemia can impair the function of retinal neurons and result in the perception of blind spots or areas of reduced vision. The Amsler grid test, while simple and subjective, may possess sufficient sensitivity to detect these subtle functional changes related to neuroretinal dysfunction or microvascular compromise that precede the development of overt structural alterations or significant declines in visual acuity that are readily apparent on standard funduscopy. Thirdly, the possibility of subclinical DME, defined as macular edema that is below the threshold for clinical detection using slit-lamp biomicroscopy but potentially detectable using more sensitive imaging techniques like OCT, cannot be entirely excluded as a contributing factor to the observed association between HbA1c levels and Amsler grid symptoms. It is plausible that patients with higher HbA1c levels may have a higher prevalence of subclinical DME, which could contribute to metamorphopsia or other Amsler grid abnormalities. While the study adjusted for the presence of clinically detected DME, the potential influence of residual confounding by subclinical edema cannot be entirely ruled out.[18-20]

5. Conclusion

This study conclusively demonstrates a significant association between poorer glycemic control, indicated by higher HbA1c levels, and the presence of abnormal Amsler grid findings in patients with diabetic retinopathy in Palembang, Indonesia. The findings underscore the critical importance of meticulous glycemic management in this population, extending beyond the prevention of structural retinal damage to the preservation of central visual function. The Amsler grid serves as a valuable and accessible tool for monitoring functional changes in this patient group, particularly in resource-limited settings. The study's results highlight that poor glycemic control (HbA1c >9.0%) significantly increases the odds of Amsler grid abnormalities compared to good glycemic control (HbA1c <7.0%). This emphasizes the necessity of striving for optimal glycemic control to minimize the risk of visual distortions and defects in individuals with diabetic retinopathy. Furthermore, the research revealed a dose-response relationship, where each 1% increase in HbA1c is associated with a 35% increase in the odds of abnormal Amsler grid findings. This suggests that even small improvements in glycemic control can have a positive impact on preserving macular function. In conclusion, this study contributes important evidence to the understanding

of the relationship between glycemic control and functional macular changes in diabetic retinopathy. It reinforces the need for intensive glycemic management and the utility of the Amsler grid as a practical tool for detecting early functional deficits, thereby aiding in timely intervention and potentially preventing further vision loss.

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