Correlation of Glycosylated Hemoglobin Level with Pupillary Parameters using the Reflex PLR© Mobile Application in Type 2 Diabetes Mellitus Patients

Eve Roxanne V. Apostol, MD, Maria Karina M. Montesines, MD

Ospital ng Makati, Taguig, Philippines

Correspondence: Eve Roxanne V. Apostol, MD
Office Address: Ospital ng Makati, 1218 Sampaguita St, Pembo, Taguig, Philippines
Contact Number: +63966-9575671
Email Address: roxanne.apostolmd@gmail.com

Disclosures: The authors report no conflicts of interest.

ABSTRACT

Objective: To determine the pupillary parameters of adult patients with type 2 diabetes mellitus (DM) using the Reflex PLR© mobile application and to correlate these parameters with glycosylated hemoglobin (HbA1C) levels.

Methods: This was a single-center, prospective, observational, cross-sectional study conducted at Ospital ng Makati from June to August 2024. Study participants were patients with type 2 DM without diabetic retinopathy and non-diabetics who served as the control group. Participants underwent blood chemistry testing and pupillometry using the Reflex PLR© mobile app. The study outcomes were maximum and minimum pupillary diameters, amplitude, and latency.

Results: There were 44 study participants: 26 non-diabetics and 18 diabetic patients. The two groups had similar pupillary baseline diameters ($p = 0.72$; $p = 0.30$), maximum pupillary diameters ($p = 0.82$; $p = 0.89$), minimum pupillary diameters ($p = 0.85$; $p = 0.89$), pupillary amplitudes ($p = 0.88$; $p = 0.55$), and pupillary latencies ($p = 0.53$; $p = 0.47$) for the right and left eyes, respectively. The relationship between pupillary parameters and HbA1C levels showed no significant variations in baseline diameter ($p = 0.21$; $p = 0.45$), maximum diameter ($p = 0.65$ for the right eye; $p = 0.46$ for the left eye), minimum diameter ($p = 0.77$; $p = 0.46$), amplitude ($p = 0.89$; $p = 0.83$), and latency ($p = 0.31$; $p = 0.22$).

Conclusion: The study did not demonstrate any significant correlation between pupillary parameters and HbA1C levels. Pupillary changes in diabetes may have been more dependent on factors such as disease duration and the presence of complications rather than glycemic control alone.

Keywords: Diabetic autonomic neuropathy, pupillary light reflex, glycosylated hemoglobin, pupillometry, light reflex parameters

Philipp J Ophthalmol 2025;50:86-92

Diabetes mellitus (DM) is the fourth leading cause of mortality in the Philippines. With more than four million Filipinos living with the disease, many still go undiagnosed until systemic complications become evident.[1] Glycosylated hemoglobin (HbA1C) has been established as a good substitute for fasting blood glucose in diagnosing, screening, and monitoring blood sugar control in DM. Several literatures have established the correlation of HbA1C and development of systemic complications in DM such as cardiovascular disease, renal failure, retinopathy, nephropathy, and autonomic neuropathy.

Diabetic autonomic neuropathy (DAN) is an often overlooked but serious and common complication of DM. It is one of the earliest complications of the disease.[2] HbA1C level and diabetes duration are the two most significant risk factors in developing DAN.[3] An indirect way to assess integrity of the autonomic nervous system in patients with DM is to test for pupillary response to light stimulus.[4] Previous research has reported abnormal baseline pupil diameter and latency in DAN.[5]

Dynamic pupillometry is the gold standard, noninvasive diagnostic tool to measure pupillary light response in patients with DAN.[5] However, it is expensive, is not easily accessible, and requires skilled technicians. With the recent advancements in smartphone technology, focus is being shifted to the potential use of smart phone mobile applications in patient evaluation. Neice *et al.* reported similar results between pupil measurements using a smartphone-based pupillometer and a traditional pupillometer and concluded that smartphone pupillometer may be an appropriate alternative to a commercial pupillometer.[6,7] Studies on concussion and neurodegenerative disorders using app-generated pupillary light reflex parameters have demonstrated an 88% accuracy with high sensitivity and specificity, supporting its use in detecting non-reactive pupils.[8,9]

The Reflex PLR© (Brightlamp, Inc., Indianapolis, IN, USA) is a Food and Drug Administration (FDA)-approved smartphone application that quantifies the pupillary light response in real time. It provides an objective, repeatable measurement of the pupillary light response, which is invaluable to clinicians.[10] In 2021, a retrospective clinical study utilizing the Reflex PLR© iPhone application was conducted to determine the potential use of the pupillary light reflex (PLR) as biomarker of concussion. Analysis of 27,439 patient records revealed that the participants with a history of concussion had smaller maximum pupillary diameter (Max PD), larger minimum pupillary diameter (Min PD) and prolonged pupillary latency than the participants without concussion. Furthermore, the participants without concussion had lower maximum constriction velocity than those with concussion.[11] Currently, there are no studies on the use of the iPhone-based PLR app in patients with DM.

This study assessed the different pupil parameters in DM patients and a healthy control group using the Reflex PLR©. It also determined correlation between the different pupil parameters and HBA1C level.

METHODS

This was a single-center, prospective, observational, cross-sectional study conducted at Ospital ng Makati from June to August 2024.

The study included adult patients with type 2 DM within three years from diagnosis who had no known DAN, aged between 18 to 60 years old, fluent in either English or Filipino, able to follow commands, and had best-corrected visual acuity of 20/20 or better in both eyes. Patients with dense cataracts, iris defects, glaucoma, optic neuropathy, diabetic retinopathy, other retinal diseases, or a history of cataract surgery were excluded. Healthy individuals without DM were also recruited and served as the control group.

Participants were categorized into two groups: Group 1 comprised patients diagnosed with type 2 DM, and Group 2 comprised non-diabetic patients who served as the control group.

The study outcomes were maximum and minimum pupillary diameters, pupillary amplitude, and pupillary latency, as measured using the Reflex PLR© application.

All study participants underwent laboratory testing for blood chemistry, including HbA1C,

fasting blood sugar, creatinine, blood urea nitrogen (BUN), lipid profile, and a 12-lead electrocardiogram (ECG), on the same morning prior to a full ophthalmologic examination and pupil testing. This was followed by a comprehensive clinical history-taking, which included a review of systems for symptoms such as sinus tachycardia, exercise intolerance, dizziness, presyncope, syncope, and orthostatic hypotension. The following demographic and clinical data were obtained: age, sex, comorbidities, duration of DM, and current medications. Vital signs were recorded.

A comprehensive ophthalmologic examination was performed, which included best-corrected visual acuity (BCVA) determination using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, slit-lamp biomicroscopy, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, and a dilated fundus examination. A fundus photograph was obtained using the Eidon Retinal Imaging (Centervue, Padua, Italy) system to document the retinal status of each participant.

Pupil measurements were performed by the primary investigator using the Reflex PLR® mobile application. Under controlled room lighting conditions, the primary investigator used the Reflex PLR® mobile application on an iPhone 12 Pro (Apple Inc. Cupertino, CA, USA) to measure pupillary reflex amplitude, velocity, latency, maximum diameter, and minimum diameter in all participants.

The smartphone, positioned in portrait orientation on a phone stand placed on a table, was aligned vertically between the participant's eyes at an approximate distance of 10-12 cm (**Figure 1**). Participants were instructed to keep their eyes open and steady while maintaining the testing distance, ensuring that both pupils remained within the video frame and were adequately sized for accurate analysis throughout the captured sequences (**Figure 2**). Upon an audio cue from the examiner, a flash stimulus was delivered using the rear-facing camera. In the event of a blink during the first flash, the video was discarded and the test was repeated.[12,13]

Data and measurements were recorded in the mobile application and subsequently tabulated for analysis.

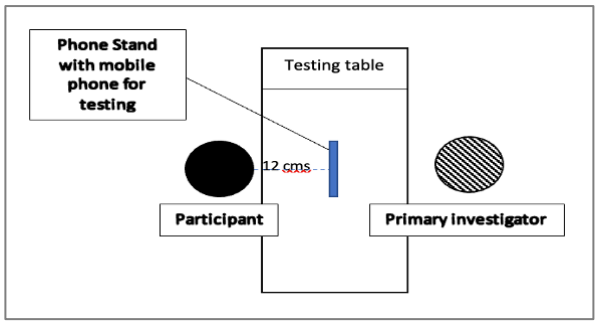

Figure 1. Testing room set-up showing positions of the participant, primary investigator and gadget.

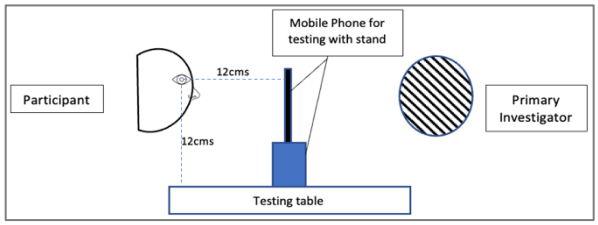

Figure 2. Position of the eye and eyelids in relation to the testing mobile phone.

Statistical Analysis

Descriptive statistics were used to report demographic data, laboratory values, and pupil parameters. An independent-samples *t*-test was used to compare pupil parameters between the two groups, while Pearson's correlation was utilized to determine the relationship between pupil parameters and HbA1C levels. A *p*-value of ≤ 0.05 was considered statistically significant.

Convenience sampling was employed in this study. The sample size was computed using G*Power software (Freeware, Heinrich Heine University Düsseldorf, Germany), a statistical tool designed to determine the minimum sample size required based on the study design. The central limit theorem was applied, and a minimum population size of 30 participants was set to ensure that statistical analyses, such as *t*-tests and confidence intervals, would yield valid and reliable results.

RESULTS

There were a total of 44 study participants: 18 patients in Group 1 and 26 in Group 2. Overall, the majority of respondents (76.74%) were aged 40 years or above with Group 1 having significantly older participants than the Group 2 (54.33 ± 9.94 vs

46.96 ± 11.23 years; p = 0.03). More than half (81.40%) of the participants were female, with similar sex distribution (p = 0.56) between the two groups. More than half of the participants in both groups have comorbidities (77.8 % in Group 1 and 57.69% in Group 2; p = 0.17). A significantly higher percentage of participants in Group 1 were on medication compared to those in Group 2 (88.89% and 57.69%; p = 0.03). Group 1 had significantly higher HbA1C levels compared to Group 2 (6.47 ± 0.59 vs 5.62 ± 0.54; p < 0.0001). Both groups had comparable levels of FBS (6.38 ± 1.30 mmol/L in Group 1 vs. 5.79 ± 1.41 mmol/L in Group 2; p = 0.16), BUN (12.01 ± 30.49 mmol/L vs. 5.57 ± 6.64 mmol/L; p = 0.39), creatinine (68.84 ± 20.2 mmol/L vs. 71.28 ± 14.66 mmol/L; p = 0.66), triglycerides (1.36 ± 0.43 mmol/L vs. 1.29 ± 0.48 mmol/L; p = 0.59), total cholesterol (4.56 ± 1.11 mmol/L vs. 5.23 ± 2.32 mmol/L; p = 0.21), LDL (2.64 ± 1.16 mmol/L vs. 3.15 ± 0.91 mmol/L; p = 0.13), VLDL (0.52 ± 0.29 mmol/L vs. 0.52 ± 0.26 mmol/L; p = 0.10) and HDL (1.36 ± 0.30 mmol/L vs. 1.28 ± 0.29mmol/L; p = 0.40). All the participants had normal 12-lead ECG results. All participants had normal dilated fundus examinations, indicating overall similarity in ocular health between both eyes **(Table 1).**

Table 2 summarizes the pupillary profile of the right eye between two groups. No statistically significant differences were found between the two groups in terms of baseline pupil diameter (3.6 ± 3.43 mm vs. 3.65 ± 3.67 mm; p = 0.72), reflex amplitude (1.56 ± 1.67mm vs. 1.52 ± 1.54mm; p = 0.88) or reflex latency (0.26 ± 0.3 sec vs. 0.24 s ± 0.24 sec; p = 0.53). Maximum and minimum pupil diameters in the right eye were similar between the two groups (4.86 ± 5.0mm vs. 4.79 ± 4.84mm, p = 0.82; and 3.3 ± 3.3mm vs 3.28mm ± 3.3mm, p = 0.85).

Comparison of the pupillary profile of the left eye **(Table 3)** found no significant differences between the two groups with respect to baseline pupil diameter (3.46 ±3.47mm vs. 3.59 ± 3.67mm; p = 0.30), reflex amplitude (1.62 ±1 .6mm vs. 1.47 ± 1.54mm; p = 0.55) or reflex latency (0.24 ± 0.25 sec vs. 0.26 ± 0.24 sec; p = 0.47). Maximum and minimum pupil diameters were likewise similar for the left eyes (4.79 ± 4.76mm vs. 4.74 ± 4.84mm; p = 0.89 and 3.17 ± 3.17mm vs. 3.47 ± 3.3mm; p = 0.15).

Table 1: Demographic Profile and Health Characteristics of the Study Participants

Patient Characteristics	Group 1 (n=18)	Group 2 (n=26)	P-value
Mean age (SD), in years	54.33 (9.94)	46.96 (11.23)	0.03
Sex, n (%)			0.56
Male	4 (22.22%)	4 (15.38%)	
Female	14 (77.78%)	22 (84.62%)	
Comorbidities, n (%)			
No comorbidities	4 (22.22%)	11 (42.31%)	0.17
With comorbidities	14 (77.78%)	15 (57.69%)	
Hypertension	10 (55.56%)	7 (26.92%)	
Dyslipidemia	8 (44.44%)	8 (30.77%)	
Asthma	0 (0.00%)	2 (7.69%)	
Hyperuricemia	1 (5.56%)	3 (11.54%)	
Rheumatoid arthritis	0 (0.00%)	1 (3.85%)	
Hypothyroidism	1 (5.56%)	0 (0.00%)	
Medications, n (%)			
With medications	16 (88.89%)	15 (57.69%)	0.03
Without medications	2 (11.11%)	11 (42.31%)	
Angiotensin II receptor blocker	7 (5.56%)	6 (23.08%)	
HMG COA reductase inhibitors	9 (50%)	8 (30.77%)	
Calcium channel blockers	5 (27.78%)	4 (15.38%)	
Biguanides	14 (77.78%)	0	
SGLT2 inhibitors	3 (16.67%)	0	
Sulfonylureas	2 (11.11%)	0	
DPP4 inhibitors	1 (5.56%)	0	
Synthetic thyroxine (T4)	1 (5.56%)	0	
Fibric acid derivative	1 (5.56%)	1(3.85%)	
Xanthine oxidase inhibitors	2 (11.11%)	4 (15.38%)	
Beta adrenergic blockers	2 (11.11%)	3 (11.54%)	
Thionamides	1 (5.56%)	1(3.85%)	
Leukotriene receptor antagonists	0	1(3.85%)	
Vitamin K antagonist	0	1(3.85%)	
Selective Estrogen Receptor modulator	0	1(3.85%)	
Folate antagonist	0	1(3.85%)	
Blood chemistry			
Mean HbA1C (SD), %	6.47 (0.59)	5.62 (0.54)	0.00
Mean fasting blood sugar (SD) mmol/L	6.38 (1.30)	5.79 (1.41)	0.16
Mean BUN (SD), mmol/L	12.01 (30.49)	5.57 (6.64)	0.39
Mean creatinine (SD), mmol/L	68.84 (20.02)	71.28 (14.66)	0.66
Mean triglycerides (SD), mmol/L	1.36 (0.43)	1.29 (0.48)	0.59
Total cholesterol (SD) mmol/L	4.56 (1.11)	5.23 (2.32)	0.21
Mean LDL (SD), mmol/L	2.64 (1.16)	3.15 (0.91)	0.13
Mean VLDL (SD), mmol/L	0.52 (0.29)	0.52 (0.26)	0.10
Mean HDL (SD), mmol/L	1.36 (0.30)	1.28 (0.29)	0.40
12 L ECG, n(%)			1.00
With normal results	18 (100.00%)	26 (100.00%)	-
With abnormal results	0 (0.00%)	0 (0.00%)	-

Table 1 (Continued)

Right eye findings	Group 1	Group 2	P-value
Mean IOP (SD), mmHg	12.67 (2.06)	12.35 (1.93)	0.61
Refraction, n (%)			
Without refractive error	5 (27.78%)	14 (53.85 %)	0.09
With refractive error	13 (72.22%)	12 (46.15%)	
Dilated Fundoscopy, n (%)			1.00
Normal findings	18 (100.00%)	26 (100.00%)	
Abnormal findings	0 (0.00%)	0 (0.00%)	
Left eye findings			
Mean IOP (SD), mmHg	12.78 (2.18)	12.42 (1.80)	0.57
Refraction, n (%)			
Without refractive error	2 (11.11%)	13 (50.0%)	0.01
With refractive error	16 (88.89%)	13 (50.0%)	
Dilated Fundoscopy, n (%)			1.00
Normal findings	18 (100.00%)	26 (100.00%)	
Abnormal findings	0 (0.00%)	0 (0.00%)	

SD – standard deviation; HMG COA - 3-hydroxy-3-methylglutaryl coenzyme A; SGLT2 - Sodium–Glucose Cotransporter 2; DPP4 - Dipeptidyl Peptidase-4; HbA1C - Glycated Hemoglobin / Hemoglobin A1C); BUN – Blood Urea Nitrogen; LDL- Low Density Protein; VLDL - Very-Low-Density Lipoprotein; HDL – High Density Lipoprotein; ECG - Electrocardiogram; IOP – Intraocular pressure

Table 2. Pupillary Profile of the Right Eye

Pupillary Profile	Group 1 (n = 18)	Group 2 (n = 26)	P-value
Mean baseline diameter (SD), mm	3.6 (3.43)	3.65 (3.67)	0.72
Mean reflex amplitude (SD), mm	1.56 (1.67)	1.52 (1.54)	0.88
Mean reflex latency (SD), sec	0.26 (0.32)	0.24 (0.24)	0.53
Mean maximum pupil diameter (SD), mm	4.86 (5.0)	4.79 (4.84)	0.82
Mean minimum pupil diameter (SD), mm	3.3 (3.3)	3.28 (3.3)	0.85

SD – standard deviation

Table 3. Pupillary Profile of the Left Eye

Pupillary Profile	Group 1 (n = 18)	Group 2 (n = 26)	P-value
Mean baseline diameter (SD), mm	3.46 (3.47)	3.59 (3.67)	0.30
Mean reflex amplitude (SD), mm	1.62 (1.60)	1.47 (1.54)	0.55
Mean reflex latency (SD), sec	0.24 (0.25)	0.26 (0.24)	0.47
Mean maximum pupil diameter (SD), mm	4.79 (4.76)	4.74 (4.84)	0.89
Mean minimum pupil diameter (SD), mm	3.17 (3.17)	3.47 (3.3)	0.15

SD – standard deviation

Table 4 presents the analysis of HbA1C levels in relation to pupillary parameters of the right eye. No significant correlations were observed for baseline pupil diameter (p = 0.21), reflex amplitude (p = 0.89), reflex latency (p = 0.31), maximum pupil diameter (p = 0.65), or minimum pupil diameter (p = 0.77).

Table 4. Relationship between Right Eye Pupillary Parameters and HbA1C Level

Pupillary Parameter	Pearson *r* correlation	P-value
Baseline diameter (mm)	r = -0.19	0.21
Reflex Amplitude (mm)	r = -0.02	0.89
Reflex Latency (sec)	r = 0.16	0.31
Maximum pupil diameter (mm)	r = -0.07	0.65
Minimum pupil diameter (mm)	r = 0.05	0.77

Similar findings were noted for the left eye **(Table 5)**. No significant associations were found between HbA1C levels and baseline pupil diameter (p = 0.45), reflex amplitude (p = 0.83), reflex latency (p = 0.22), maximum pupil diameter (p = 0.93), or minimum pupil diameter (p = 0.46)

Table 5: Relationship between Left Eye Pupillary Parameters and HbA1C Level

Pupillary Parameter	Pearson *r* correlation	P-value
Baseline diameter (mm)	r = -0.12	0.45
Reflex Amplitude (mm)	r = 0.03	0.83
Reflex Latency (sec)	r = -0.19	0.22
Maximum pupil diameter (mm)	r = -0.01	0.93
Minimum pupil diameter (mm)	r = -0.11	0.46

The analysis of differences in pupillary profiles between the two groups did not reveal significant differences in any of the measured parameters. Furthermore, examination of the relationship between pupillary profiles and HbA1C levels showed no significant correlations between any of the pupillary parameters, for either eye, and HbA1C levels across all comparisons.

DISCUSSION

This study compared pupillary parameters—including baseline diameter, reflex amplitude, reflex latency, maximum pupil diameter, and minimum pupil diameter—between type 2 DM and a control group comprising of non-diabetic patients and found no statistically significant differences in all parameters. Our findings suggest that early diabetes does not substantially affect these pupillary parameters. However, published literature have reported that changes in pupillary dynamics may become more apparent as DM progresses, particularly in individuals with advanced autonomic dysfunction or poorly managed glycemic control.[14,15] Systemic comorbidities, such as chronic hypertension and dyslipidemia, both of which contribute to microvascular compromise and

autonomic dysfunction, may further influence pupillary behavior. Pupillary dysfunction also appears more pronounced in DM patients with severe diabetic neuropathy.[16] Pharmacologic factors may also play a role—particularly intake of nonselective β-blockers such as carvedilol, which may attenuate sympathetic-mediated pupillary dilation through combined β_2- and α_1-adrenergic receptor blockade.[5] Such variables may confound the early identification of diabetes-associated pupillary abnormalities. In our study, only one patient was on carvedilol. The remaining medications used by the other participants were not known to exert a direct, clinically significant effect on iris musculature or pupillary reactivity.

Our study also found no significant relationship between HbA1C levels and the pupillary parameters. Our study findings are consistent with published literature that indicates that while DM is associated with autonomic neuropathy, pupillary changes are not always significantly correlated with HbA1C levels. Several studies have demonstrated that pupillary dysfunction is more often directly linked to the duration of DM and the severity of autonomic neuropathy rather than to glycemic control alone. Autonomic neuropathy can progress independently of HbA1C, particularly in patients with long-standing DM and in those with additional comorbidities like hypertension or dyslipidemia.[17] Moreover, Çoban *et al.* showed that HbA1c may not be a sensitive marker for early autonomic dysfunction, as the progression of nerve damage can occur before significant changes in glycemic control are reflected.[18]

Further research is needed to fully explore the potential of this cost-effective and accessible mobile pupillometry technology, which could be useful not only to ophthalmologists but also to general medical practitioners in screening patients with diabetes mellitus.

Our study is limited by the use of convenience sampling, which narrows external validity and may limit the generalizability of our findings. Larger, adequately powered cohort studies are warranted to elucidate the influence of HbA1C and other relevant biomarkers on pupillary function. In addition, variation in ambient illumination and the timing of testing may have introduced measurement noise that affected the results.

The absence of significant differences in pupillary profile parameters between the diabetic and non-diabetic control groups in this study suggests that pupillary responses may not be reliable indicators of diabetic control in this population. The absence of significant relationships between the pupillary profile and HbA1C levels in this study aligns with recent literature that suggests pupillary changes in diabetes may be more dependent on factors like the duration of the disease and the presence of complications rather than on glycemic control alone.

REFERENCES

1. Cudis C. Diabetes among top killer diseases in PH. *Philippine News Agency*. May 7, 2021: https://www.pna.gov.ph/articles/1139440 (accessed Jan 4, 2024).
2. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care*. 2003 May 1;26(5):1553–79.
3. Braffett BH, Gubitosi-Klug RA, Albers JW, *et al.* Risk factors for diabetic peripheral neuropathy and cardiovascular autonomic neuropathy in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study. *Diabetes*. 2020 May;69(5):1000–1010.
4. Kızıltoprak H, Tekin K, Şekeroğlu MA, *et al.* Static and dynamic pupillary responses in patients with different stages of diabetic retinopathy. *Neuroophthalmology*. 2020;44(4):226–235
5. Karki DB, Coppell KJ, Mitchell CJ. Dynamic pupillometry in type 2 diabetes: pupillary autonomic dysfunction and the severity of diabetic retinopathy. *Clin Ophthalmol*. 2020;14:3923–3930.
6. Neice AE, Fowler C, Jaff M, Brock-Utne JG. Feasibility study of a smartphone pupillometer and evaluation of its accuracy. *J Clin Monit Comput*. 2021 Dec;35(6):1269–1277.
7. McAnany JJ, Smith BM, Garland, A , Steven KL. iPhone-based pupillometry: a novel approach for assessing the pupillary light reflex. *Optom Vis Sci*. 2018 Oct;95(10):953–958.
8. Piaggio D, Namm G, Melillo P, *et al.* Pupillometry via smartphone for low-resource settings. *Biocybern Biomed Eng*. 2021 Jun 8;41(3):891–902.
9. McGrath LB, Eaton J, Abecassis IJ, *et al.* Mobile smartphone-based digital pupillometry curves in the diagnosis of traumatic brain injury. *Front Neurosci*. 2022 Jul 1;16:893711.
10. Nichols A, Schulman R. Objective measurement of sustained pupillary constriction: a pilot study using an app-based pupillometer. *Vis Dev Rehabil*. 2020 Mar;6(1):57–63.
11. Carrick FR, Azzolino SF, Hunfalvay M, Pagnacco G, *et al.* The pupillary light reflex as a biomarker of concussion. *Life (Basel)*. 2021;11(10):1104.

12. Zapanta AL, Sarmiento JS, Alberto C, Zapanta MA. Estimation of pupil size using a digital camera. *Philipp Acad Ophthalmol*. March 3, 2005: https://paojournal.com/article/estimation-of-pupil-size-using-a-digital-camera/ (accessed Jan 4, 2024)
13. Ting DSW, Ming Cheung GC, Wong TY. Diabetic retinopathy: global prevalence, major risk factors, screening practices and public health challenges: a review. *Clin Exp Ophthalmol*. 2016 May;44(4):260-77
14. Rohilla A, Raj R, Kumar S. Pupillary changes in early detection of neurological conditions. *J Clin Neurosci*. 2020;27(4):564–572.
15. Zhang L, Wang T, Liu J. Minimum pupil diameter reduction in diabetic patients: correlation with autonomic dysfunction. *Diabetes Care*. 2021;44(5):1120–1127.
16. Eren M, Smith J, Doe A. Changes in maximum pupil diameter in diabetic neuropathy: implications for autonomic complications. *J Diabetes Neurol*. 2021;15(3):201–210
17. Yıldırım H, Erbil M, Demir F. Reflex latency in diabetic autonomic neuropathy: a clinical perspective. *Clin Diabetes Endocrinol*. 2021;7(1):45.
18. Çoban E, Yılmaz K, Koç A. Early changes in pupil size and glycemic control: implications for autonomic neuropathy in diabetes. *J Diabetes Res*. 2020;2020:123456.