Pupil Diameter Study: Factors Effecting Pupil Size In Diabetic Patients

Pupil Çapı Çalışması: Diyabetik Hastalarda Pupil Çapını Etkileyen Etmenler

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ABSTRACT

Purpose: This study was designed to assess the factors affecting the pupillary diameter in patients with diabetic retinopathy.

Materials and Methods: One hundred and eight eyes of fifty-four patients were evaluated cross-sectionally to study the factors affecting the pupillary diameter in diabetic patients. The pupillary diameter was measured using a Pentacam 30 min after the cyclopentolate administration. The severity and duration of diabetes, phakic or intraocular lens status, pan-retinal photocoagulation history, $\alpha 1_A$-blocker use, intravitreal injection, and vitrectomy history were the items included in this study that could affect the pupillary diameter. The visual acuity and intraocular pressure were also assessed.

Results: The outcomes of the present study revealed that the pupillary diameter was smaller in those patients with proliferative retinopathy and long-term diabetes, and that the mean pupillary diameter was also smaller in the intraocular lens implanted patients. In addition, $\alpha 1_A$-blocker use and a vitrectomy surgery history were related to the pupil size. Moreover, pan-retinal photocoagulation and the number of intravitreal injections were insignificantly related to the pupillary diameter.

Conclusion: Among the factors studied, the severity and duration of diabetes were the prominent factors that played important roles in affecting the pupillary diameter in the diabetic patients.

Keywords: Pupillary diameter, diabetes mellitus, retinopathy.

ÖZ

Amaç: Bu çalışma diyabetik retinopatili hastalarda pupil çapına etki eden faktörleri değerlendirmek amacıyla dizayn edildi.

Gereç ve Yöntem: Diyabetik hastalarda pupil çapını etkileyen faktörleri incelemek amacı ile elli dört hastanın 108 gözü kesitsel olarak değerlendirildi. Pupil çapı, siklopentonat uygulamasından 30 dakika sonra Pentacam ile ölçüldü. Diyabetin şiddeti ve süresi, fakik veya göz içi lens olma durumu, panretinal fotokoagülasyon, $\alpha 1_A$-bloker kullanımı, intravitreal enjeksiyon ve vitrektomi pupil çapını etkileyebilecek etmenler olarak çalışmaya dahil edildi. Görme keskinliği ve göz içi basıncı da değerlendirildi.

Bulgular: Çalışmamızın sonuçları, proliferatif retinopati ve uzun dönem diyabetli hastalarda pupil çapının daha küçük olduğunu ve intraoküler lens yerleştirilen hastalarda da pupil çapının ortalamasının daha küçük olduğunu ortaya koymuştur. α1A-bloker kullanımı ve vitrektomi cerrahisi de pupil çapında kayda değer öneme sahipti. Pan-retinal fotokoagülasyon ve intravitreal enjeksiyon sayısı pupil çapında önemsizdi.

Sonuç: Çalışılan faktörler arasında, diyabetin şiddeti ve süresi diyabetik hastalarda pupil çapında önemli rol oynayan faktörlerden belirgin olanlarıydı.

Anahtar Sözcükler: Pupil çapı, diyabetes mellitus, retinopati.

INTRODUCTION

Diabetes mellitus (DM) is a common health problem among the worldwide systemic diseases.[1] DM has nephropathic, neuropathic, diabetic foot, and retinopathic effects due to the impairment of the micro and/or macrovascular circulation.[2] In addition, DM is a leading cause of visual disability, which is commonly caused by diabetic macular edema (DME).[3] Other than retinopathy, DM may affect the other

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ocular structures, such as the pupillary diameter. Its pupillary manifestations include a small pupil size, the pupillary response to light, and the pupillary response to pharmacological tests.[4] The most common pupillary sign is miosis, which is believed to be the consequence of diabetic neuropathy.[5] Additionally, pharmacological mydriasis is poor in diabetic patients.[6]

The pupillary diameter (PD) is controlled by the autonomic nervous system; the parasympathetic innervation of the sphincter pupillae muscle and sympathetic innervation of the dilator pupillae muscle regulate the pupillary reaction.[2,7] Several studies have indicated that sympathetic autonomic impairment develops earlier than parasympathetic impairment in diabetic patients.[8-10] Although the reason for this is not clear, it is believed to be due to the greater lengths in the sympathetic nerve pathways.[11] Thus, it has been postulated that the main mechanism of miosis in diabetic patients is a failure in the sympathetically-mediated pupillary dilation.[12] It is important to obtain adequate pupillary dilatation in fundus examinations, retinal laser photocoagulation, and cataract extractions in diabetic patients, because there may be a poor pupillary reaction to mydriatic drugs in DM.

The aim of the present study was to investigate the factors affecting the pupil size in diabetic patients, with regard to the small pupillary diameter in these patients.

MATERIALS AND METHODS

A total of 54 patients were recruited for this cross-sectional study. The study adhered to the tenets of the Declaration of Helsinki, and the Institutional Review Board approved the study protocol. All of the patients provided informed consent prior to enrollment.

Medical history was obtained by historical questioning, which included the patient's age, gender, ocular history, DM duration, and any other significant medical history, such as hypertension, cardiovascular disease, renal insufficiency, dyslipidemia, and smoking. The study included 108 eyes of 54 adult patients with diabetic retinopathy who were being followed regularly in the Division of Retina, Department of Ophthalmology. The exclusion criteria were the presence of any other ocular disorders that could affect the irises or pupils, such as ocular trauma, rubeosis iridis, pupillary synechiae, glaucoma, pseudoexfoliation syndrome, uveitis, topical pilocarpine use, and any conditions that preclude the precise measurement of the pupil size, such as significant corneal opacity, hyphema, or poor patient cooperation. The DM severity and duration, phakic or posterior chamber intraocular lens (PCIOL) status, exfoliation syndrome (XFS), $\alpha 1_A$-blocker use, vitrectomy, panretinal photocoagulation (PRP), and number of intravitreal injections [1.25 mg of bevacizumab (BEV) and/or 1 ml of 40 mg/ml triamcinolone acetonide; we did not include the cases that were administered ranibizumab because the ranibizumab was not available during the study period] were the main factors affecting the pupil size that were evaluated in this study. The severity of diabetic retinopathy was scaled according to the International Clinical Diabetic Retinopathy Disease Severity Scale, and the cataract status was determined by the Lens Opacities Classification System III.

All of the patients underwent detailed ophthalmic examinations prior to taking the pupil size measurements. The following examinations were conducted: the best-corrected visual acuity (BCVA) in logarithm of the minimum angle of resolution (logMAR) units, the intraocular pressure (IOP) measured via Goldmann applanation tonometry, the anterior segment evaluation via slit lamp examination, and fundus assessment via +90D lens. Atropine requires a long period of time to obtain maximal cycloplegia, and the recovery also takes a long time. Cyclopentolate can achieve a more cycloplegic effect than tropicamide. Therefore, standard topical 1% cyclopentolate was administered to the patients 3 times with 10-minute intervals in order to achieve pupillary dilatation. The measurements were performed 30 minutes later, following the last eye drop instillation. A single experienced and masked technician measured the PD with Pentacam's (Oculus Optikgeräte GmbH, Wetzlar, Germany) automatic release mode in diminished room light. Briefly, the subject was asked to place his/her chin on the chin rest and their forehead against the head rest. The subject was then asked to open both eyes and look at the fixation target. The examiner aligned the joystick so that the rotating Scheimpflug camera automatically captured the pupil size of each eye. The measurements were checked under the quality specification window, and only the correct measurements were accepted (comment box reading "OK"). If the comment box was marked in yellow or red, the examination was repeated. The pupillary diameters were determined by the mean of the maximum and minimum diameters in 2 right-angled meridians in oval-shaped pupils.

Statistical Package for the Social Sciences (SPSS) version 23.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis. The distributions of the data were analyzed with the Kolmogorov-Smirnov test. A bivariate analysis was done to identify those factors associated with the PD. Those variables in the bivariate analysis with *P* values of less than 0.05 were considered as candidates for inclusion in the multivariable linear regression model. The relationships between the pupil size and the other variables were assessed using Pearson's and Spearman's rank correlation coefficients. A 2-tailed P value of < 0.05 was considered to be statistically significant.

RESULTS

All data had normal distribution according to Kolmogo- rov-Smirnov analysis. The mean age of the patients was

58.13±7.29 (44-78) years old, and the average DM duration was 13.68±6.65 (2-25) years. Most of the patients were females. The intraocular pressure (IOP) of the patient's eyes ranged between 11 and 26 mmHg, with a mean of 16.56±2.82 mmHg. The descriptive and variable data of the patients are shown in Table 1.

Table 1. *The descriptive and variable data of the patients with diabetes mellitus*

	N (54)	Percent (%)
Gender		
Male	19	35.2
Female	35	64.8
DM Severity		
Mild NDR	12	22.2
Moderate NDR	14	25.9
Severe NDR	11	20.3
PDR	17	31.6
$\alpha 1_A$-blocker usage		
Use	12	22.2
Non-use	42	77.7

Table 2. *The descriptive data of diabetic eyes*

	N (108)	Percentage (%)
Lens		
Phakic	77	71.3
PCIOL	31	28.7
XFS		
Presence	19	17.6
Nil	89	82.4
PRP		
Presence	82	75.9
Nil	26	24.1
VRS		
Presence	15	86.1
Nil	93	13.9

The visual acuity of the patients was measured using the Snellen chart, and then it was converted to the logMAR and defined as the BCVA. The mean BCVA of the patients was 0.47±0.01 logMAR. The PD was measured between 2.81 mm and 7.24 mm, and the PD mean was 5.09±0.91 mm.

Eighty-five (78.7%) eyes had no intravitreal BEV injections, 9 (8.3%), 9 (8.3%), and 5 (4.6%) eyes had 1, 2, and 3 injections of intravitreal BEV, respectively. Eighty-six (79.6%) eyes had no intravitreal triamcinolone acetonide (IVTA) injections, 14 (13%), 3 (2.8%), and 5 (4.6%) eyes had 1, 2, and 3 IVTA injections, respectively. Fifteen eyes had both injections.

We found a significant negative correlation between the PD and the BCVA, DM duration, and number of intravitreal BEV and IVTA injections (Pearson correlations: r=0.404, r=0.192, r=0.244, and r=0.398, respectively; $P<0.05$ for all). Statistically significant negative Spearman's correlations were noted between the PD and the gender, DM severity, lens, XFS, $\alpha 1_A$-blocker, PRP, and vitrectomy (p=0.464, p=0.372, p=0.600, p=0.342, p=0.261, p=0.319, and p=0.283, respectively; $P<0.05$ for all). There were no significant positive correlations between the PD and any of the variables.

The results of the multivariable linear regression analysis showed that patient gender ($P<0.05$), phakic or PCIOL status ($P<0.05$), XFS ($P<0.05$), $\alpha 1_A$-blocker use ($P<0.05$), and vitrectomy ($P<0.05$) were the factors that were independently associated with the pupil size of the patients. Overall, the female patients, PCIOL patients, patients using $\alpha 1_A$-blockers, phakic eyes with XFS, and eyes that underwent vitrectomies tended to have smaller pupils.

DISCUSSION

The iris has the autofocusing ability to regulate the PD. Pupil size variability is defined as the mobility of the pupil over time, both spontaneous and when forced by external stimuli.[13] The methods for measuring the pupil size have improved over the years.[14] Currently, the Pentacam and Orbscan are in clinical use today to evaluate the anterior segment parameters, including the PD.[15] The Pentacam is based on the Scheimpflug principle, and it scans the anterior and posterior cornea with a rotating Scheimpflug camera.[16]

There are many factors that can affect the pupil size. Some examples include drugs, systemic diseases (DM, hypertension), psychological conditions, ocular pathologies, ocular injuries, refractive error, suppression amblyopia, functional anisocoria, Horner's syndrome, Adie's tonic pupil, tumors in the midbrain, internal ophthalmoplegia, luminance, and age.[17-19] In the current study, we investigated the factors affecting the PD in patients with DM. To the best of our knowledge, there are no other articles on this subject in the literature, so the present paper might be the first study with regard to this topic.

It has been shown that long-term diabetic patients are more likely to develop diabetic neuropathy.[20] Several studies have revealed that patients with a longer duration of diabetes have smaller pupils.[21-23] Moreover, a significant association between small pupils and the severity of retinopathy has also been reported.[24] Supporting the literature, in the current study, we documented a significant association between the PD and the DM severity or duration.

Guillon et al.[19] found that age was a factor affecting the pupillary diameter, with a smaller diameter in older groups, but the overall difference was only significant between the

pre-presbyopes and the established presbyopes. However, we did not find a significant correlation between the PD and age.

Koh et al.[25] reported that female patients had significantly greater anisocoria and a higher constriction ratio when compared to male patients, which supports our results indicating that females have smaller pupils.

The present paper showed that patients with PCIOL have more constricted pupils, as in the study by Li et al.[26] They found that the PD might decrease after IOL implantation under both photopic and scotopic conditions, which may be caused by mechanical contact between the intraocular lens and the posterior iris surface.

In patients using $\alpha 1_A$-blockers (tamsulosin), decreased dilated pupillary diameters have been observed when compared to the control groups.[27] Additionally, Al-Kharashi et al.[28] suggested that pupillary diameter changes are reversible. We also found a significant constrictor effect of $\alpha 1_A$-blockers on the PD in diabetic patients.

Unlike Yilmaz et al.,[29] who demonstrated via automated infrared pupillary measurements that PRP may significantly increase the pupil size, whether it is performed with a conventional laser or patterned scanning laser (PASCAL), we observed a negatively significant Spearman's correlation between the PD and PRP. However, this was not supported by the regression analysis, which means that the PD may be randomly associated with PRP.

When combined with an older age, the presence of XFS increases the probability of observing miotic pupils during the clinical evaluation.[30] We also found significant pupillary constriction in the eyes with XFS.

We did not find any papers describing the relationship between the PD and the BCVA, number of intravitreal injections (with the exception of BEV), and vitrectomy. Among these variables, only vitrectomy had a significant miotic effect on the pupil size in the diabetic patients.

In conclusion, there are many factors affecting the pupil size in diabetic patients, and the present study might be a unique paper in this field. Of these factors, the DM severity and duration were the leading reasons for pupillary constriction. Additionally, the female gender, PCIOL, vitrectomy, and $\alpha 1_A$-blocker use were the subsequent factors associated with a small pupil size. Its cross-sectional nature and small sample size were the limitations of this study. Therefore, new studies should be conducted while considering these limitations.

REFERENCES / KAYNAKLAR

1. Habib SL, Rojna M. Diabetes and risk of cancer. ISRN Oncol. 2013;2013:583786.
2. Kwon HJ, Kim HY. A pharmacologic pupillary test in the diagnosis of diabetic autonomic neuropathy. Korean J Ophthalmol. 2009;23(4):291-5.
3. Ding J, Wong TY. Current epidemiology of diabetic retinopathy and diabetic m acular edema. Curr Diab Rep. 2012;12:346-54.
4. Yang Y., Yu Y., Yao K., "Pupillary dysfunction in Type 2 diabetes mellitus to refine the early diagnosis of diabetic autonomic neuropathy," Neuro-Ophthalmology. 2006;30(1):17-21.
5. Bremner FD, Smith SE. Pupil abnormalities in selected autonomic neuropathies. J Neuroophthalmol. 2006;26:209-19.
6. Lei HL, Yang KJ, Sun CC, Chen CH, Huang BY, Ng SC, Yeung L. Obtained mydriasis in long-term type 2 diabetic patients. J Ocul Pharmacol Ther. 2011;27(6):599-602.
7. Cahill, M., Eustace, P., and de Jesus, V. Pupillary autonomic denervation with increasing duration of diabetes mellitus. Br. J. Ophthalmol. 2001;85:1225-30.
8. Pittasch D., Lobmann R., Behrens-Baumann W., Lehnert H., "Pupil signs of sympathetic autonomic neuropathy in patients with Type 1 diabetes," Diabetes Care. 2002;25(9):1545-50.
9. Adnan X, Suheimat M, Efron N, Edwards K, Pritchard N, Mathur A, Mallen EA, Atchison DA. Biometry of eyes in type 1 diabetes. Biomed Opt Express. 2015;6(3):702-15.
10. Yuan D, Spaeth EB, Vernino S, Muppidi S. Disproportionate pupillary involvement in diabetic autonomic neuropathy. Clin Auton Res. 2014;24(6):305-9.
11. Smith SA, Smith SE. Reduced pupillary light reflex in diabetic autonomic neuropathy. Diabetologia. 1983;24:330-2.
12. Straub RH, Thies U, Jeron A, et al. Valid parameters for investigation of the pupillary light reflex in normal and diabetic subjects shown by factor analysis and partial correlation. Diabetologia. 1994;37:414-9.
13. Zeng H, Wani OM, Wasylczyk P, Kaczmarek R, Priimagi A. Self-Regulating Iris Based on Light-Actuated Liquid Crystal Elastomer. Adv Mater. 2017 Jun 7. doi:10.1002/adma.201701814. [Epub ahead of print] PubMed PMID: 28589679.
14. Bootsma S, Tahzib N, Eggink F, de Brabander J, Nuijts R. Comparison of two pupillometers in determining pupil size for refractive surgery. Acta Ophthalmol Scand. 2007;85(3):324-8.
15. Quisling S, Sjoberg S, Zimmerman B, Goins K, Sutphin J. Comparison of Pentacam and Orbscan IIz on posterior curvature topography measurement in keratoconus eyes. Ophthalmology. 2006;113:1629-32
16. Serdarogullari H, Tetikoglu M, Karahan H, Altin F, Elcioglu M. Prevalence of keratoconus and subclinical keratoconus in subjects with astigmatism using pentacam derived parameters. J Ophthalmic Vis Res. 2013;8(3):213-9.
17. Spector RH. The Pupils. In: Walker HK, Hall WD, Hurst JW, editors. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition. Boston: Butterworths; 1990. Chapter 58.
18. Burley DT, Gray NS, Snowden RJ. As Far as the Eye Can See: Relationship between Psychopathic Traits and Pupil Response to Affective Stimuli. PLoS One. 2017;24:12(1).

19. Guillon M, Dumbleton K, Theodoratos P, Gobbe M, Wooley CB, Moody K. The Effects of Age, Refractive Status, and Luminance on Pupil Size. Optom Vis Sci. 2016;93(9):1093-100.

20. Tracy JA, Dyck PJ. The spectrum of diabetic neuropathies. Phys Med Rehabil Clin N Am. 2008;19(1):1-26.

21. Smith SE, Smith SA, Brown PM, et al. Pupillary signs in diabetic autonomic neuropathy. Br Med J. 1978;2:924-7.

22. Hreidarsson AB. Pupil size in insulin-dependent diabetes: relationship to duration, metabolic control and long-term manifestations. Diabetes. 1982;31:442-8.

23. Straub RH, Thies U, Jeron A, et al. Valid parameters for investigation of the pupillary light reflex in normal and diabetic subjects shown by factor analysis and partial correlation. Diabetologia. 1994;37:414-9.

24. Hayashi M, Ishikawa S. Pharmacology of pupillary responses in diabetics - correlative study of the responses and grade of retinopathy. Jpn J Ophthalmol. 1979;23:65-72.

25. Koh KM, Kim US. Characteristics of pupillo-accommodative functions according to time of onset, gender and age in tonic pupil. Int J Ophthalmol. 2013;6(5):659-61.

26. Li D, Yang Y, Su C, Yin H, Liu X. Pupil Diameter Changes in High Myopes after Collamer Lens Implantation. Optom Vis Sci. 2015;92(12):1161-9.

27. Theodossiadis P.G., Achtsidis V., Theodoropoulou S., Tentolouris N., Komninos C., Fountas K.N. The effect of alpha antagonists on pupil dynamics: implications for the diagnosis of intraoperative floppy iris syndrome. Am J Ophthalmol. 2012;153:620-6.

28. Al-Kharashi A, Azimzadeh AA, Leung J, Radomski S, Radomski L, Lam WC. Anterior segment optical coherence tomography changes with introduction and discontinuation of tamsulosin. Saudi J Ophthalmol. 2016;30(3):150-6.

29. Yılmaz İ, Perente I, Saraçoğlu B, Yazıcı AT, Taşkapılı M. Changes in pupil size following panretinal retinal photocoagulation: conventional laser vs pattern scan laser (PASCAL). Eye (Lond). 2016;30(10):1359-64.

30. Mocan MC, Üstünel S, Dikmetaş O, Bozkurt B, Irkec M. The effect of pharmacologic pupillary dilatation on anterior segment parameters in patients with exfoliation syndrome. J Optom. 2014;7(1):51-6.