Pharmacological mydriasis in patients with type 2 diabetes. A comparative study among different levels of diabetic retinopathy

Midríase farmacológica em pacientes diabéticos do tipo 2. estudo comparativo entre diferentes níveis de retinopatia diabética

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ABSTRACT

Objective: To analyze the diabetic autonomic neuropathy through the comparison between the pharmacological mydriasis in patients without diabetes and with type 2 diabetes.

Methods: This is an observational, cross-sectional, case-control study. The patients were dilated with phenylephrine 10% and tropicamide 1% eye drops. They were divided into patients without diabetes mellitus (Control or Group Zero) and patients with type 2 diabetes mellitus (Case Group). These patients with diabetes were divided into six groups according to the international classification of diabetic retinopathy study (no diabetic retinopathy or Group 1; mild non- proliferative diabetic retinopathy or Group 2; moderate non-proliferative diabetic retinopathy or Group 3; severe non-proliferative diabetic retinopathy or Group 4; proliferative diabetic retinopathy without retinal laser photocoagulation or Group 5; and proliferative diabetic retinopathy with panretinal laser photocoagulation or Group 6). Each group included 20 patients. The main variable was the pupillary diameter after pharmacological dilation, and the secondary variables were gender, and age, and diabetic retinopathy stages. Vertical and horizontal pupillary diameter were measured. Analysis of variance test F, Student's t-test and Chi-squared were used for the statistical analysis. The statistical significance was defined as 0.05.

Results: This study included 140 patients (280 eyes). The majority of the eyes had rounded pupil (240 of 280). The statistical analysis identified the smallest mean and standard deviation pupillary diameter in eyes with severe non-proliferative diabetic retinopathy (6.4 ± 0.53 mm, vertical, and 6.0 ± 0.84 mm, horizontal. Eyes with severe non-proliferative diabetic retinopathy (p = 0.00) and proliferative diabetic retinopathy treated with pan retinal photocoagulation (p=0.02) demonstrated statistical significance. When the group with no diabetes was compared with the group with diabetes, patients with no diabetes had a larger pupillary diameter (mean and standard deviation of 1.0 ± 0.2 mm) after pharmacologic mydriasis, mainly in patients with severe non-proliferative diabetic retinopathy.

Conclusion: The diabetic autonomic neuropathy may influence pupillary pharmacological dilation in late stages of diabetic retinopathy, mainly in eyes with severe non-proliferative diabetic retinopathy.

RESUMO

Objetivo: Analisar a neuropatia autonômica diabética por meio da comparação entre a midríase farmacológica em pacientes não diabéticos e em pacientes diabéticos do tipo 2.

Métodos: Este é um estudo observacional, transversal, caso-controle. Os pacientes foram dilatados com colírios de fenilefrina a 10% e tropicamida a 1%. Eles foram divididos em pacientes sem *diabetes mellitus* (Controle ou Grupo Zero) e pacientes com *diabetes mellitus* tipo 2 (grupo caso). Esses pacientes diabéticos foram alocados em seis grupos de acordo com a classificação internacional do estudo de retinopatia diabética (sem retinopatia diabética ou Grupo 1; retinopatia diabética não proliferativa leve ou Grupo 2; retinopatia diabética não proliferativa moderada ou Grupo 3; retinopatia diabética não proliferativa grave ou Grupo 4; retinopatia diabética proliferativa sem fotocoagulação a *laser* retiniano ou Grupo 5; e retinopatia diabética proliferativa com fotocoagulação a *laser* panretiniana ou Grupo 6). Cada grupo incluiu 20 pacientes. A variável principal foi o diâmetro pupilar após dilatação farmacológica, e as variáveis secundárias foram sexo, idade e estágios de retinopatia diabética. O diâmetro pupilar vertical e horizontal foram medidos. O teste de análise de variância F, o teste t de *Student* e o teste do qui-quadrado foram utilizados para a análise estatística. A significância estatística foi definida como 0,05.

Resultados: Este estudo incluiu 140 pacientes (280 olhos). A maioria dos olhos tinha pupila arredondada (240 de 280). A análise estatística identificou o menor diâmetro médio e desvio-padrão pupilar em

olhos com RDNP (Retinopatia Diabética Proliferativa) grave (6,4 ± 0,53 mm, vertical, e 6,0 ± 0,84 mm, horizontal). Os olhos com RDNP grave (p=0,00) e RDP (Retinopatia Diabética Proliferativa) tratada com PFC (Pan Fotocoagulação a Laser) (p=0,02) demonstraram significância estatística. Quando o grupo não diabético foi comparado com o diabético, os pacientes não diabéticos apresentaram diâmetro pupilar maior (média e desvio-padrão de 1,0 ± 0,2 mm) após midríase farmacológica, principalmente em pacientes com RNPG grave.

Conclusão: A neuropatia autonômica diabética pode influenciar a dilatação farmacológica pupilar em estágios avançados de retinopatia diabética, principalmente em olhos com retinopatia diabética não proliferativa grave.

INTRODUCTION

Mydriasis (pupil dilatation) is essential for ophthalmic examinations and various eye procedures.[1-3]

In common practice, pharmacological mydriasis is achieved instilling anticholinergic and sympathomimetic eye drops. Nevertheless, systemic, and neurological disorders, such as uveitis, angle-closure glaucoma, inflammatory conditions, optic neuritis, ischemic optic disease or ischemic retinal disease, very severe macular degeneration, retinal infection, retinal detachment, use of antidepressant and opioid drugs may interfere with this process, and diabetes mellitus (DM) is one of the most common diseases.[4]

Diabetes mellitus is a complex and chronic illness and can lead to microvascular complications that include neuropathy, nephropathy, and diabetic retinopathy (DR).[5-8]

Diabetic retinopathy is characterized by a wide spectrum of microvascular changes and retina lesions.[9,10] Although microvascular occlusion, leakage, and macular edema are recognized as the main pathological processes, neuroretinal alterations can be present without clinically detectable retinal vasculopathy.[11-16] Then, pupillary abnormalities may precede clinical sign of DR, which may be detectable by examining pupillomotor function through pupillary dilation.[14,17,18] Nevertheless, the majority of studies that employed pharmacological mydriasis has not been done since the last three decades, before the intravitreal antiangiogenic agents' era.

The aim of the current study is to analyze the diabetic autonomic neuropathy (DAN) through the comparison between the pharmacological mydriasis in non-diabetic patients and in type 2 diabetic patients.

METHODS

This is an observational, cross-sectional, and case-control study with the participation of patients with no diabetes and with type 2 patients, followed at the Department of Ophthalmology of the *Hospital Universitário Antônio Pedro, Universidade Federal Fluminense* (UFF), between February and December 2020. The study was conducted in accordance with the ethical principles established in the Declaration of Helsinki, after approval by the Research and Ethics Committee of UFF through the document CAAE 23635019.4.0000.5243. An Informed consent was obtained from all participants.

The inclusion criteria were patients aged over 18 years old, diagnosed with type 2 diabetes. The control group included participants aged over 18 years old, without having diabetes mellitus. A standard ophthalmological examination (visual acuity, intraocular pressure measurement, biomicroscopy and fundus examination) was performed.

The exclusion criteria included diagnosis of glaucoma, previous intraocular surgery, use of topical pilocarpine, use of antidepressant and opioids drugs, uveitis, presence of pupillary synechiae, ocular trauma, rubeosis iridis, previous laser iridotomy, demyelinating neurological diseases, and proliferative DR (PDR) with tractional retinal detachment and vitreous hemorrhage.

All patients were submitted to fundus examination, after being dilated with phenylephrine 10% and tropicamide 1%. Proxymetacaine 0.5% eyedrop was instilled five minutes prior to these drugs. Then, 40 minutes after dilation, the horizontal and vertical pupillary diameters were measured using a scale of the ZEISS SL 220 slit lamp (Carl Zeiss Meditec- Jena, Germa) (Figures 1A and 1B). The basal pupillary diameter was measured (mean and SD of 4.9 +-1.56 mm).

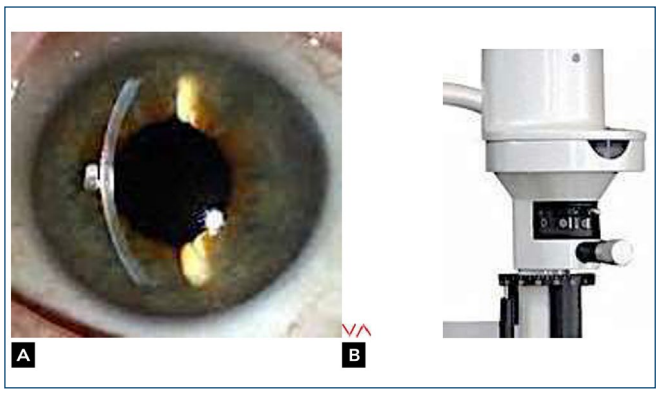


Figure 1. Detail of measuring pupillary diameter with slit lamp.

Table 1. Groups and demographic data

Groups	n (Patients) [eyes]*	%	Gender Male/Female	p- value*	Age (years old) (mean ± SD)	p-value†
1- Control (Patients with no diabetes)	(20) [40] *	14.28	08/12	0.93	52.1 ± 8.41	0.19
2- Patients with diabetes without DR	(20) [40]	14.28	10/10		63.4 ± 6.84	
3- Mild NPDR	(20) [40]	14.28	11/09		60.1 ± 14.09	
4- Moderate NPDR	(20) [40]	14.28	10/10		60.1 ± 7.24	
5- Severe NPDR	(20) [40]	14.28	10/10		61.4 ± 7.19	
6- PDR post Laser PRP	(20) [40]	14.28	09/11		59.7 ± 6.12	
7- PDR previous Laser	(20) [40]	14.28	09/11		57.9 ± 8.51	

* Chi-squared statistical test; † analysis of variance; F test statistical analysis. SD: standard deviation; NPDR: non-proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy.

Table 2. Pupillary characteristics

Groups	Eyes (n)	VPD, mm (mean ± SD)	HPD, mm (mean ± SD)	p-value*	Pupillary format
1- Control (Nondiabetics patients)	40	7.5 ± 0.53	7.3 ± 0.48	0.38	Rounded
2- Patients with Diabetes without DR	40	7.4 ± 0.38	7.3 ± 0.38	0.20	Rounded
3- Mild NPDR	40	7.4 ± 0.52	7.2 ± 0.56	0.43	Rounded
4- Moderate NPDR	40	7.1 ± 0.55	7.0 ± 0.54	0.09	Rounded
5- Severe NPDR	40	6.4 ± 0.53	6.0 ± 0.84	0.02†	Irregular
6- PDR after laser PRP	40	7.3 ± 1.15	7.0 ± 0.66	0.21	Rounded
7- PDR previous Laser	40	6.5 ± 0.72	6.3 ± 0.48	0.42	Rounded

* Student's – t-test statistical analysis; † statistical significative data. VPD: vertical pupillary diameter; SD: standard deviation; HPD: horizontal pupillary diameter; NPDR: no proliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy.

The entire examination was accomplished by the same ophthalmologist. The fundus exam was performed with the 78 Diopter Volk lens and the slit lamp (Volk Optical; Mentor; Ohio, United States).

For greater accuracy of pupillary measurements, they were measured in vertical diameter (pupillary vertical diameter; PVD) and horizontal diameter (pupillary horizontal diameter; PHD).

The diabetic patients were grouped into six groups according to the International Clinical Diabetic Retinopathy Severity Scales. [8] No DR (Group 1), mild non-PDR (Group 2), moderate non-PDR (Group 3) and severe non-PDR (Group 4). Patients with PDR were divided into two groups: PDR without retinal laser photocoagulation (Group 5) and PDR with pan retinal laser photocoagulation (Group 6). The patients with no diabetes (Group Zero) were defined as the control group. [8,9] Each grouped comprised 20 patients.

INVESTIGATED VARIABLES

The demographic data as gender and age were considered as secondary variables.

The pupil was classified into round or irregular according to the vertical and horizontal pupillary diameters.

Intragroup research was defined as statistical test performed between vertical and horizontal pupillary diameter in the same stage of DR classification.

Intergroup research was defined as statistical test performed between vertical and horizontal pupillary diameter among the several different stages of DR classification.

STATISTICAL ANALYSIS

The IBM Statistical Package for the Social Sciences, 2015, Chicago, United States, version 23.0 was used for statistical analysis. Mean and standard deviation (SD) were employed for continuous variables such as age and pupillary diameter. Student's t-test was used to compare the vertical and horizontal pupillary diameter, defining the pupil as round, circle, and irregular. The analysis of variance (ANOVA) F test was applied to compare the pupillary diameters between the seven groups (intergroups). The Chi-squared test was used to evaluate categorical nominal data as gender. The investigated data was displayed through tables and box plot chart. The statistical significance level was defined as 5 % ($p < 0.05$).

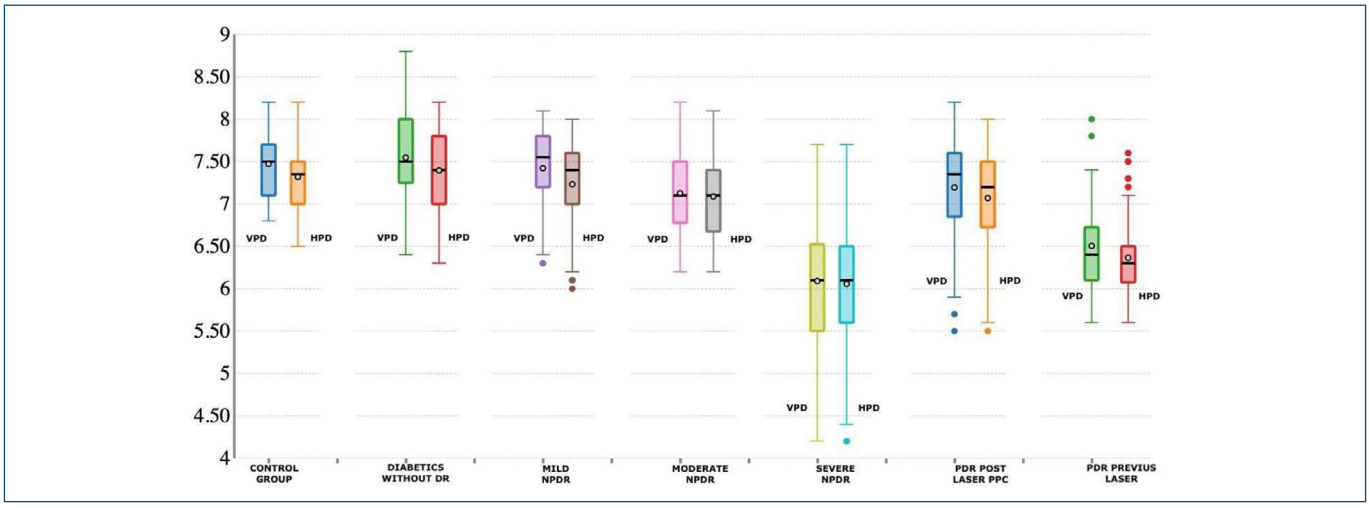
RESULTS

A total of 140 patients participated in this study. The demographic characteristics and each group are displayed in table 1.

Regarding the demographic characteristics, of 140 patients, 73 (52.1%) were female, and the mean age ranged from 52.1 ± 8.41 to 63.4 ± 6.84 years. With respect to gender and age, there were no statistical significance between the seven groups.

The pupillary shape and diameters are displayed in table 2.

The intragroup consistency was considered satisfactory, except for the eyes with severe non-proliferative diabetic retinopathy (NPDR) that demonstrated an irregular pupillary shape and great



VPD: vertical pupillary diameter; HPD: horizontal pupillary diameter; DR: diabetic retinopathy; NPDR: non- proliferative diabetic retinopathy; PRP: Pan Retinal Photocoagulation

Figure 2. Box-plot chart. Distribution and comparison between the groups: control group, diabetics patients without diabetic retinopathy, no proliferative diabetic retinopathy group, and proliferative diabetic retinopathy group.

variability. Moreover, Group 5 showed the smallest pupillary diameters.

Figure 2 revealed a good intragroup homogeneity between VPD and HPD. Table 3 displayed the intergroup detailed results. The severe NPDR group exhibited the greatest intragroup homogeneity between VPD and HPD among all groups, whereas the moderate NPDR had the lowest one. When comparing the intragroup homogeneity between VPD and HPD, eyes with PDR plus PRP (Pan Retinal Photocoagulation) had significant similarity with eyes with severe NPDR, while eyes with PDR without PRP demonstrated significant homogeneity with early stages of NPDR.

The pupillary diameter differences among the intergroups researched are displayed at the table 3.

When intergroups were compared, the pupillary diameter changes after pharmacological dilation that reached statistical significance was the comparison between Group Zero versus Group 4 (VPD/HPD) and Group

Table 3. Analysis of variance, and F test pairwise intergroup comparison values with the Tukey statistical test, and significant pupillary diameters differences.

Groups	Pupil Size	1 Control values)		2 Diabetes without DR (p values)		3 Mild NPDR (p values)		4 Moderate NPDR (p values)		5 Severe NPDR (p values)		6 PDR Post Laser PRP (p values)	
		VPD	HPD	VPD	HPD	VPD	HPD	VPD	HPD	VPD	HPD	VPD	HPD
1 - Control	VPD												
	HPD												
2 - Diabetes without DR	VPD	0.24											
	HPD		0.23										
3 - Mild NPDR	VPD	0.93		0.70									
	HPD		0.97		0.81								
4 - Moderate NPDR	VPD	0.34		0.14		0.66							
	HPD		0.38		0.17		0.71						
5 - Severe NPDR	VPD	0.00* 1.0± 0.00		0.00* 1.0± 0.14		0.02* 0.9± 0.00		0.09					
	HPD		0.00* 1.2± 0.36		0.00* 1.2± 0.45		0.02* 1.1± 0.27		0.09				
6 - PDR post PRP	VPD	0.44		0.25		0.65		0.82		0.02* 1.1± 0.13			
	HPD		0.37		0.21		0.55		0.78		0.02* 1.0±0. 17		
7 - PDR previous PRP	VPD	0.02* 1.0± 0.01		0.01* 0.9± 0.13		0.03* 0.9± 0.00		0.38		0,59		0.13	
	HPD		0.02* 1.0± 0.00		0.01* 1.0± 0.09		0.03* 0.9± 0.08		0.34		0.61		0.11

Analysis of variance and f-ratio value is 6.29962. The p-value is 0.000373. The result is significant whether $p < 0.05$. * Statistical significative data. VPD: vertical pupillary diameter; HPD: horizontal pupillary diameter; PDR: proliferative diabetic retinopathy.

2 versus Group 5 (VPD/HPD). These groups presented a mean and SD pupillary diameter of 1,0 ± 0.2 mm.

DISCUSSION

Diabetic autonomic neuropathy is a common complication of diabetes; thus, pupillary abnormalities can be found in early stages of DR, progressing as its severity increases. [11] In the current study, instead of evaluating the pupillary light reflex, we focused on pharmacological mydriasis at different stages of DR and in non-diabetic patients.

Jain et al., comparing the pupillary dynamic in varying stages of DR and patients without diabetes, observed a smaller baseline pupil diameter (BPD), reduced amplitude of pupillary constriction (APC), velocity of pupillary constriction (VPC) and velocity of pupillary dilatation (VPD) in response to light in subjects with diabetes. [11]

In a study by Fujii et al. [15], they investigated the ultrastructure of iris muscles forming iris specimens in patients with DM by electron microscopy. The iris specimen showed significant structural changes at the dilator pupillae, sphincter nerve endings, and evidence of nerve fibers loss. Multifactorial pathways, such as increased oxidative stress, reduced nitric oxide production, and autoimmune mechanisms can lead to cell necrosis and activation of genes involved in neuronal damage. [19,20] Direct lesion of motor plaque could be suggested due to the bad response to sympathetic and parasympathomimetic eye drops. [20]

Coblentz et al. compared mydriasis in patients with type 2 diabetes and without diabetes, yet no difference was observed between these groups. They concluded that diabetic patients can achieve mydriasis as satisfactory as non-diabetic patients.[13] However, Lei et al. showed that patients with long-term diabetes had poorer response to pharmacological mydriasis than patients with no diabetes. [12] The difference between these studies can be explained by the fact that Lei et al. selectively included patients with *Diabetes mellitus* for 10 years or more and it is well known that the rate of diabetic complications increases with duration of disease, while Coblentz et al. did not make any kind of selective sort based on the DR classification.[12,13]

Our outcomes demonstrated a smaller pupillary diameter in eyes with severe NPDR and PDR, according to the International DR classification. Anyway, our data confirms the study by Jain et al. and Lei and al. [11,12] In fact, the denervation process has been implicated as a process that may occur before DR microangiopathy, besides the participation of the cardiovascular disorders. [17]

Another interesting result of our study was the improvement in pupillary diameter after laser PRP in eyes with PDR, even though it did not reach statistical significance. This outcome has been described in the literature. [15,16,18]

Despite the necessity of a larger number of patients in this study, our findings confirm the usefulness of a better care with pupillary dilation in patients with diabetes who underwent ophthalmologic procedures such as cataract extraction and other intraocular surgeries, especially those with severe DR. [19,20] Since the 8th decade of the last century, many studies have tried to explain the correlation between DAN and DR stages. [21-27]

LIMITATIONS OF THE STUDY

In the current study, the small number of patients may generate some sort of limitations. Another limitation is the indirect assessment of parasympathetic and sympathetic abnormalities of pupillary function in diabetic patients through pharmacological dilation.

CONCLUSION

Diabetic autonomic neuropathy diminishes pharmacological mydriasis in patients with diabetic retinopathy, particularly in those with severe non-proliferative diabetic retinopathy and with proliferative diabetic retinopathy previously treated with PRP.

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