ISSN 0004-2749
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Arquivos Brasileiros de Oftalmologia

PUBLICAÇÃO OFICIAL DO CONSELHO BRASILEIRO DE OFTALMOLOGIA
JANEIRO/FEVEREIRO 2021
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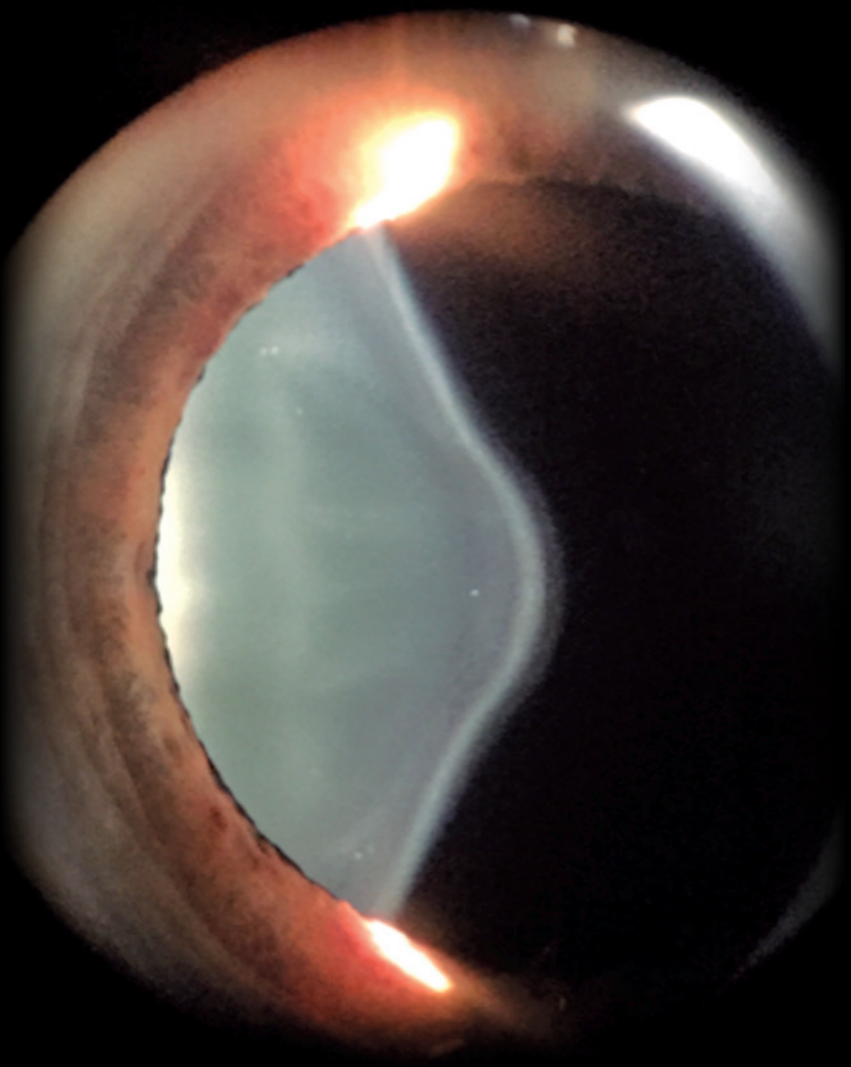

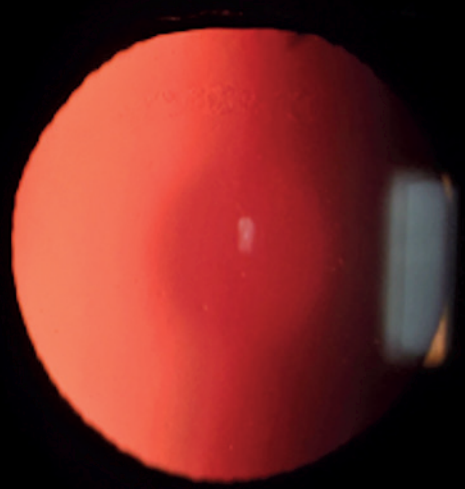

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1. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. Ocul Surf. 2017 Jul;15(3):276-283. **2.** Baudouin C, Aragona P, Messmer EM, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. Ocul Surf. 2013 Oct;11(4):246-58. **3.** Ng A, Keech A, Jones L. Tear osmolarity changes after use of hydroxypropylguar based lubricating eye drops. Clin Ophthalmol. 2018;12:695–700. **4.** Ecofilm®: carmelose sódica. Bula do medicamento. **5.** Plenigell®: carmelose sódica. Bula do medicamento.

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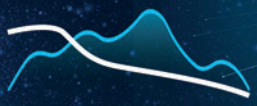

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E-mail: aboonline@cbo.com.br - www.scielo.br/abo

ISSN 0004-2749
(Printed version)
ISSN 1678-2925
(Electronic version)

Frequency of publication: Bimonthly

Arq Bras Oftalmol. São Paulo, v. 84, issue 1, pages 1-102, Jan/Fev. 2021

Divulgation: Brazilian Council of Ophthalmology
Circulation: 8.000 copies

Cover: Female, 32 years old with Alport Syndrome and anterior lenticonus OU, hypoacusis, and nephropathy since 11 years old. Authors: Ronald Rocha da Silva, MD and Ana Isaura Longo Moitinho de Vasconcelos, MD. Hospital de Olhos HCOE, Feira de Santana, Bahia, Brazil.

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ARQUIVOS BRASILEIROS DE
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Arq Bras Oftalmol. São Paulo, v. 84, issue 1, pages 1-102, Jan/Fev. 2021

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EDITORIAL

Ocular Oncology in Brazil: What is our past, present, and future?

Oncologia Ocular no Brasil: Qual o nosso passado, presente e futuro?

Eduardo F. Marback[1,2], Virginia Laura Lucas Torres[2,3], Priscilla Lupi Ballalai Bordon[2,4], Marcelo Krieger Maestri[2], Luiz Fernando Teixeira[2,5]

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Ophthalmic oncology encompasses the care of tumors of the eye and ocular adnexa. In Brazil, ophthalmic oncology is not listed as a medical specialty by the Federal Council of Medicine, so it is a part of Ophthalmology[1]. In 1998, during the XIII Congresso Brasileiro de Prevenção da Cegueira e Reabilitação Visual in Rio de Janeiro, RJ, Brazil, a group of Ophthalmologists founded the *Sociedade Brasileira de Oncologia em Oftalmologia* (Brazilian Society of Ocular Oncology, SBOO). This group was led by Dr Clelia Maria Erwenne in collaboration with other great names in Brazilian Ophthalmology, including Drs Jacobo Melamed, Joaquim Marinho de Queiroz, José Vital Filho, José Wilson Cursino, Mário Motta, and Roberto L Marback, as well as a number of other younger physicians interested in the topic. Most of these great ophthalmologists were, at first, involved in the care of eye and adnexal tumors as a consequence of their primary area of interest in ophthalmology, such as pathology, pediatrics, genetics, the retina, orbital and eyelid surgery, uveal diseases, and cornea and external diseases[2].

Looking back, the history of ophthalmic oncology, in Brazil and elsewhere, was no different from that of clinical oncology, surgical oncology, and other subareas of oncology. Here in Brazil, the Clinical and Surgical Oncology Societies were founded in the 1980s; before that, their activities were performed by clinicians and surgeons with special interest and dedication to the field. Similar to what occurred for clinical and surgical oncology, the pioneers of ophthalmic oncology were general ophthalmologists or ophthalmologists with training in other subareas who because of personal or circumstantial interest started to take care of eye cancer patients; a famous example was Prof. Sérgio Cunha from Universidade de São Paulo, a retinal surgeon who was renowned in laser treatment of intraocular tumors.

The contribution of Brazilian ophthalmologists to the care of eye cancer patients can be traced back many years. Hilário de Gouvêa first described the familial tendency in retinoblastoma in 1886[3]. In the 1950s and 1960s, Prof. Heitor Marback, interested in gaining a deeper knowledge of eye diseases, started to send enucleated eyes for pathologic study to the Armed Forces Institute of Pathology (AFIP; Washington, DC, USA), which was at that time headed by Dr Lorenz Zimmerman, who spread a long list of great ocular pathologists all over the world. This approach was amplified by Prof. Hilton Rocha, who started to encourage and send young Brazilian ophthalmologists and general pathologists to the specific ocular pathology training at the AFIP.

The first specific ambulatory care clinic for ocular cancer patients in Brazil was at the Hospital AC Camargo in the 1950s with Dr José Carlos Gouvea Pacheco. Dr Pacheco was the starting point of ophthalmic oncology, and Dr Clelia Maria Erwenne, whose primary initial focus was ophthalmic genetics, started to work with him during the 1980s. Dr Erwenne was the driving force of

Submitted for publication: June 24, 2020
Accepted for publication: July 27, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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E-mail: eduardomarback@uol.com.br

ophthalmic oncology in Brazil, training a great number of new ophthalmologists in the field of oncology and also providing an exemplary link for further specific training in many international services. In the next decade, she was involved with another eye cancer ambulatory care clinic in Escola Paulista de Medicina-Universidade Federal de São Paulo. This service worked in conjunction with the one in Hospital do Câncer AC Camargo up to 2000, at which time Dr Erwenne left the former.

Nowadays, oncology-trained ophthalmologists have spread to most of the Brazilian states and SBOO is present at all major Brazilian ophthalmic events. SBOO actively participates in general ophthalmic education programs as well as the Brazilian Ophthalmic Book Series. Another important achievement was the acceptance of ocular oncology and pathology, in a shared book with ocular plastic and orbital surgery, as the official theme for the 65th Congresso Brasileiro de Oftalmologia (Brazilian Congress of Ophthalmology) to be held in Natal, RN in 2021. This publication is expected to function as a general reference in the ocular oncology field for Brazilian ophthalmologists.

At the present time, ocular oncology care is distributed over a series of universities and cancer hospitals throughout the country; unfortunately, some expensive treatment modalities, like plaque brachytherapy, are still a major problem for the public health system in every Brazilian state. We know that Brazil is a country of continental proportions with a number of social problems and many deficits in the public health system. These difficulties obviously affect ocular oncology services and patients. But we are also aware of the commitment of Brazilian ocular oncologists. Although still few in number, like most health professionals that choose to treat cancer patients, ocular oncologists are passionate people that do their very best to improve eye and adnexal cancer care in Brazil.

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ORIGINAL ARTICLE

Evaluation of retinal and choroidal microvascular changes in patients who received hydroxychloroquine by optical coherence tomography angiography

Avaliação de alterações microvasculares da retina e coroide em pacientes sob hidroxicloroquina através da angiografia por tomografia de coerência óptica

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2. Ophthalmology Clinic, İzmir Tepecik Training and Research Hospital, University of Health Sciences, Izmir, Turkey.
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ABSTRACT | Purpose: The aim of the study is to evaluate the retinal and choroidal microvascular changes via optical coherence tomography angiography in patients who received hydroxychloroquine. **Methods:** In total, 28 eyes of 28 patients (24 females, and 4 males) receiving treatment with hydroxychloroquine were assessed in this cross-sectional cohort study (hydroxychloroquine group). The high-and low-risk groups consisted of patients receiving hydroxychloroquine for ≥5 years (14 eyes of 28 patients) and <5 years (14 eyes of 28 patients), respectively. A total of 28 age- and gender-matched volunteers were enrolled as the control group. The macular flow area (superficial, deep, and choriocapillaris), superficial and deep vessel density, foveal avascular zone area, central foveal thickness, and subfoveal choroidal thickness parameters were measured by optical coherence tomography angiography. **Results**: The mean age of the 28 patients who received hydroxychloroquine and the 28 age-matched controls was 45.5 ± 11.1 years (range: 29-70 years) and 44.5 ± 13.9 years (range: 28-70 years), respectively. In patients who received hydroxychloroquine, the values for the superficial, deep, and choriocapillaris macular flow areas were 13.578 ± 0.30, 13.196 ± 0.31, and 17.617 ± 0.42, respectively. In controls, these values were 16.407 ± 0.95, 13.857 ± 0.31, and 18.975 ± 0.76, respectively ($p<0.05$ for all). The superficial, deep, and choriocapillaris flow areas were significantly smaller in patients who received hydroxychloroquine than those in controls ($p<0.05$ for all). Superficial and deep vessel densities were significantly reduced in patients who received hydroxychloroquine in all regions (i.e., foveal, parafoveal, temporal, superior, nasal, and inferior) ($p<0.05$ for all). Moreover, significant difference was observed between the groups in the foveal avascular zone area (superficial and deep), central foveal thickness, and subfoveal choroidal thickness ($p<0.05$ for all). **Conclusions**: Retinochoroidal microvascular flow and vessel density of the macular area were significantly decreased in patients who received hydroxychloroquine. Hydroxychloroquine may damage the retinochoroidal microvascular architecture. Optical coherence tomography angiography may contribute to the early detection of hydroxychloroquine-induced retinal toxicity.

Keywords: Retina/drug effects; Choroid/drug effects; Optical coherence tomography; Hydroxychloroquine; Fluorescein angiography/methods

RESUMO | Objetivo: O objetivo do estudo foi de avaliar as alterações microvasculares da retina e da coroide em pacientes sob hidroxicloroquina, através da angiografia por tomografia de coerência óptica. **Métodos:** Este é um estudo transversal de coorte que avaliou um total de 28 olhos de 28 pacientes (24 mulheres e 4 homens) submetidos a tratamento com hidroxicloroquina (grupo da hidroxicloroquina). Catorze olhos de 28 pacientes em uso de hidroxicloroquina por mais de 5 anos foram definidos como sendo o grupo de alto risco, ao passo que o grupo de baixo risco consistiu em 14 olhos de 28 pacientes em uso de hidroxicloroquina por menos de 5 anos. Foram ainda incluídos 28 voluntários como grupo de controle, pareados por idade e sexo. Através de angiografia por tomografia de coerência óptica, foram medidos os seguintes parâmetros: área do fluxo macular (superficial, profundo e coriocapilar), densidade vascular superficial e profunda, área da zona avascular foveal e espessura da coroide subfoveal. **Resultados:** Foram recrutados para o estudo um total de 28 pacientes sob tratamento com

Submitted for publication: June 11, 2019
Accepted for publication: December 8, 2019

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Alanya Antalya, Turkey, Alaaddin Keykubat University School of Medicine Clinical Researches (#2-17/2019).

hidroxicloroquina, com idade média de 45,5 ± 11,1 (29-70) anos, e 28 membros do grupo de controle, pareados por idade e sexo, com idade média de 44,5 ± 13,9 (28-70) anos. As áreas superficial, profunda e coriocapilar do fluxo macular foram respectivamente de 13,578 ± 0,30, 13,196 ± 0,31 e 17,617 ± 0,42 nos pacientes em tratamento com hidroxicloroquina e, respectivamente de 16,407 ± 0,95, 13,857 ± 0,31 e 18,975 ± 0,76 no grupo de controle (p<0,05 para todos os valores). As três medições de área do fluxo macular foram significativamente menores nos pacientes em uso de hidroxicloroquina em comparação com os indivíduos do grupo de controle (p<0,05 para todos os valores). As densidades vasculares superficial e profunda mostraram-se significativamente reduzidas em todas as regiões (foveal, parafoveal, temporal, superior, nasal e inferior) nos pacientes em uso de hidroxicloroquina (p<0,05 para todos os valores). Finalmente, também foi observada uma diferença significativa entre os grupos em relação à área da zona avascular foveal (superficial e profunda), à espessura foveal central e à espessura da coroide subfoveal (p<0,05 para todos os valores). **Conclusão:** O fluxo microvascular retinocoroidal e a densidade vascular da área macular mostraram-se significativamente diminuídos nos pacientes sob hidroxicloroquina. Este fármaco pode danificar a arquitetura microvascular retinocoroidal e a angiografia por tomografia de coerência óptica pode contribuir para a detecção precoce da toxicidade retiniana induzida pela hidroxicloroquina.

Descritores: Retina/efeitos dos fármacos; Coroide/efeitos de fármacos; Tomografia de coerência óptica; Hidroxicloroquina; Angiofluoresceinografia/métodos

INTRODUCTION

Hydroxychloroquine (HCQ) is an antimalarial drug, which is widely used in rheumatology and dermatology clinics for the treatment of numerous autoimmune diseases[1]. However, there is hesitation among clinicians regarding its use due to its irreversible retinal toxicity[2]. Although the mechanism involved in this process remains unclear, its destructive effect on the retinal pigment epithelium (RPE), photoreceptors, and retinal ganglion cell-inner plexiform layer complex due to its affinity to melanin pigment has been demonstrated[3-6]. The effect of HCQ on the vascular structure and its role in retinal toxicity are unclear. Analysis of the superficial and deep retinal vascular layers became possible only recently, and the data concerning this topic are newly presented.

Avoidance of the irreversible visual loss related to HCQ-induced retinal toxicity is crucial for the detection of retinal toxicity prior to the onset of RPE damage[7]. In their revised protocol in 2016, the American Academy of Ophthalmology stated that the visual field test, optical coherence tomography (OCT), multifocal electroretinogram (ERG), microperimetry, and fundus autofluorescence may be used as needed to screen the retinal toxicity in patients who receive HCQ[5].

OCT angiography (OCTA) is a new, non-invasive method that allows the evaluation of the superficial and deep flow and vessel density of the macula[8-10].

The aim of this study is to compare the retinal superficial capillary plexus (SCP), deep capillary plexus (DCP), choroidal thickness, and foveal avascular zone (FAZ) area between patients who received HCQ and healthy subjects by OCTA imaging.

METHODS

Participants

Twenty-eight eyes from 28 patients (24 females and 4 males) who received HCQ and 28 sex- and age-matched controls were enrolled in the study. The study protocol was approved by Alanya Alaaddin Keykubat University School of Medicine Clinical Researches Ethics Committee (№ 2-17/2019). The research adhered to the tenets of the Declaration of Helsinki, and detailed written informed consent was provided by all individuals prior to their participation in the study.

Study design

This was a cross-sectional cohort study. Patients who had a history of continuous treatment with HCQ for ≥12 months and ongoing treatment with HCQ (200 mg/day) were included in our study group. There was no restriction applied for the maximum duration of treatment with HCQ, and all participants who fulfilled the minimum criteria were included. One eye (randomly selected) of each patient was analyzed in both the study and control groups.

The high- and low-risk groups consisted of patients receiving HCQ for ≥5 years (14 eyes of 28 patients) and <5 years (14 eyes of 28 patients), respectively. A total of 28 age-and sex-matched volunteers, selected from patients who presented to the ophthalmology outpatient clinic for routine ophthalmologic examination, were enrolled as the control group.

Exclusion criteria for all participants were as follows: nystagmus; corneal opacity; cataract; glaucoma; congenital or acquired retinal disorders, including any vascular disease; or a history of ocular trauma or surgery. Individuals with any systemic disease (except rheumatoid arthritis, Sjögren's syndrome, connective tissue disease, and systemic lupus erythematosus), including diabetes

mellitus, arterial hypertension, anemia, renal disease, and cardiovascular disease, were excluded. In addition, participants who had a history of any chronic drug use, including analgesics, antihistamines, vasodilators, decongestants, anticoagulants, oral contraceptives, and sildenafil, were excluded.

Examination

Age, systolic blood pressure, and diastolic blood pressure were recorded. A comprehensive ophthalmic examination included the following: best-corrected visual acuity assessment using the Snellen chart; slit-lamp anterior segment examination; axial length measurement by the IOLMaster device (ver. 3.02; Carl Zeiss, Meditec, Jena, Germany); intraocular pressure measurements by Goldmann applanation tonometry; dilated fundus examination with a 90-D lens, central 10° visual field test using Octopus 900 (Interzeag AG, Schlieren-Zurich, Switzerland); and OCTA measurement (RT Vue XR100-2; Optovue Inc., Fremont, CA, USA). The retinochoroidal structure in all individuals was evaluated using OCTA. All OCTA scans were performed in the morning (between 10:00 a.m. and 12:00 p.m.) to avoid diurnal fluctuations.

OCTA measurements

Optovue Angio-Vue system technology (Software Version 2015.1.1.98; Optovue Inc.) allows for quantitative analysis. The inner and outer boundaries for SCP were assumed to be 3 μm below the internal limiting membrane and 16 μm below the inner plexiform layer, respectively. The inner and outer boundaries were 16 and 70 μm below the inner plexiform layer for DCP, respectively. The outer retina was located 70 and 30 μm below the inner plexiform layer and the RPE, respectively[11-13]. The OCTA software automatically outputs the flow area value. The vessel density was separately calculated in five regions (i.e., fovea, temporal, superior, nasal, and inferior) based on the Early Treatment Diabetic Retinopathy Study contour. A 3 × 3 mm macular angiogram of the choriocapillaris (CC) layer was analyzed using the Optovue software with flow function to measure the CC flow area[13]. The flow area of CC was calculated automatically as vessel areas of CC divided by selected areas. FAZ and central foveal thickness are measured automatically using OCTA. Subfoveal choroidal thickness (SFCT) is defined as the distance between the hyper-reflective line corresponding to the base of the RPE and the hyper-reflective line corresponding to the chorio-scleral interface. It was measured thrice by two independent observers using manual calipers in the horizontal and vertical sections beneath the fovea. Average values were recorded and analyzed.

Statistical analysis

One eye from each participant was randomly selected for analysis using the SPSS for Windows version 21.0 (IBM Corp., Armonk, NY, USA) software. This selection was based on the absence of a significant difference between the right and left eyes. The simple randomization technique of computer-generated random numbers was used to select the eyes. For each continuous variable, normality was determined using the Kolmogorov-Smirnov test, which showed a normal distribution for all parameters. The categorical variables were analyzed using the chi-squared test. OCTA measurements of the groups were compared using the independent t-test. Spearman correlation analysis was applied between macular perfusion parameter data and daily and cumulative doses in the HCQ group. Statistically significant differences are denoted by p-values <0.05.

RESULTS

This cross-sectional study analyzed 28 eyes of 28 patients who received treatment with HCQ and 28 eyes of 28 age-and sex-matched controls. There were no significant differences observed between the study and control groups in terms of age, spherical equivalent, axial length, systolic blood pressure, diastolic blood pressure, visual acuity, and intraocular pressure parameters. Demographic data, clinical diagnosis, mean daily dose, cumulative drug dose, and mean duration of treatment are shown in table 1.

The macular flow area, including the superficial retinal flow area, deep flow area, and CC, was significantly smaller in HCQ-treated patients than that in controls ($p<0.05$ for all) (Table 2). Moreover, the FAZ area was significantly enlarged in the HCQ group versus that in the control group (superficial: $p=0.034$ and deep: $p=0.013$) (Table 2). The boxplot analysis representing the macular flow area measurements (superficial, deep, and CC) and FAZ area for both groups is shown in figure 1.

Superficial and deep vessel densities were significantly reduced in HCQ-treated patients for all macular regions (i.e., foveal, parafoveal, temporal, superior, nasal, and inferior) ($p<0.05$ for all) (Table 2).

Table 1. The demographic and clinical characteristics of the HCQ and control groups

Characteristic	HCQ group (n=28)	Control group (n=28)	p
Age (mean, years)	45.5 ± 11.1	44.5 ± 13.9	0.935
SBP (mmHg)	113.75 ± 5.3	115.61 ± 5.1	0.901
DBP (mmHg)	77.1 ± 4.7	75.8 ± 3.1	0.788
IOP (mmHg)	14.2 ± 1.3	13.9 ± 1.2	0.915
SE (D)	0.232 ± 0.41	0.224 ± 0.43	0.762
AL (mm)	23.17 ± 0.68	23.19 ± 0.49	0.947
BCVA (Snellen)	0.621 ± 0.74	0.648 ± 0.68	0.503
Cummulative drug dose (g)	593.714 ± 450	-	-
Duration of drug use (months)	63 ± 11.2 (12–132)	-	-
Daily dose (mg/day)	292.857 ± 85 (200-400)	-	-
Systemic diseases			
Rheumatoid arthritis	5		
Sjögren's syndrome	5		
Connective tissue disease	8		
Systemic lupus erythematosus	10		

Values are presented as the mean ± SD.
HCQ= hydroxychloroquine; SE= spherical equivalent; AL= axial length; SBP= systolic blood pressure; DBP= diastolic blood pressure; IOP= intraocular pressure; BCVA= best-corrected visual acuity; SD= standard deviation.

Table 2. Macular perfusion and perimetric parameters of the HCQ and control groups

Parameter	HCQ group n=28	Control group n=28	p
Superficial retinal flow area (mm^2)	13.578 ± 0.30	16.407 ± 0.95	0.001*
Deep retinal flow area (mm^2)	13.196 ± 0.31	13.857 ± 0.31	0.012*
CC flow area (mm^2)	17.617 ± 0.42	18.975 ± 0.76	0.002*
FAZ area (superficial, mm^2)	0.331 ± 0.014	0.310 ± 0.018	0.034*
FAZ area (deep, mm^2)	0.357 ± 0.010	0.309 ± 0.018	0.013*
Superficial vessel density (%)			
Fovea	34.053 ± 1.83	36.635 ± 1.22	0.013*
Parafoveal	53.520 ± 1.27	55.771 ± 1.28	0.011*
Temporal	54.135 ± 0.97	56.292 ± 1.21	0.014*
Superior	53.678 ± 1.36	56.760 ± 0.86	0.002*
Nasal	53.496 ± 0.61	56.492 ± 1.00	0.002*
Inferior	53.910 ± 0.94	56.428 ± 1.06	0.001*
Deep vessel density (%)			
Fovea	36.157 ± 0.71	37.978 ± 0.55	0.032*
Parafoveal	55.446 ± 1.01	57.285 ± 0.56	0.030*
Temporal	54.903 ± 1.66	56.685 ± 1.07	0.025*
Superior	54.956 ± 1.41	57.214 ± 0.58	0.016*
Nasal	52.635 ± 0.93	56.225 ± 0.93	0.023*
Inferior	52.867 ± 1.01	55.575 ± 1.08	0.015*
Central foveal thickness	236.783 ± 3.8	244.829 ± 4.2	0.044*
Subfoveal choroidal thickness	308.099 ± 9.2	322.082 ± 11.47	0.041*
Perimetry			
Mean defect (dB)	2.84 ± 1.79	0.93 ± 0.37	0.027*
Standard loss variance (dB)	1.92 ± 0.85	0.62 ± 0.39	0.013*

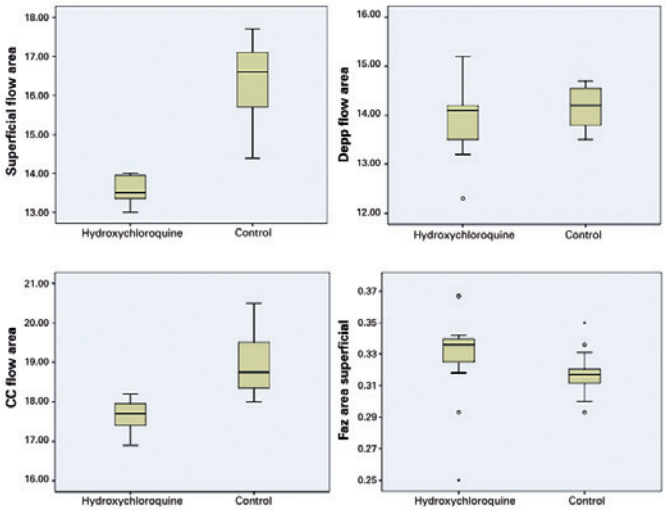
Values are presented as the mean ± SD. *= statistically significant.
HCQ= hydroxychloroquine; CC= choriocapillaris; FAZ= foveal avascular zone; SD= standard deviation.

When compared with those in the healthy controls, central foveal thickness and SFCT in HCQ-treated patients were significantly decreased (p=0.044 and 0.041, respectively) (Table 2).

The perimetric data (10° visual field test) were evaluated using two parameters; both the mean defect (dB) and standard loss variance (dB) were significantly increased in the HCQ group (Table 2).

Spearman correlation analysis between macular perfusion parameters (superficial, deep, and CC flow area), FAZ area, perimetric data, and daily and cumulative doses in the HCQ group showed weak statistical significance. However, the duration of disease was not correlated with any of those parameters. Table 3 presents the results of Spearman correlation analysis.

Patients were divided into two subgroups based on the duration of treatment with HCQ: high-risk group (duration of treatment ≥5 years) and low-risk group (duration of treatment <5 years). Comparison between the high- (14 patients) and low-risk (14 patients) groups revealed statistically significant differences in terms of superficial retinal flow area, deep retinal flow area, CC flow area, and FAZ area (p<0.05) (Table 4). Moreover, the measurement of superficial and deep vessel densities in the HCQ group revealed significant differences between the high-and low-risk groups in all macular regions (i.e., foveal, parafoveal, temporal, superior, nasal, and inferior) (p<0.05 for all) (Table 4).



CC= choriocapillaris; FAZ= foveal avascular zone.
Figure 1. The boxplot analysis representing the macular flow area measurements (superficial, deep, and CC) and FAZ area for both groups.

The correlation between OCTA parameters and visual acuity was assessed in the high- and low-risk groups. There was no correlation detected between the OCTA parameters and visual acuity in either group (p>0.005, for all).

Patients treated daily with ≥6.5 mg/kg HCQ (high-risk for retinopathy) and <6.5 mg/kg HCQ (low-risk for retinopathy) were compared. Significant differences were observed in all locations (foveal, parafoveal, temporal, superior, nasal, and inferior) both in the SCP and DCP layers of the macula between the high- and low-risk groups. Furthermore, visual field parameters were worse in the high-risk group than those in the low-risk group, and the difference was statistically significant (details shown in table 5).

In addition, we compared data from the low-risk group and healthy control group. The low-risk group exhibited significantly lower superficial and deep vessel densities compared with the healthy controls (details are shown in table 6). Parameters for both eyes of HCQ-treated patients are presented in table 7.

In patients treated with HCQ, OCTA imaging showed loss of the perifoveal photoreceptor inner segment/outer segment junction (three patients), perifoveal thinning of the outer nuclear layer (two patients), and an apparent posterior displacement of the inner retinal structures toward the RPE (one patient).

DISCUSSION

HCQ-induced retinopathy is a clinical condition occurring in patients who receive >6.5 mg/kg daily dose, characterized by impairment in visual acuity and deterioration in visual field[5]. Risk factors for toxic retinopathy are >6.5 mg/kg daily dose; >1,000 g cumulative dose; >5 years of treatment; increased age (>60 years);

Table 3. Correlation analysis with the disease duration, cumulative dose, and the duration of drug use

	Duration of disease		Cumulative dose		Duration of drug use	
	p	r	p	r	p	r
Superficial retinal flow area (mm^2)	0.695	-0.078	0.001*	-0.001	0.000*	-0.730
Deep retinal flow area (mm^2)	0.280	0.211	0.045*	-0.471	0.000*	-0.550
CC flow area (mm^2)	0.978	-0.001	0.032*	-0.521	0.022*	-0.121
FAZ area (superficial, mm^2)	0.067	0.351	0.046*	0.144	0.034*	0.185
FAZ area (deep, mm^2)	0.071	0.414	0.041*	0.213	0.021*	0.431
Superficial vessel density (%)						
Fovea	0.951	0.012	0.023*	-0.230	0.041*	-0.160
Parafovea	0.978	0.005	0.034*	-0.187	0.040*	-0.123
Temporal	0.840	0.040	0.016*	-0.560	0.013*	-0.501
Superior	0.435	0.154	0.033*	-0.191	0.014*	-0.441
Nasal	0.381	-0.172	0.025*	-0.222	0.013*	-0.291
Inferior	0.335	-0.189	0.006*	-0.797	0.001*	-0.798
Deep vessel density (%)						
Fovea	0.259	-0.221	0.029*	-0.203	0.020*	-0.299
Parafovea	0.123	-0.298	0.036*	-0.178	0.010*	-0.513
Temporal	0.512	-0.129	0.045*	-0.104	0.029*	-0.207
Superior	0.885	-0.029	0.028*	-0.510	0.029*	-0.452
Nasal	0.402	-0.165	0.028*	-0.156	0.037*	-0.246
Inferior	0.795	-0.051	0.001*	-0.811	0.003*	-0.638
Central foveal thickness	0.381	0.172	0.037*	-0.287	0.012*	-0.239
Subfoveal choroidal thickness	0.196	0.174	0.043*	-0.285	0.036*	-0.301
Perimetry						
Mean defect (dB)	0.004	0.508	0.001*	0.797	0.001*	0.852
Standard loss variance (dB)	0.003	0.602	0.001*	0.678	0.001*	0.924

P-values are presented with Spearman's correlation coefficient tests. *= statistically significant
CC= choriocapillaris; FAZ= foveal avascular zone.

concomitant liver or kidney dysfunction; and presence of any basal maculopathy[6]. The early detection of HCQ-induced retinal toxicity is important because of the risk of irreversible vision loss[5].

The primary aim of this study is to evaluate the retinal vascular structure in patients who received HCQ. The secondary aim is to investigate whether OCTA is valuable in detecting HCQ-induced retinal toxicity. In this study, SCP (crucial for ganglion cell layer nutrition) and vascular density were evaluated as superficial retinal flow area and superficial vessel density, respectively. Both values were significantly decreased in the HCQ group. The outer retina and DCP, which consists of photoreceptors, were evaluated as deep retinal flow area and deep vessel density; these values were also significantly decreased in the HCQ group. Our analysis showed significantly decreased CC flow area and SFCT in the HCQ group compared with those in the control group. Both perimetric parameters (i.e., mean defect and standard loss variance values) were higher in the HCQ group. The FAZ area (superficial and deep) was significantly enlarged in the HCQ group compared with that in the control group. The results of this study revealed a significant deterioration in macular microvascular circulation in patients treated with HCQ.

Two previous reports evaluated the retinal microvascular structure by OCTA in patients treated with HCQ. Bulut et al.[14] evaluated a total of 60 patients in two groups: a high-risk group (duration of treatment ≥5 years) and a low-risk group (duration of treatment <5 years). Both groups were evaluated for HCQ-induced retinal toxicity using the visual field test, OCTA, and spectral domain OCT (SD-OCT). The findings revealed that vascular density, retinal and choroidal flow rates, and choroidal thickness parameters were significantly decreased in the high-risk group compared with those in the

Table 4. Macular perfusion and perimetric parameters of the high- and low-risk groups

	High-risk group	Low-risk group	p
Superficial retinal flow area (mm^2)	13.674 ± 0.33	14.221 ± 0.85	0.021*
Deep retinal flow area (mm^2)	13.258 ± 0.37	14.114 ± 0.21	0.032*
CC flow area (mm^2)	16.987 ± 0.44	17.955 ± 0.46	0.024*
FAZ area (superficial, mm^2)	0.330 ± 0.018	0.311 ± 0.22	0.033*
FAZ area (deep, mm^2)	0.328 ± 0.018	0.308 ± 0.011	0.025*
Superficial vessel density (%)			
Fovea	34.167 ± 1.63	35.835 ± 1.12	0.023*
Parafovea	53.540 ± 1.17	54.111 ± 1.37	0.028*
Temporal	53.935 ± 0.97	55.311 ± 1.87	0.013*
Superior	53.278 ± 1.38	55.360 ± 0.45	0.013**
Nasal	53.444 ± 0.52	54.687 ± 1.52	0.028*
Inferior	53.463 ± 0.81	55.328 ± 1.24	0.010*
Deep vessel density (%)			
Fovea	36.211 ± 0.78	36.978 ± 0.55	0.042*
Parafovea	55.101 ± 1.21	56.962 ± 0.55	0.038*
Temporal	53.803 ± 1.45	55.289 ± 1.37	0.015*
Superior	54.384 ± 1.28	56.814 ± 0.84	0.025*
Nasal	52.666 ± 0.90	55.125 ± 0.87	0.022*
Inferior	52.966 ± 1.10	54.324 ± 1.33	0.027*
Central foveal thickness	223.241 ± 9.5	231.829 ± 4.2	0.033*
Subfoveal choroidal thickness	311.997 ± 9.8	319.821 ± 11.47	0.047*
Perimetry			
Mean defect (dB)	2.72 ± 1.81	2.21 ± 1.21	0.041*
Standard loss variance (dB)	1.65 ± 0.75	1.62 ± 0.39	0.845*

Values are presented as the mean ± SD. *= statistically significant.
CC= choriocapillaris; FAZ= foveal avascular zone.

Table 5. Macular perfusion and perimetric parameters of analysis with lower doses versus higher doses in patients treated with HCQ

	Lower dose (<6.5 mg/kg daily) n=16	Higher dose (≥6.5 mg/kg daily) n=12	p
Superficial retinal flow area (mm^2)	15.333 ± 0.97	13.189 ± 0.48	0.001*
Deep retinal flow area (mm^2)	13.423 ± 0.44	13.001 ± 0.59	0.043*
CC flow area (mm^2)	18.211 ± 0.70	17.859 ± 0.84	0.032*
FAZ area (superficial, mm^2)	0.304 ± 0.018	0.300 ± 0.010	0.039*
FAZ area (deep, mm^2)	0.348 ± 0.017	0.365 ± 0.02	0.043*
Superficial vessel density (%)			
Fovea	36.031 ± 0.92	35.214 ± 0.98	0.044*
Parafoveal	54.456 ± 1.17	53.274 ± 1.15	0.023*
Temporal	55.951 ± 1.34	55.001 ± 1.27	0.034*
Superior	55.276 ± 0.99	54.102 ± 1.19	0.042*
Nasal	55.853 ± 1.24	54.267 ± 1.40	0.021*
Inferior	55.3789 ± 1.12	55.007 ± 1.07	0.045*
Deep vessel density (%)			
Fovea	36.249 ± 0.59	35.308 ± 0.96	0.026*
Parafoveal	56.173 ± 0.65	55.179 ± 0.93	0.020*
Temporal	55.127 ± 1.84	54.178 ± 1.37	0.018*
Superior	56.851 ± 0.79	55.164 ± 0.63	0.039*
Nasal	55.441 ± 1.10	54.227 ± 1.07	0.037*
Inferior	54.012 ± 1.22	53.278 ± 1.32	0.024*
Central foveal thickness	240.257 ± 4.9	238.521 ± 5.12	0.054
Subfoveal choroidal thickness	318.002 ± 11.88	311.542 ± 12.21	0.030*
Perimetry			
Mean defect (dB)	0.88 ± 0.33	0.90 ± 0.22	0.043*
Standard loss variance (dB)	0.51 ± 0.44	0.54 ± 0.17	0.026*

Values are presented as the mean ± SD. *= statistically significant
HCQ= hydroxychloroquine; CC= choriocapillaris; FAZ= foveal avascular zone; SD= standard deviation.

low-risk group. However, the study conducted by Bulut et al.[14] lacked a control group. In the present study, a control group was included, and the high- and low-risk subgroups were further analyzed. Consistent with the findings reported by Bulut et al.[14], the results obtained from the subgroup analyses in the present study revealed greater decrease in retinochoroidal flow and vascular density in the high-risk group. Our study evaluating the superficial and deep vascular plexus in the foveal, parafoveal, superior, inferior, temporal, and nasal regions revealed significant decrease in flow and vascular density in the HCQ group. In contrast, in the study conducted by Bulut et al.[14], these parameters were evaluated as a whole (i.e., in the foveal and parafoveal areas, but not in the superior, inferior, nasal, or temporal regions). A study performed by Ozek et al.[15] evaluated retinal toxicity in 40 patients who received HCQ for rheumatoid arthritis. The patients were assigned to high-and low-risk groups and compared with age-matched controls. Ozek et al.[15] observed that the deep vascular density in the temporal and inferior regions was significantly lower in the high-risk group than that in the control group; nevertheless, these differences were not detected in the low-risk group. There was no significant difference observed in the density of the superficial vascular structure between the HCQ and control groups. Moreover, there was no significant difference between the high-and low-risk groups in terms of superficial and deep vascular density. However, we noted a significant decrease in both superficial and deep vascular densities in the HCQ group. These findings are in accordance with those of Ozek et al.[15] for the deep vascular structure but not for the superficial vascular structure. Additionally, there is a disagreement between the two studies in terms of the findings in the high- and low-risk groups. In the present study, we demonstrated significant impairment in macular

Table 6. Macular perfusion and perimetric parameters of the low-risk and healthy control groups

	Low-risk group n=14	Control group n=28	p
Superficial retinal flow area (mm²)	14.221 ± 0.85	16.407 ± 0.95	0.013*
Deep retinal flow area (mm²)	14.114 ± 0.21	13.857 ± 0.31	0.509
CC flow area (mm²)	17.955 ± 0.46	18.975 ± 0.76	0.044*
FAZ area (superficial, mm²)	0.311 ± 0.22	0.310 ± 0.018	0.665
FAZ area (deep, mm²)	0.308 ± 0.011	0.309 ± 0.018	0.711
Superficial vessel density (%)			
Fovea	35.835 ± 1.12	36.635 ± 1.22	0.043*
Parafovea	54.111 ± 1.37	55.771 ± 1.28	0.041*
Temporal	55.311 ± 1.87	56.292 ± 1.21	0.041*
Superior	55.360 ± 0.45	56.760 ± 0.86	0.022*
Nasal	54.687 ± 1.52	56.492 ± 1.00	0.023*
Inferior	55.328 ± 1.24	56.428 ± 1.06	0.028*
Deep vessel density (%)			
Fovea	36.978 ± 0.55	37.978 ± 0.55	0.046*
Parafovea	56.962 ± 0.55	57.285 ± 0.56	0.103
Temporal	55.289 ± 1.37	56.685 ± 1.07	0.024*
Superior	56.814 ± 0.84	57.214 ± 0.58	0.045*
Nasal	55.125 ± 0.87	56.225 ± 0.93	0.025*
Inferior	54.324 ± 1.33	55.575 ± 1.08	0.040*
Central foveal thickness	231.829 ± 4.2	244.829 ± 4.2	0.007*
Subfoveal choroidal thickness	319.821 ± 11.47	322.082 ± 11.47	0.026*
Perimetry			
Mean defect (dB)	2.21 ± 1.21	0.93 ± 0.37	0.013*

Values are presented as the mean ± SD. *= statistically significant.
CC= choriocapillaris; FAZ= foveal avascular zone; SD= standard deviation.

Table 7. Macular perfusion and perimetric parameters of the right eye and left eye in the HCQ group

	Right eye n=28	Left eye n=28	p
Superficial retinal flow area (mm²)	13.468 ± 0.34	13.511 ± 0.81	0.964
Deep retinal flow area (mm²)	13.211 ± 0.38	13.607 ± 0.28	0.657
CC flow area (mm²)	17.573 ± 0.39	17.459 ± 0.37	0.843
FAZ area (superficial, mm²)	0.338 ± 0.011	0.330 ± 0.015	0.745
FAZ area (deep, mm²)	0.351 ± 0.010	0.362 ± 0.014	0.635
Superficial vessel density (%)			
Fovea	34.127 ± 1.44	34.531 ± 1.37	0.523
Parafoveal	53.613 ± 1.32	53.695 ± 1.39	0.631
Temporal	54.933 ± 0.88	54.954 ± 1.34	0.901
Superior	53.294 ± 1.25	53.137 ± 0.70	0.886
Nasal	53.524 ± 1.66	53.397 ± 1.22	0.832
Inferior	53.317 ± 0.99	53.328 ± 1.11	0.991
Deep vessel density (%)			
Fovea	36.112 ± 0.96	36.038 ± 0.87	0.874
Parafoveal	55.408 ± 1.22	55.507 ± 0.98	0.663
Temporal	54.119 ± 1.13	54.222 ± 1.24	0.658
Superior	54.953 ± 1.34	54.284 ± 1.18	0.503
Nasal	52.111 ± 0.98	54.862 ± 0.91	0.846
Inferior	52.779 ± 1.22	52.973 ± 1.35	0.542
Central foveal thickness	237.114 ± 5.5	237.004 ± 4.9	0.411
Subfoveal choroidal thickness	306.867 ± 9.8	308.222 ± 10.1	0.327
Perimetry			
Mean defect (dB)	2.88 ± 1.65	2.94 ± 1.35	0.203
Standard loss variance (dB)	1.87 ± 0.94	1.91 ± 0.97	0.855

Values are presented as the mean ± SD.
HCQ= hydroxychloroquine; CC= choriocapillaris; FAZ= foveal avascular zone; SD= standard deviation.

microcirculation in the high-risk group. In contrast, Ozek et al.[15] did not reveal a significant difference. This inconsistency may be attributed to the evaluation criteria. In the present study, we assessed macular perfusion using flow measurements and vascular density analysis. However, in the study conducted by Ozek et al., only vascular density was evaluated[15].

We demonstrated a significant correlation between the retinochoroidal flow, vascular density, and the cumulative dose of HCQ; there was no significant correlation noted between the retinochoroidal flow, vascular density, and the duration of treatment with HCQ in accordance with the report by Bulut et al.[14] Lyons et al.[16] reported a significant correlation between the cumulative HCQ dose and multifocal ERG anomalies in their study comparing 67 patients treated with HCQ and 62 healthy controls. In a large group consisting of 3,995 HCQ-treated patients, Wolfe et al.[3] reported that retinal toxicity induced by HCQ was significantly frequent in patients who received the treatment for >7 years with a cumulative dose of >1,000 g. Collectively, these results confirm the recommendation from the American Academy of Ophthalmology, indicating that the main determinants of retinal toxicity are the daily and cumulative doses[3,17,18]. In the present study, there was no significant correlation recorded between the duration of treatment and macular perfusion, which was compatible with the results of previous studies[3,14,17,18].

Similar to the findings reported by Bulut et al.[14], the FAZ area in our study was significantly enlarged in both the superficial and deep retinal layers and correlated with the daily and cumulative doses of HCQ. However, this finding was not observed by Ozek et al.[15].

In a study evaluating choroidal vascular dysfunction through OCTA, Ahn et al.[19] revealed a significant decrease in choroidal thickness and CC equivalent thickness value that was correlated with the cumulative dose and body weight. The investigators observed that richly pigmented CC with thinner vessels is markedly more affected than large or medium calipered choroidal vessels. Bulut et al.[14] reported a significant decrease in choroidal flow and thickness. Concordant with previous reports, our study revealed a significant decrease in both choroidal flow and thickness, suggesting choroidal vascular dysfunction that may be related to HCQ toxicity[14,19].

The 10-2 visual field test requires the cooperation of the patients and is thus characterized by subjectivity. Therefore, it is more valuable to objectively evaluate the retinal toxicity of HCQ. We found a significant correlation between perimetric values (i.e., mean defect and standard loss variance), cumulative dose, duration of treatment, and retinochoroidal perfusion parameters (i.e., superficial retinal flow area, deep flow area, and CC). These findings support the positive correlation between the deterioration of the visual field and retinochoroidal flow and vascular density, similar to the study conducted by Bulut et al.[14]. Marmor et al.[20] revealed a paracentral scotoma in 10% (11 patients) despite the lack of any pathological finding in SD-OCT in patients who received >6.5 mg/kg daily or cumulative >1,000 g dose for >9 years. Hence, they suggested to use the visual field test in conjunction with SD-OCT. Chen et al.[21] reported that nine of 25 patients had fundus pathologies. However, four of those patients had normal SD-OCT and visual field findings, and one patient had normal SD-OCT findings despite visual field defects. Although they reported visual field defects in eight patients, only one of those had pathological SD-OCT findings. The study conducted by Chen et al.[21] indicated that neither the visual field test nor SD-OCT individually is capable of detecting retinal toxicity induced by HCQ. In our study, evaluation using an objective measurement technique showed a correlation between the visual field parameters and retinochoroidal flow and a decrease in vascular density. This approach offers valuable data regarding the usage of OCTA as an objective complementary test in patients treated with HCQ. Considering that the probability of experiencing an adverse effect related to HCQ is 6.5% and the discontinuation rate of HCQ due to retinal toxicity is 1.8%, the determination of HCQ-induced retinal toxicity becomes increasingly important[3]. Accumulation of HCQ in the RPE has been well documented in previous studies[1]. OCTA could not demonstrate these deposits in the RPE layer; therefore, our OCTA findings concerning vascular damage attributed to HCQ toxicity in this study may serve as an adjunctive indirect marker rather than a direct indicator of HCQ toxicity. Furthermore, OCTA may be an alternative approach to the rapid and objective measurement of the macular flow in uncooperative patients who are incapable of confidently answering the visual field test.

Central retinal thickness was significantly reduced and negatively correlated with the HCQ dose in our study. Bulut et al.[14] did not observe any significant difference between the low- and high-risk groups with regard to central macular thickness in OCTA measurements. This discrepancy may be due to the inclusion of healthy controls in the present study. Ozek et al.[15] determined

that retinal thickness was significantly reduced in the temporal and inferior parafoveal areas in both the low- and high-risk groups versus those in the control group. Yulek et al.[22] reported that parafoveal retinal thickness was significantly decreased at 6 months post treatment compared with the pretreatment measurements by SD-OCT in 46 newly diagnosed and HCQ-treated patients. Notably, the perifoveal retinal thickness, ganglion cell complex, and retinal nerve fiber layer did not change. Yulek et al.[22] revealed that HCQ toxicity occurred mostly in the central parafoveal retina. It was especially significant in the superior, nasal, and temporal areas but not significant in the inferior parafoveal area. Using an adaptive optics camera that enables the evaluation of the photoreceptor layer, Babeau et al.[23] showed that HCQ-induced retinal toxicity in 38 HCQ-treated patients was significantly correlated with the daily dose and cumulative dose, especially in the inferior parafoveal area. Marmor et al.[17] reported that initial signs of HCQ-induced retinal toxicity were first detected in the inferior parafoveal area. In our study, the daily and cumulative doses were correlated with the superficial and deep vascular densities in all areas. Furthermore, daily dose and cumulative dose were highly correlated ($r>-0.7$) with the inferior area and poorly correlated ($r<-0.2$) with the whole other areas vessel density, in accordance with the previous studies indicating the localization of the retinal toxicity[15,17,23]. The correlation between the initial inferior parafoveal area of retinal damage and vessel density may lead to further studies for the early detection of retinal toxicity.

Fluorescein angiography (FA) is an established invasive imaging method. This technique requires the use of a dye, which is associated with the occurrence of adverse effects[24]. Although FA is useful for visualizing the retinal vasculature, its inability to show the distinct vascular structures of the different retinal layers may be a shortcoming in comparison with OCTA. OCTA allows the independent examination of the superficial and deep vascular plexi. Therefore, it may reveal early changes in the vascular tissue that arise in the nascent stages of certain diseases of vascular origin (e.g., diabetes) earlier than FA[25]. In addition, visualization of the deep retinal vascular plexus is not possible with FA. Ozek et al.[15] demonstrated vascular signs of HCQ toxicity only in the deep vascular plexus, which cannot be visualized using FA. We propose that HCQ-related vascular damage can be detected earlier and localized more effectively with OCTA versus FA.

The limitations of this study were the relatively small sample size and cross-sectional design. We are currently examining a larger sample and planning to present our data regarding long-term outcomes in the future. Longitudinal studies are warranted to determine the predictive value and clinical importance of such findings (especially the inferior area vessel density) in the screening of HCQ-induced maculopathy. Data of five patients who had deterioration of inner retinal layers were compared with those of other patients. Additionally, there are only two other studies in the literature that evaluated HCQ-induced retinal toxicity by measuring the macular microcirculation via OCTA. Thus, our findings need to be confirmed by other studies. Although rheumatic diseases are associated with vascular pathologies, our study was not homogeneous in terms of the presence of systemic diseases. This heterogeneity may also be a limitation of our study. Patients in the HCQ group had a significantly lower retinal thickness than healthy controls. Some researchers have reported that retinal thinning may significantly alter the retinal segmentation in SCP and DCP and cause errors in automatic calculations[26]. The choroid was measured using OCTA, which functions very poorly in visualizing the retinochoroidal interface and may significantly affect the reliability of the results. This should be taken into account in our statements regarding retinal and choroidal thickness or vascular density.

Early detection of HCQ-induced toxicity is crucial to avoid permanent retinal damage. However, achieving this aim through the use of only one monitoring modality may be difficult. We suggest that a combination of OCT, OCTA, visual field, and multifocal ERG tests within the capability of the clinic may offer earlier detection of HCQ-induced retinal toxicity. The OCTA approach provided objective macular perfusion measurements and revealed correlations between the cumulative and daily doses and between the inferior parafoveal deterioration and HCQ-induced retinal toxicity. Hence, this method may be useful as a complementary technique to visual field analysis and other monitoring techniques for HCQ-induced retinal toxicity.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

Influence of upper blepharoplasty on intraocular lens calculation

A influência da blefaroplastia superior no cálculo da lente intraocular

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ABSTRACT | Purpose: To determine the effect of upper blepharoplasty on corneal topography and intraocular lens power calculation using Galilei and IOLMaster. **Methods:** Thirty patients submitted to upper blepharoplasty from May 2014 to March 2017 at the Hospital Oftalmológico de Sorocaba (São Paulo, Brazil) were included in this observational case series. All patients underwent imaging sessions with Galilei and IOLMaster preoperatively (baseline) and at 1 and 6 months postoperatively. Primary outcome measures using both devices included flattest, average, and steepest corneal curvature, corneal astigmatism, and blepharoplasty-induced corneal astigmatism. Determination of axial length and lens power calculation were performed using only IOLMaster (Holladay formula). Paired t-test and vectorial analysis were used for statistical analysis. **Results:** Sixty eyes from 30 patients were prospectively included. Vectorial analysis showed that 6 months after surgery, blepharoplasty induced on average 0.39 D and 0.31 D of corneal astigmatism, as measured with Galilei and IOLMaster, respectively. IOLMaster measurements showed that average corneal curvature (44.56 vs 44.64 D, p=0.01), steepest corneal curvature (45.17 vs 45.31, p=0.01) and corneal astigmatism (1.22 vs 1.34, p=0.03) were higher 6 months after surgery. IOLMaster measurements also showed that intraocular lens power was significantly smaller 6 months after surgery (22.07 vs 21.93, p=0.004). All other parameters showed no change for comparisons between baseline and 6 months (p>0.05 for all comparisons). **Conclusion:** Upper eyelid blepharoplasty influenced intraocular lens calculation using the IOLMaster. However, the influence was not clinically significant. No topographic changes were found using Galilei.

Keywords: Blepharoplasty; Intraocular lens; Keratometry; Corneal topography; Biometry

RESUMO | Objetivo: Determinar o efeito da blefaroplastia superior na topografia corneana e no cálculo do poder das lentes intraoculares usando Galilei e IOLMaster. **Métodos:** Trinta pacientes submetidos a blefaroplastia superior de maio de 2014 a março de 2017 no Hospital Oftalmológico de Sorocaba, São Paulo, Brasil foram incluídos neste estudo de série de casos observacional. Todos os pacientes foram submetidos a sessões de imagem com Galilei e IOLMaster antes da cirurgia (exame de base) e no 1º e 6º mês pós-operatório. Os resultados primários utilizando os dois aparelhos incluíram ceratometria, astigmatismo corenano e astigmatismo corneano induzido pela blefaroplastia. O comprimento axial e o cálculo do poder da lente intraocular foram realizados unicamente com o IOLMaster (fórmula de Holladay). Teste-t pareado e análise vetorial foram usados na análise estatística. **Resultados:** Sessenta olhos de 30 pacientes foram incluídos prospectivamente. A análise vectorial mostrou que após 6 meses da cirurgia, a blefaroplastia superior induziu na média 0,39 D de astigmatismo corneano medido com o Galilei e 0,31 D com IOLMaster. As medidas com o IOLMaster mostraram que a ceratometria média (44,56 vs 44,64 D, p=0,01), ceratometria máxima (45,17 vs 45,31, p=0,01) e o astigmatismo corneano (1,22 vs 1,34, p=0,03) foram maiores após 6 meses da blefaroplastia. As medidas com IOLMaster mostraram que o poder da lente intraocular foi significativamente menor 6 meses após a blefaroplastia (22,07 vs 21,93, p=0,004). Todos os outros parâmetros não mostraram mudanças entre o pré-operatório e o 6º mês da cirurgia (p>0,05 para todas as comparações). **Conclusões:** A blefaroplastia superior influenciou o cálculo da lente intrao-

Submitted for publication: July 12, 2019
Accepted for publication: December 8, 2019

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Hospital Oftalmológico de Sorocaba (042/2011 FR:391914).

cular utilizando o IOLMaster. Contudo, a influência não foi clinicamente significativa. Não foram encontradas mudanças topográficas com o Galilei.

Descritores: Blefaroplastia; Lentes intraoculares; Ceratometria; Topografia da córnea; Biometria

INTRODUCTION

Dermatochalasis is an age-related condition, characterized by excessive skin at the upper eyelid, which can only be treated with surgery (i.e., upper blepharoplasty). Cataract is more frequent in the elderly and also only treated with surgery. Upper blepharoplasty and cataract surgery are two of the most commonly performed procedures in ophthalmology[1,2]. The timing of the procedures is an important concern for the ophthalmologist, because the pressure exerted by the superior eyelid can affect the corneal curvature and therefore influence the intraocular lens (IOL) power calculation for cataract surgery[3].

IOL power calculation has gained great interest in the era of refractive cataract surgery. In recent years, a growing number of devices have been developed to measure the clinical parameters necessary for the calculation of the IOL power[4]. These parameters include the flattest, average, and steepest corneal curvature, as well as the axial length.

Although previous studies have evaluated the changes on corneal curvature following blepharoplasty, this is the first study to use the Galilei and IOLMaster devices for this purpose. It is also the first study that evaluated the induced corneal astigmatism after superior blepharoplasty using vectorial analysis.

METHODS

This observational case series study, conducted from May 2014 to March 2017, included patients from the oculoplastic clinic at the Hospital Oftalmológico de Sorocaba (São Paulo, Brazil). Informed consent was obtained from all participants and all protocols were approved by the Hospital Ethics Committee. Methods attended to the tenets of the Declaration of Helsinki.

All patients underwent comprehensive ocular examination, including best-corrected visual acuity, ocular pressure measurement using Goldmann applanation tonometry, anterior biomicroscopy, and fundus examination at the preoperative visit (baseline). Moreover, at baseline and follow-up (1 and 6 months), patients underwent ancillary examinations with Galilei Dual Scheimpflug Analyzer G4 (Ziemer, Switzerland) and ocular biometry with IOLMaster 500 (Carl Zeiss Meditec Inc., Dublin, CA, USA). Inclusion criteria were best-corrected visual acuity of ≥20/40, ametropia <6 D, and dermatochalasis. Patients with coexisting corneal disease, macular pathology, glaucoma, uveitis, ptosis, and/or history of previous ocular or palpebral surgery were excluded.

Thirty patients scheduled for upper eyelid blepharoplasty were recruited from the oculoplastic clinic. Surgery was performed by residents or fellows using the same technique. After marking, the excessive skin was removed using a blade and scissors. If a prominent fat pad was present it was removed using cautery and scissors. The skin was sutured with 6-0 nylon sutures that were removed 1 week after surgery. To be included in the study patients had to attend to all visits.

Ancillary exams

The Galilei is a non-invasive device designed for the analysis of the anterior segment of the eye. It is based on a rotating dual-Scheimpflug camera integrated with a Placido topographer. This device captures slit images from opposite sides of the illuminated slit and averages the elevation data obtained from corresponding opposite slit images. The following corneal parameters provided by the Galilei were included and analyzed in our study: corneal curvature (flattest, average, and steepest) and corneal astigmatism (i.e., arithmetical difference between the flattest and steepest corneal curvatures). Anterior chamber depth (ACD) and axial length were not available for us. Therefore, Galilei was not used as a biometer.

The IOLMaster is an optical biometry device that emits infrared light at 780 nm and uses partial coherence interferometry to measure the ACD and axial length. For measurements of ACD, it uses a 0.7-mm-wide slit beam of light directed at a 30° angle into the anterior chamber. Subsequently, it measures the distance between the light reflection on the anterior corneal surface and the anterior crystalline lens surface. The device uses an average of five serial measurements along the visual axis to determine the final ACD value[5].

The IOLMaster also provides measurements of the corneal curvature. Together, these parameters are used to calculate the IOL power. Parameters provided by the IOLMaster and analyzed in our study included flattest corneal curvature, average corneal curvature, steepest corneal curvature, corneal astigmatism, axial length, and IOL power calculation using Holladay's formula for emmetropia. For a better description of the results, we

divided the IOL power changes in three groups: 1) changes ≤0.5 D; 2) changes >0.5 and ≤1 D; 3) changes >1 and ≤2 D

Statistical analysis

We performed a sample size analysis. Alpha (type I error) and beta (type II error) levels were set at 0.05 and 0.2, respectively. Effect size was set at 0.2. A conservative standard deviation of the outcome (in our case, the difference between IOL powers at 6-month follow-up and baseline) of 0.75 was used. Within-subject correlation of the outcome was set at 0.875. The number of eyes was estimated as 28[6].

Vectorial analysis was performed to evaluate the magnitude and axis of the blepharoplasty-induced corneal astigmatism. This approach for the study of the corneal astigmatism was first described by Alpins et al., in patients subjected to refractive surgery[7]. In our study, blepharoplasty-induced astigmatism was defined as the vectorial difference between the corneal preoperative and postoperative astigmatism (Figure 1). The following are the definitions used in this study:

a = preoperative astigmatism vector
b = postoperative astigmatism vector
c = blepharoplasty-induced astigmatism

As shown in figure 1, the vector ***c*** can be mathematically defined as

$$c = b - a$$

Any vector *v* can be described by its coordinates (x, y) in a Cartesian plane. In this study, the magnitude of the vector *c* was calculated using the following formula:

$$c = \left| \frac{y_b - y_a}{\sin\left\{\tanh^{-1}\left[\frac{(y_b - y_a)}{(x_b - x_a)}\right] \times 180/\pi\right\}} \right|$$

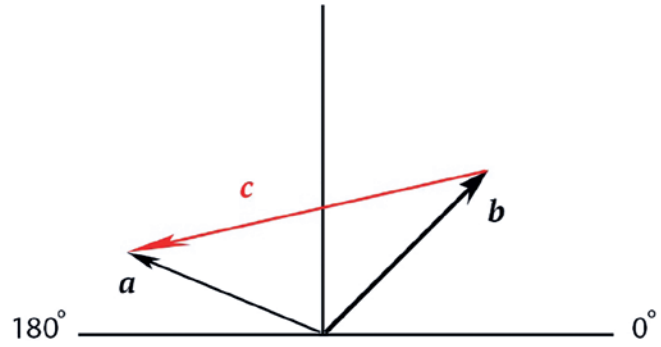

Figure 1. Diagram representing the relationship between preoperative astigmatism (***a***), postoperative astigmatism (***b***), and blepharoplasty-induced astigmatism (***c***).

The coordinates x and y can be determined by the following formulas, where *m* and *n* represent the magnitude and the axis of any astigmatism vector *v*:

$$x = m \times cos(2 \times n \times \pi/180)$$
$$y = m \times sin(2 \times n \times \pi/180)$$

Finally, the axis of the vector *c* can be determined by the following formula:

$$axis = \{\tanh^{-1}[(y_b - y_a), (x_b - x_a)]\times 180/\pi\}+90$$

Descriptive statistics included mean, standard deviation, 25th and 75th percentiles. In order to compare the studied parameters between visits a paired t-test was used. To account for potential correlation between eyes, the cluster of data for the studied subject were considered as the unit of resampling when calculating standard errors. This procedure has been used to adjust for the presence of multiple correlated measures of the same unit[8]. Specifically, in the ophthalmic literature, this procedure has been used to adjust for the presence of both eyes of the same patient in the study[9].

Statistical analyses were performed with Stata (version 12, StataCorp, College Station, TX, USA) and Microsoft Excel (version 16.12; Microsoft, Redmond, WA, USA) software. The alpha level (type I error) was set at 0.05.

RESULTS

A total of 60 eyes from 30 patients (27 females and 3 males), aged 47.7-74.4 years (mean: 58.5 years ± 6.9 years) were included in the study.

Table 1 shows the mean values (± standard deviation, 25th and 75th percentiles) of blepharoplasty-induced corneal astigmatism after 1 and 6 months using vectorial analysis. At 6 months, upper blepharoplasty induced on average 0.39 D of corneal astigmatism, as measured with Galilei and 0.31 D as measured with IOLMaster. After 6 months, 51 eyes had an IOL power change ≤0.5 D, 8 eyes had an IOL power change >0.5 and ≤1 D and only 1 eye had an IOL power change >1 and ≤2 D.

Figure 2A shows the vectorial display of induced corneal astigmatism 6 months after blepharoplasty measured with the Galilei. Figure 2B shows the vectorial display of induced corneal astigmatism 6 months after blepharoplasty measured with the IOLMaster. Vectors means on figures 2A and 2B are represented in red.

Table 2 shows mean values of Galilei and IOLMaster parameters at baseline and follow-up (1 and 6 months). Comparisons between baseline and 1-month parameters showed no change with both devices (p>0.05 for

Table 1. Mean ± SD (25th and 75th percentiles) of blepharoplasty induced corneal astigmatism 1 and 6 months after surgery measured with Galilei and IOLMaster using vectorial analysis.

	1 month		6 months	
	BIA (diopters)	BIA (degrees)	BIA (diopters)	BIA (degrees)
Galilei	0.41 ± 0.29 (0.17, 0.56)	81.32 ± 52.40 (32.92, 126.84)	0.39 ± 0.31(0.18, 0.56)	85.69 ± 48.84 (44.50, 130.00)
IOLMaster	0.43 ± 0.28 (0.22, 0.56)	101.56 ± 53.98 (59.74, 144.30)	0.31 ± 0.32 (0.09, 0.41)	89.70 ± 52.05 (41.00, 134.00)

BIA= Blepharoplasty-induced astigmatism; SD = Standard deviation.

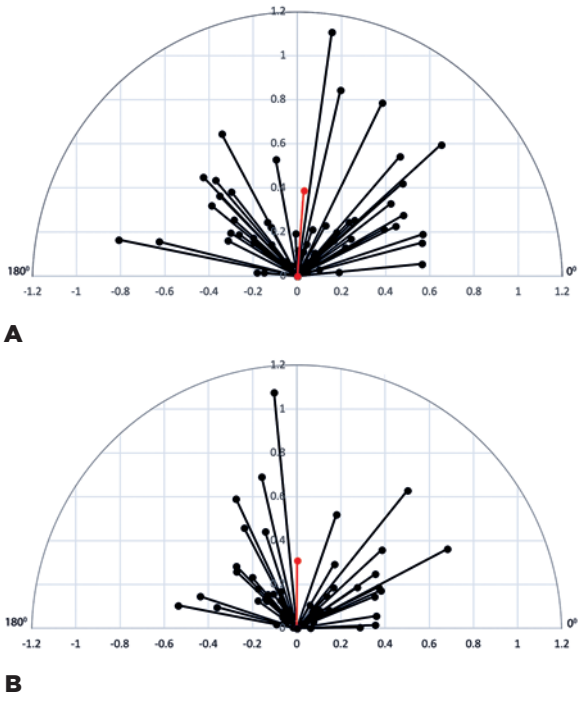

Figure 2. A) Vectorial display of induced corneal astigmatism 6 months after surgery measured with the Galilei. Vector mean (0.39 D at 85.69°) is represented in red. B) Vectorial display of induced corneal astigmatism 6 months after surgery measured with the IOLMaster. Vector mean (0.31 D at 89.70°) is represented in red.

all comparisons). Comparison between baseline and 6 months showed differences for four parameters provided by the IOLMaster. Average corneal curvature (44.56 vs 44.64, p=0.01), steepest corneal curvature (45.17 vs 45.31, p=0.01) and corneal astigmatism (1.22 vs 1.34, p=0.03) were higher after 6 months. IOL power was significantly smaller (22.07 vs 21.97, p=0.004) after 6 months of upper blepharoplasty. All other parameters showed no change for comparisons between baseline and 6 months (p>0.05 for all comparisons).

Figures 3 and 4 show box plot graphics for axial length and IOL power at baseline and follow-up (1 and 6 months) provided by the IOLMaster.

DISCUSSION

Corneal keratometry and axial length are parameters that have a large influence on IOL power calculation[10]. In our study, we analyzed the influence of upper blepharoplasty on these parameters and showed that this surgery influences IOL power calculation for cataract surgery. To the best of our knowledge, this is the first study to reach this conclusion using IOLMaster. Moreover, it is the first study to evaluate blepharoplasty-induced corneal astigmatism after upper blepharoplasty using vectorial analysis.

It is well established that the pressure of the upper eyelid on the cornea influences its shape[3]. Previous studies reported that eyelid surgery changes corneal curvature and that the extent of these changes is associated with more profound palpebral modifications. Removal of skin with blepharoplasty may lead to redistribution of the pressure applied by the lids over the cornea and consequently result in changes in the corneal shape and axial length measurements[11-13].

Dogan et al. described in a study with 30 patients that repositioning the upper eyelid through blepharoplasty seems to cause steepening in the steepest corneal curvature only in patients with some degree of ptosis (i.e., superior margin reflex distance <2.5 mm). There were no topographic changes found in patients with a superior margin reflex >2.5 mm[13]. Upper eyelid height also has an influence on corneal curvature. Although repair of ptosis influences the corneal curvature, we excluded patients with ptosis in this study. Therefore, we did not take into consideration the eyelid height in our analysis[14-17]. We used this approach to avoid possible confounding factors between surgeries on the interpretation of our results.

On the other hand, we cannot disregard the induced astigmatism calculated by the vectorial analysis. Minimal variations in corneal astigmatism may influence the indication of a toric IOL, especially for those who undergo implantation of bifocal or trifocal lenses[18]. Re-

Table 2. Mean values ± SD (25th and 75th percentiles) of Galilei and IOLMaster parameters during the follow-up (for baseline, 1 month and 6 months of follow-up).

Parameter	Baseline	1 month	6 months	p-value for baseline vs 1 month	p-value for baseline vs 6 months
Galilei					
Flattest corneal curvature (diopters)	44.05 ± 1.27 (43.06, 45.00)	44.03 ± 1.27 (43.00, 44.77)	44.07 ± 1.29 (43.15, 45.16)	0.68	0.61
Average corneal curvature (diopters)	44.65 ± 1.21 (43.95, 45.52)	44.65 ± 1.24 (43.86, 45.33)	44.69 ± 1.24 (43.86, 45.57)	0.93	0.29
Steepest corneal curvature (diopters)	45.26 ± 1.39 (44.20, 46.23)	45.27 ± 1.42 (44.33, 46.22)	45.30 ± 1.42 (44.38, 46.28)	0.80	0.19
Corneal astigmatism (diopters)	1.20 ± 1.12 (0.49, 1.45)	1.24 ± 1.05 (0.55, 1.42)	1.22 ± 1.10 (0.51, 1.35)	0.54	0.66
Corneal astigmatism axis (degrees)	91.83 ± 35.85 (72.50, 104.50)	90.60 ± 41.39 (73.50, 109.00)	93.48 ± 39.72 (74.50, 105.00)	0.82	0.54
IOLMaster					
Flattest corneal curvature (diopters)	43.95 ± 1.30 (42.99, 44.94)	43.94 ± 1.30 (42.88, 44.91)	43.96 ± 1.29 (43.02, 44.88)	0.81	0.49
Average corneal curvature (diopters)	44.56 ± 1.26 (43.73, 45.39)	44.60 ± 1.26 (43.82, 45.44)	44.64 ± 1.25 (43.92, 45.32)	0.17	0.01
Steepest corneal curvature (diopters)	45.17 ± 1.46 (41.14, 45.98)	45.25 ± 1.44 (44.26, 46.11)	45.31 ± 1.47 (44.41, 46.26)	0.07	0.01
Corneal astigmatism (diopters)	1.22 ± 1.14 (0.47, 1.33)	1.31 ± 1.10 (0.61, 1.40)	1.34 ± 1.16 (0.52, 1.52)	0.08	0.03
Corneal astigmatism axis (degrees)	98.51 ± 65.87 (21.50, 162.50)	93.50 ± 66.41 (10.50, 161.00)	101.6 ± 65.47 (37.50, 165.50)	0.54	0.71
Axial length (millimeters)	22.92 ± 0.76 (22.43, 23.55)	22.92 ± 0.76 (22.44, 23.55)	22.92 ± 0.76 (22.45, 23.54)	0.45	0.13
Intraocular lens power (diopters)	22.07 ± 2.09 (20.08, 23.54)	22.00 ± 2.06 (20.81, 23.34)	21.93 ± 2.10 (20.64, 23.39)	0.08	0.004

SD= standard deviation.

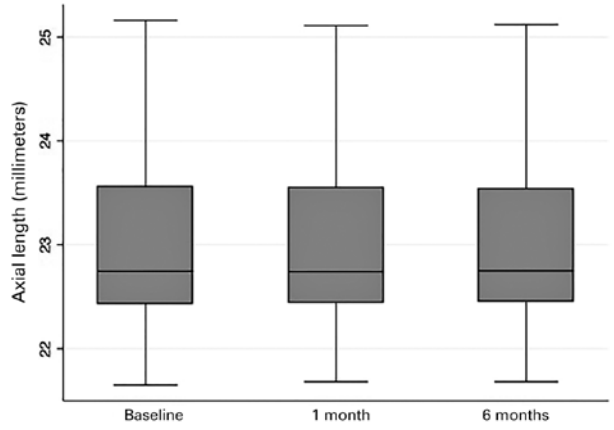

Figure 3. Box plot graphic for axial length at baseline and follow-up (1 and 6 months visits) measured with the IOLMaster.

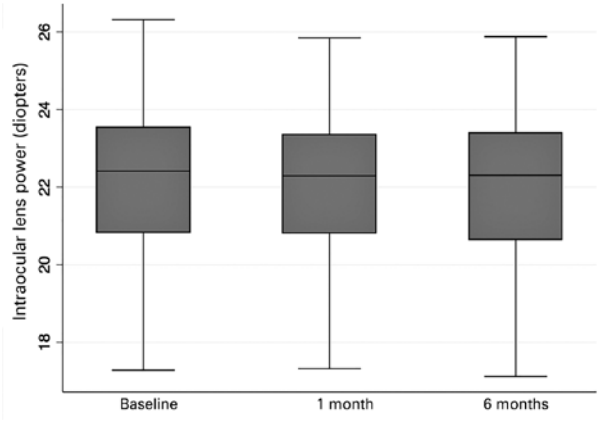

Figure 4. Box plot graphic for intraocular lens power at baseline and follow-up (1 and 6 months) provided by the IOLMaster.

sidual postoperative astigmatism after cataract surgery is an important source of visual complaints in these patients[19].

Interestingly, statistically significant corneal changes were found only in IOLMaster measurements. Our findings may be explained by the different methodology used by Galilei and IOLMaster to measure the corneal curvature. Galilei uses Placido rings and a series of Scheimpflug images to measure the corneal curvature using data from 1 to 4 mm of the central cornea. Conversely, the IOLMaster measures corneal curvature by the reflection of projected points in the 2.50 mm central cornea. The instrument measures the distances between opposite points, securing three meridians, and calculates the corneal curvature. Lopez de La Fuente et al. had previously reported differences between Galilei and IOLMaster when measuring the corneal curvature[20]. As discussed by the author, although these differences can be statistically significant, they are probably not clinically significant.

Changes on corneal curvature following upper blepharoplasty were probably responsible for changes in IOL power between baseline and after 6 months (22.07 D vs. 21.93 D, p=0.004). Although a statistical decrease in IOL power was found in our study, this change was not clinically significant, as a 0.14 D difference on lens selection will not greatly influence the visual outcome after cataract surgery. However, it is important to highlight that nine of 60 eyes (15%) had a change in IOL power calculation >0.5 D, which may lead to patient dissatis-

faction. Therefore, we suggest a personalized analysis in clinical practice, especially for patients with higher expectations and more severe dermatochalasis. In these cases, cataract surgery should be performed at least 6 months after palpebral surgery.

Our study had limitations. We did not perform IOL power calculations using the Galilei. According to the Galilei device, the corneal curvature remained unaltered after surgery. Thus, it was expected that the IOL power would also be similar after upper eyelid surgery. Moreover, differences in IOL calculations between Galilei and IOL Master in healthy patients were assessed by other authors and although minor differences have been reported they were not clinically significant[21]. We only used the Holladay formula to calculate the IOL power. Hence, further investigations are warranted to compare the results obtained using different formulas.

In conclusion, upper eyelid blepharoplasty influenced IOL power calculation for cataract surgery using the IOLMaster; however, this influence was not clinically significant. This change on IOL power is probably secondary to corneal curvature changes. Similar changes were not found in corneal tomographic parameters provided by the Galilei. Our findings are relevant due to the growing number of cataract and upper blepharoplasty surgeries performed on elderly patients.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

Association between keratoconus, ocular allergy, and sleeping behavior

Associação entre ceratocone, alergia ocular e comportamento ao dormir

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ABSTRACT | Purpose: To compare the severity and laterality of keratoconus according to allergic rhinitis, scratching and sleeping habits, and manual dexterity. **Methods:** Objective assessments regarding allergic rhinitis, eye itching, and sleeping position among patients with keratoconus (diagnosed based on corneal tomography) were conducted. Diagnostic criteria and classification were based on the Amsler-Krumeich classification. **Results:** Ocular pruritus was reported by 29 of 34 participants (85.29%). Eighteen participants (62.07%) reported equal scratching of both eyes, six (20.69%) more on the right eye, and five (17.24%) more on the left eye. Comparison of the main sleeping position and the eye with more severe presentation of the disease using Fisher's exact test revealed some correlations (0.567 and 0.568 in the right and left eye, respectively). However, these correlations were not statistically significant. **Conclusions:** The association between higher keratometry values and sleeping position appears to be more significant than that reported between keratometry and itching, or manual dexterity.

Keywords: Keratoconus; Hypersensitivity; Sleep/physiology; Rhinitis, allergic; Cornea; Tomography

RESUMO | Objetivo: Comparar a gravidade e a lateralidade do ceratocone de acordo com a rinite alérgica, os hábitos de coçar e dormir e a destreza manual. **Métodos:** Foram realizadas questões objetivas sobre rinite alérgica, prurido ocular e posição do sono em pacientes com ceratocone, diagnosticados com base na tomografia corneana. Esses exames foram analisados e classificados de acordo com a classificação de Amsler-Krumeich. **Resultados:** O prurido ocular foi referido por 29 (85,29%) dos 34 voluntários. Dezoito sujeitos (62,07%) relataram coçar ambos os olhos igualmente, 6 (20,69%) mais no olho direito e 5 (17,24%) mais no olho esquerdo. Comparando-se a posição de dormir principal e o olhos com apresentação mais grave da doença, foi encontrada alguma relação baseada no teste exato de Fisher (0,567 no olho direito e 0,568 no olho esquerdo), embora nenhuma comparação parecesse estatisticamente significante. **Conclusões:** A associação entre maiores valores de ceratometria e posição do sono parece ser mais importante do que entre ceratometria e prurido ou destreza manual.

Descritores: Ceratocone; Hipersensibilidade; Sono/fisiologia; Rinite alérgica; Córnea; Tomografia

INTRODUCTION

Keratoconus is the most common ectasic corneal disease. It is a noninflammatory disease characterized by a focal thinning of the cornea with increased corneal curvature due to the reduced biomechanical strength of the corneal collagen fibers. This condition ultimately leads to decreased visual acuity. Keratoconus is a progressive disease, especially in the first decade of life when the cornea exhibits less rigidity[1-6]. Although asymmetric, the disease is bilateral[7]. In a review of genetic studies, the majority of keratoconus in families present an autosomal-dominant inheritance pattern with a known genomic loci[1].

The prevalence of keratoconus in the general population is approximately 1 in 2,000 individuals (0.05%)[7]. Its etiology is multifactorial, combining environmental, genetic, and behavioral factors. Of note, its distribution differs worldwide; countries with less sun exposure have a lower prevalence than those with greater exposure[1-6]. However, it is thought that the higher prevalence may be attributed to ethnic and behavioral characteristics rather than direct sun exposure. However, the association between atopy and the act of eye rubbing has been esta-

Submitted for publication: February 27, 2019
Accepted for publication: December 8, 2019

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: Walton Nosé is a consultant of ALCON - a Novartis Division. Rodrigo Teixeira Santos, Bernardo Kaplan Moscovici, Flávio Hirai, Cláudia Maria Francesconi Benício, and Eliane Mayumi Nakano have no conflicts of interest to declare.

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Approved by the following research ethics committee: Universidade Federal de São Paulo (# 1.636.206)

blished as a trigger for the disease development and progression. In numerous studies, half of the participants with keratoconus reported that they rub their eyes, although these findings are variable in the literature. Other influential factors are the frequency and intensity of eye rubbing[8-11].

Microtrauma caused in the epithelium through the friction of the corneas generates high levels of matrix metalloproteinases (MMPs) (i.e., MMP-1 and MMP-13) and inflammatory mediators, including interleukin-6 (IL-6) and tumor necrosis factor-5 (TNF-5). The release of these factors is part of the processes that lead to the manifestation and progression of the disease. These processes include apoptosis of keratocytes as a result of the increased levels of IL-1 with subsequent loss of stromal volume[5,8].

Other factors, such as ethnicity, geographic location (possible exposure to ultraviolet radiation), and socioeconomic factors, are controversial[1-4]. Associations between keratoconus and other conditions, such as floppy eyelid syndrome (FES) and obstructive sleep apnea, were described in some studies presented at the Association for Research in Vision and Ophthalmology Meeting in 2012[12,13]. The strongest association was found with FES compared with sleep apnea. This finding could be due to the fact that the compression of eyes on the pillow may be sufficiently strong, leading to changes in the palpebral tarsus structure and keratoconus development[12,13].

The purpose of this study was to verify the relationship between the severity of keratoconus, eye rubbing, sleeping habits, manual dexterity and allergic rhinitis.

METHODS

Study design

This was a non-interventional comparative case series, conducted between May 2015 and July 2016 in the Department of Ophthalmology and Visual Sciences of the Federal University of São Paulo (São Paulo, Brazil). The study included individuals with keratoconus who were candidates for intrastromal corneal ring surgery. The study was approved by the Institutional Review Board (number: 1.636.206) and followed the tenets of the Declaration of Helsinki. All patients provided written informed consent.

Participants

Individuals with documented keratoconus were enrolled. The exclusion criteria were any previous ocular surgery, pregnancy or breastfeeding, presence of corneal degenerations (except keratoconus), and other ocular diseases that could influence the ocular examination. Individuals with major comorbidities, such as diabetes and collagen-related diseases, were also excluded.

The diagnosis of keratoconus was based on corneal tomography mapping (mean simulated keratometry >45.2 diopter (D), central corneal power >47.2 D, or inferior-superior asymmetry >1.4 D) using a Pentacam (OCULUS Optikgerate GmbH, Wetzlar, Germany).

Measurements

An examiner asked the participants objective questions regarding allergic rhinitis, eye rubbing, manual dexterity, and sleeping position. Another examiner collected the corneal tomography data of both eyes. We used the simulated central keratometry data of each eye, maximum keratometry (Kmax) in each eye, and Amsler-Krumeich classification for the analysis.

Statistical analysis

All data were collected and presented in contingency tables. Means ± standard deviation and frequencies (proportions) were presented for continuous and categorical variables, respectively. For categorical variables, between-group analysis was conducted at each follow-up visit using Fisher's exact test. Continuous variables were compared using the Mann-Whitney U test and the Pearson coefficient was used for correlation analysis. Statistical analysis was conducted using the Stata v.14 software (College Station, TX, USA), and p-values <0.05 indicated statistical significance.

RESULTS

A total of 34 individuals were evaluated, of whom 14 were females (41.2%) and 20 were males (58.8%). The mean ± standard deviation age was 26.5 ± 7.5 years (range: 17-49 years; median: 25.5 years). There was a weak negative correlation between age and Kmax values of the right eye (Pearson correlation coefficient: -0.321) and left eye (-0.189). There were no associations between age and the preferred eye for rubbing and preferred side for sleeping.

Table 1 presents the main characteristics of the study participants. The presence of allergic rhinitis and ocular itching was reported in 26 (76.5%) and 29 (85.3%) participants, respectively. All participants with allergic rhinitis reported ocular pruritus. Regarding the preferred rubbing eye, the distribution among the right, left,

and both sides was similar. Almost half of the participants were unsure of their preferred eye. When asked, 14 participants (41.2%) responded that they sleep most of the time on the right side, and 25 (73.5%) confirmed that they wake up in a position different from their initial sleeping position.

In this study, 19 participants (55.9%) had the worst degree of keratoconus in the right eye; 28 right eyes (82.3) versus 21 left eyes (65.6%) were classified as degree 4 (Table 2).

We compared the Kmax values of the right and left eyes between groups to investigate the influence of three characteristics (i.e., preferred rubbing eye, preferred sleeping side, and hand dominancy). We hypothesized that the keratometric values of these characteristics would be higher in accordance with the preferred side (Table 3). Although none of the differences were statistically significant, we observed a tendency for Kmax values to be higher in accordance with the preferred side for sleeping.

Table 1. Characteristics of the study participants (*N*=34)

Allergic rhinitis	
Yes	26 (76.5)
No	8 (23.5)
Ocular itching	
Yes	29 (85.3)
No	5 (14.7)
Eye rubbing, preferred eye	
Right eye	5 (14.7)
Left eye	6 (17.6)
Both	5 (14.7)
Not sure	18 (53.0)
Sleeping position, preferred side	
Right	14 (41.2)
Left	7 (20.6)
Other position	13 (38.2)
Change of position during sleep	
Yes	25 (73.5)
No	9 (26.5)

Data are expressed as frequency (proportion).

Table 2. Amsler-Krumeich classification of each eye of study participants

Amsler-Krumeich classification	Right eye (*N*=34)	Left eye (*N*=32)
0	1 (2.9)	2 (6.3)
1	1 (2.9)	3 (9.4)
2	2 (5.9)	5 (15.6)
3	2 (5.9)	1 (3.1)
4	28 (82.4)	21 (65.6)

Data are expressed as frequency (proportion).

DISCUSSION

The analysis of these data indicates the tendency between higher keratometric values and preferred side for sleeping; however, we did not observed the tendency between higher keratometric values and preferred eye for rubbing. Other studies found a relationship between keratoconus and ocular itching. We could not find a statistically significant relationship between eye rubbing and increased keratometry. However, in our daily practice, we observed that eye rubbing is strongly correlated with keratoconus.

In an investigation including only individuals with clinical unilateral keratoconus, the authors observed a tendency for patients to sleep on the same side with the eye that is most severely affected or the eye with a progressing disease. Some of these patients slept with their hand or fist positioned directly against their eyelid and were more likely to hug their pillow in a manner that caused compression around their eyes[14].

A study investigating the sleeping position through lisamine green staining demonstrated a difference between back sleeping and left-side sleeping (analysis of variance, p=0.005). The Ocular Surface Disease Index score was also increased in patients who slept on their right or left side (36.4 and 34.1, respectively) as opposed to those who sleep on their back (26.7) (p=0.05).

Table 3. Comparison of maximum keratometry (Kmax) of right and left eyes according to the characteristics of the participants (*N*=34)

	Rubbing		
	Prefer right eye	Prefer left eye	*p*-value
Kmax, OD	59.8 ± 10.4	59.5 ± 7.6	0.952
Kmax, OS	56.8 ± 5.2	54.4 ± 7.0	0.552
	Sleeping side		
	Prefer right side	Prefer left side	*p*-value
Kmax, OD	63.6 ± 5.6	58.6 ± 7.7	0.103
Kmax, OS	57.7 ± 7.7	61.2 ± 5.8	0.329
	Dominant hand		
	Right	Left	*p*-value
Kmax, OD	61.8 ± 5.8	59.9 ± 5.9	0.598
Kmax, OS	58.4 ± 6.3	58.0 ± 10.7	0.921

Data are expressed as mean ± standard deviation.
OD= oculus dexter; OS= oculus sinister.

There was no statistically significant correlation between the sleeping position and degree of meibomian gland dysfunction[15]. In a Japanese study, poor sleep quality was associated with dry eye disease, especially dry eye symptoms[16,17].

Normal eyelid closure has also been linked to the development of several ocular surface disorders. Sleep disorders are common; obstructive sleep apnea (the most common disorder) is associated with a number of serious systemic diseases and several eye disorders, including FES, optic neuropathy, glaucoma, anterior ischemic optic neuropathy, and papilledema secondary to increased intracranial pressure. At the onset of sleep, the lids are closed, and the position of the globes, as judged by the position of the cornea behind the closed lids, is generally elevated. Lagophthalmos may cause corneal exposure that results in pain and foreign body sensation upon waking[18,19]. These effects could induce eye rubbing.

In another study, Bawazeer et al. found an association between keratoconus and atopy, as well as eye rubbing and family history of keratoconus. However, in the multivariate analysis, only eye rubbing remained a significant risk factor for the development of keratoconus (odds ratio = 6.31)[20]. These findings support the hypothesis that eye rubbing is the most significant cause of keratoconus. Atopy may contribute to keratoconus, most probably *via* eye rubbing due to itching. In that study, there were no other variables significantly associated with the etiology of keratoconus[20].

In a study investigating the association between corneal curvature and eye itching severity, it was verified that the most curved corneas were present in the eyes with more frequent and intense pruritus[21]. A series of cases also verified the asymmetric expression of keratoconus and found that individuals habitually rubbed the most affected eye[21-23].

The technique used by many individuals with keratoconus to rub their eyes is usually different from that used by those without keratoconus[24]. Individuals with keratoconus tend to use more often the fingertips or even the distal interphalangeal joints to vigorously rub their eyes[14].

An Australian study, involving 64 participants wearing contact lenses (half with keratoconus and half without corneal ectasia), found a significant increase in ocular pruritus after contact lens removal in the keratoconus group. The mean duration of pruritus was significantly longer in the group with keratoconus than without ectasia (27.7 vs. 14.4 s, respectively)[10].

Recently, an increasing body of evidence suggests that inflammatory pathways may play a significant role in the development of keratoconus. Several studies have investigated the role of proteolytic enzymes, such as MMPs, in keratoconus. MMPs are involved in the degradation of the extracellular matrix or activation of cellular apoptosis[25]. In the human cornea, MMPs are secreted by epithelial cells, stromal cells, and neutrophils[26]. In keratoconus, the cornea expresses increased levels of MMP-117 and MMP-13[27]. The tear analysis in keratoconus has revealed increased levels of MMP-1, MMP-3, MMP-7, and MMP-13[28]. Increased gelatinolytic and collagenolytic activities have also been reported in the cornea[29-31] and tear film of patients with keratoconus[28].

MMP-9 activity is also high in the tear fluid of patients with keratoconus. Hence, the increase in MMP-9 levels is correlated with corneal thinning, probably as a result of stromal collagen degradation[28]. In addition, TNF-α disrupts the barrier function of corneal epithelial cells. The type of cell from which the production of TNF-α in keratoconus originates remains unknown. However, TNF-α can be produced by a variety of cells, including all three major cell types in the cornea: the corneal epithelium, stromal keratocytes, and endothelial cells. Perhaps, corneal damage induced by environmental factors causes the production of TNF-α. For example, eye rubbing and dry eye disease are major risk factors for developing KC and are associated with the induction of TNF-α production by corneal epithelial cells[32-34].

The total tear protein level was significantly reduced in individuals with keratoconus (4.1 ± 0.9 mg/ml) compared with healthy individuals (6.7 ± 1.4 mg/ml) ($p<0.0001$) or those who had undergone corneal collagen cross-linking (5.7 ± 2.3 mg/ml) ($p<0.005$)[28]. In a study of healthy participants, there was an increase in the concentration of MMP-13 and inflammatory molecules IL-6 and TNF-α after 60 s of ocular pruritus[8].

The exact mechanism through which keratoconus worsens due to the mechanical trauma caused by eye rubbing or scratching has not yet been elucidated. It has been proposed that IL-1 plays a major role in this process. Wilson et al. suggested that the increased expression of the IL-1 receptor sensitizes the keratocytes to IL-1 released from the epithelium or endothelium. This effect causes loss of keratocytes through apoptosis and a decrease in stromal mass over time. This hypothesis supports that the occurrence of keratoconus is related to eye rubbing, use of contact lenses, and atopy, presuming that epithelial microtrauma leads to an increased release of IL-1 from the epithelium[35,36].

Our study had some limitations. First, this study may have not been statistically powered to detect associations due to the small sample size. Second, characteristics, such as eye rubbing and sleeping side, were reported by the participants without a more objective assessment. However, our findings support the importance of allergy control and eye trauma avoidance among those at risk of developing keratoconus.

In conclusion, our study revealed a tendency of the eyes with most advanced degrees of keratoconus to be associated with allergy, eye rubbing, and preferred sleeping side.

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ORIGINAL ARTICLE

Arquivos Brasileiros de Oftalmologia

Thermography in clinical ophthalmic oncology

Termografia em oncologia oftalmológica clínica

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ABSTRACT | Purpose: The aim of this study was to present our own experience with the use of thermography as a complementary method for the initial diagnosis and differentiation of intraocular tumors, as well as for the evaluation of the efficacy of treatment of intraocular melanomas. **Methods:** The study group comprised 37 patients with intraocular tumors, including 9 with uveal melanoma, 8 with uveal melanoma after I^{125} brachytherapy, 12 with a focal metastasis to the uvea, and 8 with retinal capillary hemangioblastoma. A FLIR T640 camera was used to capture images in the central point of the cornea, eye area, and orbital cavity area. **Results:** Eyes with uveal melanoma had higher temperature compared with the fellow normal eye of the patient in the range of all measured parameters in the regions of interest. In the group of patients with melanoma after unsuccessful brachytherapy, higher temperature was observed at the central point of the cornea. In patients with tumor regression, all measured parameters were lower in the affected eye. We observed lower temperatures in the range of all tested parameters and areas in eyes with choroidal metastases. Eyes with diagnosed intraocular hemangioblastoma were characterized by higher parameters for the regions of interest versus eyes without this pathology. **Conclusions:** A thermographic examination of the eye can be used as an additional first-line diagnostic tool for the differentiation of intraocular tumors. Thermography can be a helpful tool in monitoring the treatment outcome in patients with intraocular melanoma.

Keywords: Thermography; Uveal neoplasm; Melanoma; Neoplasm metastasis; Eye neoplasm/secondary; Hemangioblastoma

RESUMO | Objetivo: O objetivo deste estudo foi de apresentar a nossa experiência no uso da termografia como método complementar para o diagnóstico inicial e a diferenciação de tumores intraoculares, bem como para a avaliação da eficácia do tratamento de melanomas intraoculares. **Métodos:** O grupo estudado compunha-se de 37 pacientes com tumores intraoculares, sendo 9 com melanoma uveal, 8 com melanoma uveal após braquiterapia com I^{125}, 12 com metástases focais na úvea e 8 com hemangioblastoma capilar retiniano. As imagens do ponto central da córnea, da área do olho e da área da cavidade orbital foram obtidas com uma câmera FLIR T640. **Resultados:** Os olhos dos pacientes com melanoma uveal tinham temperaturas mais elevadas do que as dos olhos normais dos mesmos, em toda a faixa dos parâmetros medidos nas regiões de interesse. No grupo de pacientes com melanoma após braquiterapia mal sucedida, encontrámos temperaturas maiores no ponto central da córnea. Nos pacientes com regressão do tumor, todos os parâmetros medidos foram menores no olho acometido. Encontrámos temperaturas mais baixas em toda a faixa dos parâmetros testados e das áreas medidas nos olhos com metástases na coroide. Os olhos com hemangioblastoma intraocular diagnosticado caracterizaram-se por parâmetros mais elevados nas regiões de interesse, em comparação com olhos sem essa patologia. **Conclusões:** O exame termográfico do olho pode usar-se como ferramenta de diagnóstico adicional de triagem na diferenciação de tumores intraoculares. A termografia pode ser uma ferramenta útil no acompanhamento do desfecho do tratamento em pacientes com melanoma intraocular.

Descritores: Termografia; Neoplasias uveais; Melanoma; Metástases neoplásicas; Neoplasias oculares/secundário; Hemangioblastoma

INTRODUCTION

Thermography is an imaging technique which detects radiation in the long-infrared range of the electromagnetic spectrum emitted by various objects, including human tissues. Radiation is emitted at temperatures above absolute zero, i.e., -273.15°C or 0 K(1). A ther-

Submitted for publication: March 22, 2019
Accepted for publication: December 8, 2019

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Bioethics Committee of the Medical University (# KB-0012/141/15)

mographic camera shows the exact value and distribution of the temperature of the examined surface, which depends on the vascularization and metabolism of the tissue. This technique captures thermal images, which are actually visual displays of the amount of infrared energy transmitted, emitted, or reflected by the tissue.

The search for thermal imaging applications in medicine was initiated in the 20th century. Thus far, most attempts focused on the use of this technique in the detection of breast cancer. Studies have demonstrated that thermography can be used to define the boundary between the area of normal tissue and the area of tissue affected by cancer[2,3]. Thermography is a safe, noninvasive, and reproducible imaging technique that can be used for screening in the early diagnosis of cancer. However, this diagnosis has to be confirmed by mammography, ultrasonography (US), and histopathological examination.

It is often difficult to differentiate between malignant and benign intraocular tumors or to determine the tumor grade and its type, especially in cases of amelanotic changes and those accompanied by retinal detachment. The diagnosis usually relies on the examination of morphological changes in the fundus, US in A and B projections, color Doppler imaging (CDI), optical coherence tomography, fluorescein angiography (FA), or indocyanine green angiography[4]. The diagnosis and qualification for treatment strongly depend on the experience of the examiner or person assessing the results of the tests. Aside from histopathological examination, there are very few objective methods for differentiating neoplastic lesions and evaluating the efficacy of treatment in patients with intraocular tumors.

This article presents our own experience with the use of thermography as a complementary method for the initial diagnosis and differentiation of intraocular tumors, as well as for the evaluation of the efficacy of treatment of intraocular melanomas.

METHODS

This was an analytical, prospective, cross-sectional study. The study group comprised patients with suspected intraocular tumors treated at the Ophthalmology Department, Pomeranian Medical University (Szczecin, Poland), from 2016 to 2018 (convenience sampling). A total of 37 patients were diagnosed with intraocular tumors based on clinical examination and imaging studies (i.e., US, CDI, FA, and optical coherence tomography). The study group included 9 patients with uveal melanoma, 8 patients with uveal melanoma after 6-month brachytherapy with I^{125} (4 without improvement after treatment and 4 in remission), 12 patients with a focal metastasis to the uvea (4 with primary breast cancer, 1 with lung cancer, and 7 with primary cancer of unknown location), and 8 patients with retinal capillary hemangioblastoma with Von Hippel-Lindau syndrome. Remission of tumor after brachytherapy involves a decrease in tumor height and increase in internal reflectivity[5]. Patients with ophthalmic conditions (e.g., dry eye syndrome, glaucoma, ocular inflammation, age-related macular degeneration) and fever, potentially disturbing the measurement of thermal emission on the eye surface were excluded from the study. An ophthalmic interview was conducted in the study group. A FLIR T640 thermographic camera was used to capture facial images (thermographic and optical) of each patient in three replications, perpendicularly to the examined area, 3 s after blinking, at a distance of 1 m after resting for 15 min in the examination room. Room temperature and air humidity were relatively stable, and the examination room was isolated from external sources of heat, air conditioning, or solar radiation. Images were captured at short intervals (every 1 s), which reduced the impact of variability on the external environment. The average of three measurements in each patient did not exhibit a significant standard deviation. The test area (eyeball) did not change its metabolic activity over time; hence, it can be assumed that the temperature of the test area was constant throughout the examination.

The protocol was approved by the Bioethics Committee of the Medical University (Approval No. KB-0012/141/15).

Images were processed using the ImageJ software for image analysis in the MATLAB environment. The following regions of interest were analyzed: the central point of the cornea in the left and right eyes, left and right eyes (area), and left and right orbital cavities (area). The area of the eye was delineated manually after the superimposition of the thermographic image as the surface of the eye between eyelids and the orbital cavity (Figure 1A). The last area was delineated as an ellipse with a minor axis equal to a double distance between the center of the pupil and the upper edge of the eye, and the major axis equal to 0.6 of the distance between the center of the pupil and the left/right margin of the eye (Figure 1B), and superimposed onto the optical image.

All thermal imaging tests and digital image analysis were conducted by a single investigator. The investigators were not aware which eye was affected or which type of tumor was diagnosed. Informed consent for the capture and publication of images was provided by all participants in this study.

For the statistical analysis of the results obtained from individual groups, Student's t-test for paired samples was employed to compare the mean values of individual temperature parameters (mean, standard deviation, minimum, maximum, median, and mode) in the affected and normal eyes.

The effect of age, sex, tumor type, and the presence of an intraocular tumor (affected vs. normal eye) on the median temperature was analyzed using a general linear model with repeated measures.

All calculations were performed using the Statistica software (v. 13; Dell Inc., Tulsa, OK, USA). A $p \leq 0.05$ indicated statistical significance.

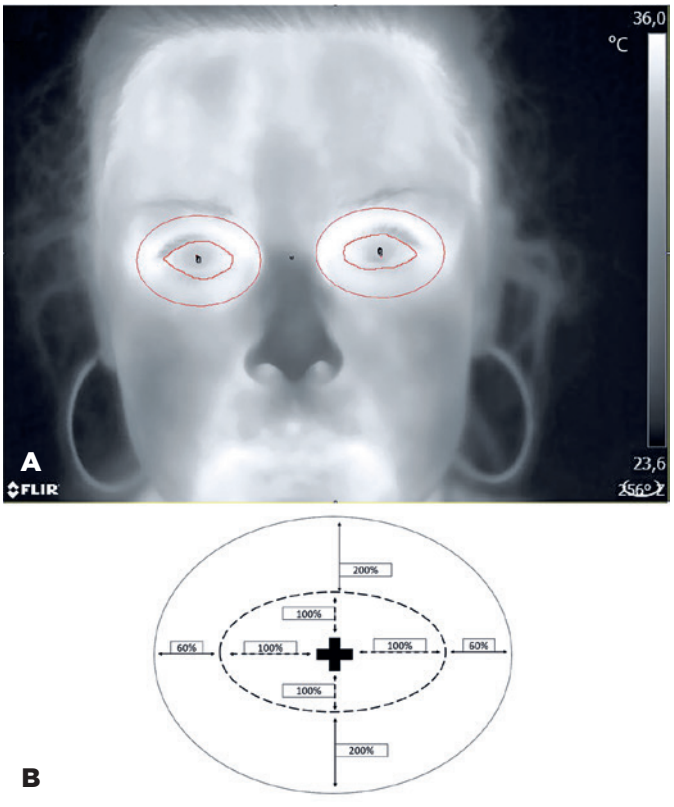

Figure 1. A) The analyzed area of the eye delineated as the surface between the eyelids and the orbital cavity delineated on the optical image and superimposed on the thermal image. B) Margins of the orbital cavity in the form of an ellipsoidal area with a minor axis equal to a double distance between the center of the pupil and the upper edge of the eye and the major axis equal to 0.6 of the distance between the center of the pupil and the left/right margin of the eye.

RESULTS

The characteristics of the study group are presented in table 1. The results of the thermographic analysis of intraocular tumors in the study group (without classification to specific types of tumor) are presented in table 2. The median temperature was selected for further study due to its desired properties (i.e., insensitivity to outliers and strong statistically significant correlations with the remaining temperature parameters). There were no significant differences between the affected and normal eyes; however, the affected eyes had a higher temperature than the normal eyes.

Selected thermal images of patients from specific subgroups are presented in figures 2-4. The results of the thermographic analysis of intraocular tumors with classification to specific types of tumor (five groups) are presented in table 3. Significant differences in the mean values ($p \leq 0.05$) between the affected and normal eyes were observed in Group 1 (uveal melanoma) for the temperature at the central point of the cornea, median and mode temperature of the eye, and mean, median, and mode of the temperature of the area of the orbital cavity; standard deviation for the temperature of the area of the eye in Group 3 (melanoma after successful treatment); and mean and median temperature of the area of the orbital cavity in Group 4 (intraocular metastases).

Table 1. Demographic characteristics of examined patients

			Age (years)		Female		Male	
Group	Description	n	Mean	SD	n	%	n	%
1	Melanoma without treatment	9	73.89	9.78	2	22.22	7	77.78
2	Melanoma after treatment (relapse)	4	67.50	19.23	2	50.00	2	50.00
3	Melanoma after treatment (regression)	4	57.50	12.07	1	25.00	3	75.00
4	Metastasis	12	67.92	12.77	9	75.00	3	25.00
5	Retinal capillary hemangioblastoma	8	44.50	22.05	5	62.50	3	37.50
Total		37	63.14	18.11	19	51.35	18	48.65

n= number of patients; SD= standard deviation.

Table 2. Mean, median, and standard deviations for temperatures measured at the three regions of interest of affected and normal eyes (*n*=37)

		Affected		Normal	
ROI	Variable	Mean	SD	Mean	SD
Central point of the cornea	Mean	33.63	1.07	33.54	1.14
Area of the eye	Median	34.31	0.90	34.27	0.93
Area of the orbital cavity	Median	34.44	0.81	34.37	0.82

Median denotes the middle value in a series arranged from the lowest to the highest, separating the same number of observations on both sides.
ROI= region of interest; SD= standard deviation.

A significant effect of the investigated factors on the median temperature was only noted in subgroups distinguished based on the presence of the intraocular tumor and the type of tumor (p≤0.05). There were significant differences in the median surface temperature of the orbital cavity between Group 1 (untreated uveal melanoma) and Group 3 (uveal melanoma after successful brachytherapy), as well as between Group 2 (uveal melanoma after unsuccessful brachytherapy), Group 3 (uveal melanoma after successful brachytherapy), and Group 5 (retinal capillary hemangioblastoma) (p≤0.05).

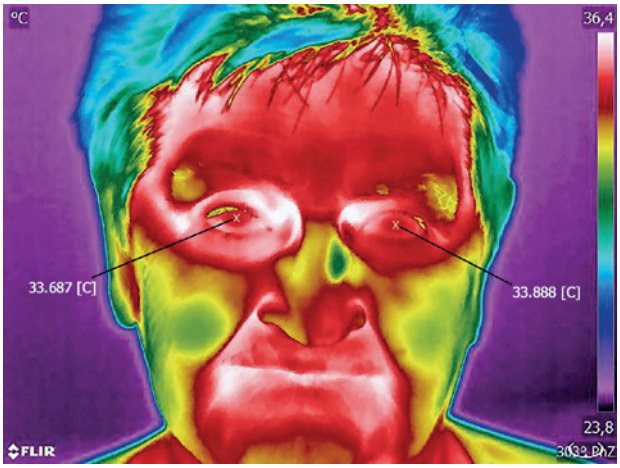

Figure 2. Uveal melanoma of the right eye.

DISCUSSION

According to the analysis of the available literature, the mean temperature of the surface of the eye was 34.02°C ± 0.22 (standard deviation [SD]). There was no significant difference found in temperature between the right and left eyes, or between males and females[6]. There was no correlation between the thickness and density of the cornea, the length of the anterior chamber of the eye, and the temperature of the surface of the eye[7]. Other studies did not report differences in the thermo-

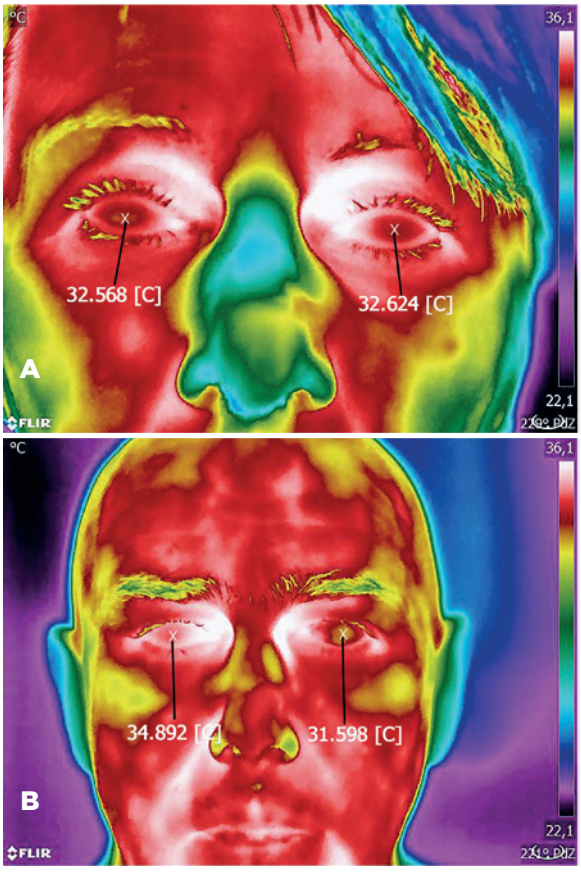

Figure 3. A) Uveal melanoma in the left eye after unsuccessful brachytherapy. B) Uveal melanoma in the left eye after successful brachytherapy.

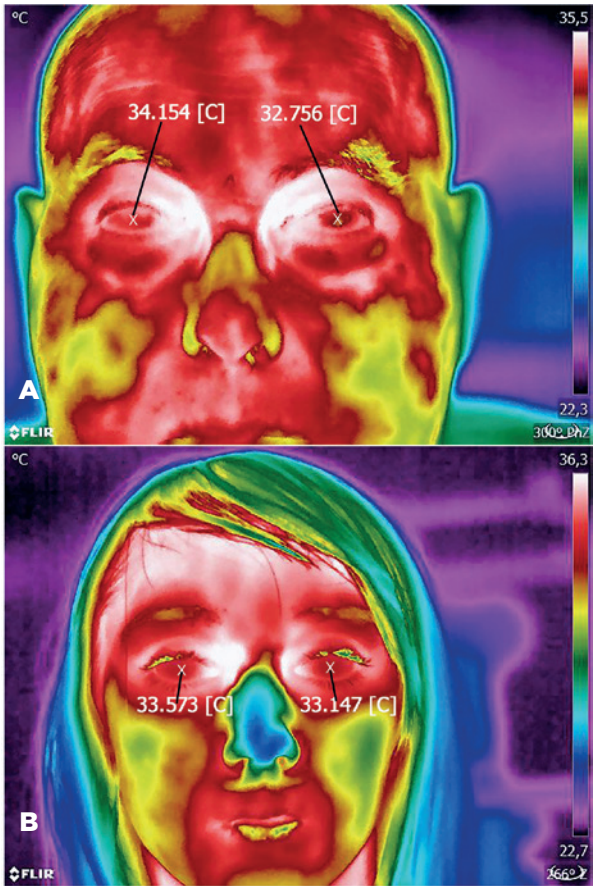

Figure 4. A) Focal metastasis to the uvea in the left eye. B) Retinal capillary hemangioblastoma in the right eye.

Table 3. Mean and standard deviations for temperatures measured at the three areas of affected and normal eyes, grouped according to the types of intraocular tumors

			Affected		Normal	
Group	**ROI**	**Variable**	**Mean**	**SD**	**Mean**	**SD**
1. Melanoma without treatment (n=9)	Central point of the cornea	T	34.25[a]	0.78	33.75[b]	0.89
	Area of the eye	Mean	34.60	0.85	34.38	0.76
		SD	0.84	0.76	0.63	0.21
		Median	34.72[a]	0.68	34.27[b]	0.83
		Mode	34.72[a]	0.92	34.00[b]	1.00
	Area of the orbital cavity	Mean	34.49[a]	0.64	34.13[b]	0.58
		SD	1.12	0.39	1.01	0.15
		Median	34.62[a x y]	0.70	34.04[b]	0.64
		Mode	35.26[a]	0.65	34.23[b]	1.21
2. Melanoma after treatment (relapse) (n=4)	Central point of the cornea	T	34.13	1.10	33.15	0.97
	Area of the eye	Mean	34.83	0.46	34.25	0.46
		SD	0.85	0.36	0.91	0.39
		Median	34.86	0.68	34.14	0.61
		Mode	34.87	1.58	34.04	1.41
	Area of the orbital cavity	Mean	34.96	0.53	34.52	0.24
		SD	1.04	0.26	1.14	0.17
		Median	35.09[x]	0.71	34.61	0.42
		Mode	36.33	0.40	34.98	1.20
3. Melanoma after treatment (regression) (n=4)	Central point of the cornea	T	33.37	1.38	34.71	1.19
	Area of the eye	Mean	34.20	0.98	35.10	1.18
		SD	0.86[a]	0.34	0.54[b]	0.24
		Median	34.13	1.05	35.09	1.20
		Mode	33.40	1.34	35.22	1.32
	Area of the orbital cavity	Mean	33.70	0.23	34.58	1.38
		SD	1.36	0.39	0.95	0.44
		Median	33.82[z]	0.24	34.70	1.36
		Mode	34.27	1.35	35.27	1.66
4. Metastasis (n=12)	Central point of the cornea	T	33.23	1.06	33.37	0.99
	Area of the eye	Mean	34.02	0.89	34.30	0.75
		SD	0.80	0.23	0.83	0.33
		Median	33.99	0.98	34.28	0.81
		Mode	33.73	1.12	34.52	0.87
	Area of the orbital cavity	Mean	34.28[a]	0.82	34.51[b]	0.76
		SD	1.06	0.21	1.01	0.13
		Median	34.37[a x y z]	0.93	34.62[b]	0.82
		Mode	34.88	1.28	35.33	1.24
5. Retinal capillary hemangioblastoma (n=8)	Central point of the cornea	T	33.40	1.04	33.14	1.44
	Area of the eye	Mean	34.13	0.81	33.99	1.10
		SD	0.80	0.24	0.80	0.33
		Median	34.13	0.94	33.92	1.16
		Mode	34.14	1.08	33.36	1.46
	Area of the orbital cavity	Mean	34.29	0.68	34.08	0.71
		SD	1.08	0.35	1.09	0.39
		Median	34.32[y z]	0.81	34.10	0.78
		Mode	35.07	1.30	34.94	1.30

Differences among groups calculated only for the median temperature. [a, b]= different superscript letters within rows indicate significant differences ($p \leq 0.05$), [x, y, z]= different superscript letters within columns indicate significant differences ($p \leq 0.05$). Median denotes the middle value in a series arranged from the lowest to the highest, separating the same number of observations on both sides. Mode denotes the value that appears most often or the value that is most likely to be sampled.
T= temperature of a single pixel; SD= standard deviation.

graphic analysis between the left and right sides of the face[8]. It is also thought that the physical characteristics of patients (i.e., body hair, obesity, and skin lesions) exert a limited effect on the acquired thermograms due to the analyzed body region[9].

The analysis of demographic data in the studied groups revealed that intraocular hemangiomas were usually detected in younger subjects at a mean age of 44.5 years (SD: ±22.05) and more often in females; metastases and intraocular melanomas were more frequent in elderly subjects. The mean age at diagnosis was 67.92 years (SD: ±12.77) and 73.89 years (SD: ±9.78) for intraocular metastasis and uveal melanoma, respectively. Intraocular metastases and melanoma were more frequent in females and males, respectively (Table 1).

In the examined group, melanoma in the ophthalmoscopic examination appeared as a dark brown tumor, usually located in temporal quadrants; metastases appeared as a bright, off-white tumors. In the ophthalmoscopic examination, retinal hemangioblastoma appeared as a red-orange tumor that lifted the retina, usually with a diameter of 1-1.5 dd (size of the optic disc), occasionally accompanied by retinal exudate, exudative retinal detachment, and dilated and tortuous retinal vessels.

Uveal melanoma

There are single reports regarding the use of thermography as a diagnostic method for intraocular tumors. In 1971, Kruszewski reported that certain cancers (e.g., uveal melanoma or vascular tumors) are visualized in thermography as hot lesions[10]. This hypothesis has been supported by other investigators who observed higher corneal surface temperature in melanoma of the uvea and conjunctiva compared with the normal eyes[11]. Santa Cruz et al. found higher temperature by approximately 2-4 K in cutaneous melanoma compared with normal skin[12]. Other researchers reported the suitability of thermography for the differentiation between melanoma and benign cutaneous tumors with a size >15 mm[13]. Uveal melanoma on CDI examination is characterized by a greater mean maximum blood flow in the central retinal artery and posterior ciliary arteries compared with benign orbital cavernous hemangioma and eyes without any pathology[14].

There are also studies indicating that melanomas are tumors with significant thermal activity, which is caused by neoangiogenesis and abnormal vessel morphology in the tumor mass and the high metabolic activity of tissues[15]. Yang et al. reported increased pulsatile ocular blood flow and total choroidal blood flow in eyes with uveal melanoma[16].

There are also reports emphasizing the significant role of the microenvironment and immune system in the progression of melanoma[17]. Uveal melanoma is a tumor that secretes macrophage pro-inflammatory cytokines, triggering an inflammatory reaction[1]. Studies on melanoma have demonstrated that chemokines, e.g., growth-regulated oncogene α (GROα)/CXCL1, GROβ/CXCL2, GROγ/CXCL3, and interleukin-8 (IL-8)/CXCL8, control the proliferation of cancer cells[18]. Another study revealed increased levels of pro-inflammatory and pro-angiogenic cytokines, such as IL-6, IL-8, interferon gamma-γ, monocyte chemoattractant protein-1, and vascular endothelial growth factor, in eyes with uveal melanoma compared with controls[19]. A relationship between cancer and inflammation was first described in 1863 by Virchow. Since then, numerous studies have confirmed the impact of chronic inflammation on the progression and growth of melanoma[20].

Our study supports the above observations. Examination using a thermal imaging camera indicated that eyes in patients from Group 1 were characterized by higher temperature compared with the fellow normal eye of the patient in the range of all measured parameters in regions of interest (i.e., central point of the cornea, area of the eye, and orbital cavity) and lower minimum temperature. Significant differences were found in the mean temperature at the central point of the cornea, median, and mode temperature of the eye area and mean, maximum, median, and mode temperature at the orbital cavity area (Table 3). This is most likely related to the fact that melanoma is characterized by high local vascular density, which ensures the supply of oxygen and nutrients necessary for tumor growth[21].

Interestingly, in the group of patients with melanoma after brachytherapy (Group 2), we found higher values of the mean temperature at the central point of the cornea, mean, maximum, median, and mode temperature in the area of the eye and orbital cavity in four patients treated unsuccessfully. However, lower minimum temperature was recorded in eyes with diagnosed melanoma.

In patients from Group 3 with tumor regression, all measured parameters were lower in the affected eye. However, statistical analysis did not reveal any significant differences between these variables, which may be attributed to the small group size (Table 3).

The lower values of the analyzed variables may indicate insufficient blood supply to the retinal areas in the affected eye caused by radiation therapy. This effect leads to retinal occlusion, ischemia, partial retinal atrophy, and the formation of scar tissue[22]. Features that may indicate successful therapy include a reduced number of vascularized areas, increased vascular resistance, and increased tumor echogenicity[23]. Reduction in peak systolic frequency was reported for choroidal melanoma treated with episcleral brachytherapy. The vessels in the orbital cavity also receive a certain dose of radiation during the treatment of uveal melanoma, which may cause ischemia within the healthy orbital vessels and a lower surface temperature in this region (Table 3). Some researchers presume that the developing radiogenic vasculopathy of the small orbital vessels is the cause of increased vascular resistance[24]. This hypothesis was confirmed by other researchers, who revealed a decreased blood flow velocity in the central retinal artery and an increased resistance index in small ocular arteries during the 2-year follow-up of eyes with choroidal melanoma after stereotactic radiotherapy using the Gamma Knife[25].

Choroidal metastases

Currently, there are no studies on thermal emission in eyes with choroidal metastases. According to Konstantinidis et al., metastatic tumors are rather poorly vascularized[26]. The metastatic tumor uses blood vessels at the target tissue, which are necessary for metastatic growth in the distant organ. The anatomy and course of vessels are similar to those of the primary tumor from which the metastasis arises[21].

Our study revealed lower temperatures in the range of all tested parameters and areas in eyes with choroidal metastases. The analysis revealed significant differences in the maximum temperature of the eye area and the mean and median temperatures of the orbital cavity (Table 3). Metastatic tumors most likely develop within the vasculature of the affected site. We suggest that metastatic tumor tissue receives blood and nutrients from the vascular membrane around the lesion, and high metabolic activity is limited to a small area of the metastasis. This may explain the similar temperature measured for the entire ocular area to that of the normal eye. However, the mechanism involved in this process is not entirely clear. Recent reports suggest that if the metastasis is located in well-vascularized areas, the tumor may not create its own system of blood vessels but instead use the existing local vasculature. These reports present different variants of vasculature for metastatic tumors, which may also be other than neo-angiogenic, as in non-small-cell lung carcinoma[27]. Ocular metastases may be low-metabolic metastases or secondary avascular tumors; therefore, they do not increase eyeball metabolism, but they could take activity from the choroid around them.

This effect may also be caused by the characteristics of secondary neoplasm growth and compression on adjacent vessels (e.g., retinal arteries) causing ischemia (tissue pushing) or by vasoconstriction of conjunctival blood vessels, which are all consequences of a decrease in ocular surface temperature. Further research is warranted to confirm this trend in a greater number of cases.

Retinal capillary hemangioblastoma

According to the literature, cutaneous hemangiomas are benign vascular tumors characterized by a greater perfusion compared with normal skin, resulting in increased thermal emission observed using a thermal imaging camera[28]. There are reports regarding the use of thermography for monitoring and assessing the treatment of proliferative infantile hemangiomas with beta blockers[29] and predicting their growth. Other studies revealed a median initial temperature of 36.7°C for stable hemangiomas, 37°C for the slightly growing group, and 37.4°C for the growing group[30].

In our study, eyes with diagnosed intraocular hemangioma (Group 5) were characterized by higher parameters for the regions of interest, except for the minimum temperature versus eyes without this pathology; however, there were no significant differences between the analyzed variables.

Despite the small size of the study group, the infrared investigation of intraocular tumors appears to be an interesting concept. Information regarding the tumor vasculature obtained at an early stage of the diagnostic process can provide valuable diagnostic and prognostic indications. Analysis of larger groups of patients may help assess the efficacy of brachytherapy against melanoma.

The limited availability of highly specialized tests and lack of insight into the fundus of the eye caused by secondary complications of tumor growth have stimulated the search for easily available and rapid methods for the assessment of features of intraocular tumors. Diagnostic tests, such as FA and indocyanine green angiography,

are invasive techniques and provide subjective assessment, depending on the experience of the investigator. Moreover, histopathological biopsy is not always feasible. On the other hand, Iveković et al. indicated that CDI, despite its noninvasive nature, may provide biased findings with a significant error. The inaccuracy of CDI may be attributed to the fact that the velocity of blood flow in the cancerous vessel is never measured exactly at the same point, the direction of blood flow is frequently unidentifiable, and the angle between the tested vessel and the probe is often >60°[14].

Thermography is a helpful method, especially when fundus examination of the eye is not possible, due to corneal opacity, a mature cataract, or vitreous hemorrhage. These disorders do not have their own vascularization; hence, they do not cause thermal emission disturbances arising from uveal tumors. The evaluation of thermograms is not dependent on the experience of the examiner, because the camera software independently determines the temperature of the tested area. Potential limitations of ocular thermography include measurement error, lack of standardization during image acquisition (different angle, distance, and environmental conditions), and the failure to exclude other ocular diseases that may affect the test result.

Thermography is an undervalued diagnostic technique; after developing relevant standards for image acquisition, it could be used for the screening and differential diagnosis of intraocular tumors, as well as for the assessment of therapeutic efficacy. Currently, it has been replaced by invasive angiographic or histological examinations. Owing to its simplicity and cost-effectiveness, thermography can be used in specialized ocular oncology centers. The authors intend to conduct further studies on the diagnosis and monitoring of intraocular tumors using thermography and compare this method with other imaging tests. This comparison is expected to determine not only the role of thermography in the diagnosis of intraocular tumor but also the usefulness of thermography in monitoring treatment results. Thermography may become an important complementary or monitoring study of treatment outcomes.

A thermographic examination of the eye and orbital cavity can be used as an additional first-line diagnostic tool for differentiating intraocular tumors.

Thermography can be a helpful tool in monitoring the treatment outcome in patients with intraocular melanoma.

Uveal melanoma prior to treatment is visualized as a hot tumor in thermography, which may indicate its increased vascularization and metabolism.

Intraocular metastases do not appear to be hot tumors in thermography, suggesting their lower vascularization compared with that of uveal melanoma.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

Prevalence of depressive and anxiety disorders in patients with glaucoma: a cross-sectional study

Prevalência de depressão e ansiedade em pacientes com glaucoma

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ABSTRACT | Purpose: Our goal was to analyze the prevalence of depression and anxiety among patients with glaucoma and to identify risk factors related to these disorders. **Methods:** A cross-sectional study was carried out between August 2016 and August 2017 at the Hospital das Clínicas of Universidade Estadual de Campinas and at the Hospital Oftalmológico de Brasília to evaluate the prevalence of depressive and anxiety disorders among patients diagnosed with glaucoma. All patients underwent a complete ophthalmologic examination with standard automated perimetry to confirm the diagnosis of glaucoma. All participants were asked to complete the Hospital Anxiety and Depression Scale questionnaire. **Results:** One hundred and twenty-nine patients were included in the study. Seventy-four were men (57.36%) and 55 (42.64%) were women. The mean age of the patients was 70.14 ± 15.8 years. Ninety participants were white (69.77%) and 38 (29.46%) were black. The study demonstrated a prevalence of depression and/or anxiety at 10.08%. Logistic regression revealed that women were at higher risk for anxiety and/or depression (OR: 5.25, p=0.015) and patients with a larger number of co-morbidities also were at higher risk for anxiety and/or depressive disorders (OR: 2.82, p=0.038). **Conclusion:** A significant proportion of patients with glaucoma present with depression and/or anxiety. Females and patients with co-morbidities are at greater risk for these disorders.

Keywords: Glaucoma; Depression/epidemiology; Anxiety/epidemiology; Cross-sectional studies

RESUMO | Objetivo: Avaliar a prevalência de transtornos de depressão e ansiedade em pacientes com glaucoma e identificar fatores de riscos associados. **Métodos:** Estudo transversal em pacientes com glaucoma, avaliados durante Agosto de 2016 e Agosto de 2017 no Hospital das Clínicas da Universidade de Campinas e no Hospital Oftalmológico de Brasília. Todos pacientes foram submetidos à exame oftalmológico completo para confirmar o diagnóstico de glaucoma. Todos pacientes preencheram o questionário "Hospital Anxiety and Depression Scale". **Resultados:** Foram incluídos 129 pacientes no estudo, sendo 74 homens (57.36%) e 55 (42.64%) mulheres, 90 pacientes eram brancos (69.77%) e 38 (29.46%) eram negros. A idade média foi de 70.14 ± 15.8 anos. O estudo demonstrou uma prevalência de 10.08% de transtornos depressivo e/ou ansiedade. A regressão logística demonstrou que mulheres apresentam maior risco de desenvolver transtornos depressivos e/ou ansiedade (Risco relativo: 5.25, p=0.015), assim como pacientes com maior número de co-morbidades clínicas (Risco relativo: 2.82, p=0.038). **Conclusão:** Uma proporção significativa dos pacientes com glaucoma podem apresentar transtornos de depressão e/ou ansiedade. Pacientes com glaucoma do sexo feminino e que apresentem maiores co-morbidades clínicas apresentam maior risco de apresentar esses transtornos.

Descritores: Glaucoma; Depressão/epidemiologia; Ansiedade/epidemiologia; Estudos transversais

INTRODUCTION

Glaucoma is the most common cause of irreversible blindness in the world; the diagnosis of glaucoma has been associated with anxiety and depression, the two of the most prominent and pervasive psychiatric disorders[1,2]. As in psychiatric disorders, age is an important risk factor for the development of glaucoma[3]. Mental health may have an impact on clinical factors such as adherence to antihypertensive medication and treatment follow-up[4]. By contrast, the prevalence of depressive disorders in patients with glaucoma may be

Submitted for publication: July 22, 2019
Accepted for publication: January 15, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Faculdade de Ciências Médicas da Universidade Estadual de Campinas (CAAE: 48898515.5.1001.5404).

high due to the fact that visual loss leads to a significant decrease in quality of life[5,6].

Studies have already documented a relationship between psychiatric disorders and glaucoma using depression and anxiety scales; the prevalence of these specific psychiatric disorders is higher among glaucoma patients compared to control groups matched by both sex and age[7]. Previous studies have estimated that the prevalence of depressive symptoms in patients with glaucoma is ~10 – 12%. When compared to healthy control subjects, the prevalence of depression was on average 32% higher in patients diagnosed with glaucoma[1,4]. Interestingly, Mabuchi et al.[7] found that visual acuity and severity of visual field defects were not associated with severity of the depressive disorder. However, Diniz-Filho et al.[8] reported that progressive visual field loss was associated with the prevalence of depressive symptoms in patients with glaucoma.

Several tools are used to identify patients with depression and anxiety[9,10]. The Hospital Anxiety and Depression Scale (HADS) which is divided into anxiety and depression subscales, was developed by Zigmond and Snaith in 1983 to identify anxiety and depression among patients in non-psychiatric hospital clinics[11]. HADS is used widely and has been shown to be effective at assessing symptoms of anxiety and depression in primary care clinic patients as well as in the general population[12,13].

The primary objective of this study was to analyze the prevalence of depressive and /or anxiety disorders using the HADS instrument in a group of Brazilian patients diagnosed with glaucoma and to identify potential disease-related risk factors.

METHODS

Study design

This cross-sectional study was conducted between August 2016 and August 2017 in accordance with the ethical principles of the Helsinki Declaration and the principles of the current Good Clinical Practices. The study protocol was approved by the Clinical Research Ethics Committee of the Faculty of Medical Sciences of the State University of Campinas. All patients provided written informed consent. The study was carried out by all authors; the second author ensured data integrity and accuracy and study analysis.

Study population

Patients were selected for study enrollment at the glaucoma outpatient clinic of the Hospital das Clínicas of the State University of Campinas and Hospital Oftalmológico de Brasília. Inclusion criteria included typical glaucomatous changes in the optic nerve (cup/disc ratio >0.6, cup/disc ratio asymmetry >0.2, atrophy of the nerve fiber layer, localized loss of neuro-retinal tissue). Enrollees also displayed characteristic defects identified by standard automated perimetry (SAP), including at least two consecutive abnormal SAP results at baseline with corresponding optic nerve damage in at least one eye. Abnormal SAP results were defined as a pattern standard deviation with $p<0.05$, glaucoma hemi-field test results outside normal limits, or both findings[14].

All patients underwent a complete ophthalmologic examination, including logMAR best corrected visual acuity, slit lamp biomicroscopy, Goldmann aplannation tonometry, Possner lens gonioscopy, and examination of the fundus through a dilated pupil. Patients with retinal diseases such as age macular degeneration were excluded. All patients also underwent standard automated perimetry (Humphrey, Sita Standard 24-2) and filled out questions in the previously Portuguese-language-validated HADS instrument together with a form requesting socio-demographic data[15].

The stage of glaucomatous damage was defined according to Hodapp, Parish and Anderson criteria[14]. We classified patients with advanced glaucoma when the mean deviation (MD) was <-12dB. We also identified patients with low vision according to International Classification of Diseases and Related Health Problems from World Health Organization, including patients with corrected visual acuity that was <20/70[16].

We also reviewed past and present medical histories for any of the following co-morbidities: diabetes mellitus, arthritis, hypertension, heart disease, depression, asthma, and cancer[5]. A simple summation score was used to generate a co-morbidity index[17].

Data on gender, age, race, level of education, previous glaucoma surgery, use of antihypertensive eye drops, use of psychoactive substances and past or present psychiatric disorders and/or a specific history of depression and/or anxiety were also documented.

The Hospital Anxiety and Depression Scale (HADS) includes 14 items, seven of which are focused on the assessment of anxiety and seven on depression. Each of the items score from 0 to 3, with a maximum score of 42 points, 21 points for each scale. All patients who had a score greater than or equal to 12 on the depression or the anxiety scale were referred to psychiatric services for follow-up. All forms administered personally by the

investigators (RYA, LNS and DMS) to provide support and ensure full comprehension of the questionnaire.

Statistical analysis

The normality of the sample distribution was evaluated by the inspection of histograms. Student's t test was used for statistical evaluation continuous variables and for samples that showed a normal distribution. Categorical variables were compared using the Chi-square or Fisher's test.

We performed a logistic regression to define the odds ratio of depression and/or anxiety disorder. We used as dependent variable patients who had a score greater than or equal to 12 on the HADS scale (coded as 0 or 1). The following parameters were used as independent variables (adjusted for continuous and categorical data): age, gender, race, marital status, education, family income, employment status, co-morbidity index, number of glaucoma eye drops used per day, presence of advanced glaucoma in one or both eyes, the degree of mean eye deviation, visual acuity, presence of low vision in one or both eyes, pseudophakia, use of topical beta-blockers and history of glaucoma surgery. Values of $p<0.05$ were considered statistically significant. All data analyses were performed using the statistical program Stata (version 13; StataCorp LP, CollegeStation, TX).

RESULTS

From January 2016 to January 2017, we identified 129 patients diagnosed with glaucoma who were eligible for the study and were included in the analysis. Seventy-four were men (57.4%) and 55 (42.6%) were women. The mean age (± SD) of the patients was 70.14 ± 15.8 years. Ninety participants were white (69.77%) and 38 (29.46%) were black. Table 1 summarizes the clinical and demographic characteristics of the individuals included in the study.

Best corrected logMAR visual acuities were 0.32 ± 0.52 and 0.93 ± 0.99 in the better and worse eye, respectively. Mean deviations in the better and worse eyes were -5.27 ± 6.34 dB and -11.32 ± 9.24 dB, respectively (Table 2). Among the 129 patients, 13 (10.1%) presented depression and/or anxiety; of this group, 3 (2.3%) presented with depression only, 6 (4.7%) presented with anxiety only and 4 (3.10%) presented with both depression and anxiety (Table 2).

Logistic regression revealed that gender and co-morbidity indices were risk factors for anxiety and/or depressive disorders in patients with glaucoma (Table 3). Female patients had an increased risk for anxiety and/or depression compared to male patients (OR: 5.25, $p=0.015$) and patients with more co-morbidities also had a higher risk for have anxiety and/or depression (OR: 2.82, $p=0.038$).

DISCUSSION

In this study, we determined the prevalence of depression and/or anxiety disorders among 129 patients diagnosed with glaucoma to be 10.1%. We also found that female glaucoma patients and glaucoma patients

Table 1. Demographic characteristics of study subjects

Characteristic	Value
Age, years	
Mean ± SD	70.14 ± 15.8
Gender n (%)	
Male	74 (19.38%)
Female	55 (42.64%)
Race n (%)	
White	90 (69.77%)
Black	38 (29.46%)
Asian	1 (0.78%)
Income n (%)	
Up to R$1499,00	64 (50.39%)
R$1.450,00 - R$2.989,00	27 (21.26%)
R$2.990,00 - R$7.249,00	20 (15.75%)
R$7.250,00 - R$14.499,00	7 (5.51%)
Above R$14.499,00	9 (7.09%)
Marital status n (%)	
Single	25 (19.38%)
Married	84 (65.12%)
Widower	18 (13.95%)
Divorced	2 (1.55%)
Education n (%)	
Illiterate	20 (15.50%)
1st degree incomplete	46 (35.66%)
1st degree complete	20 (15.50%)
2nd degree incomplete	10 (7.75%)
2nd degree complete	16 (12.40%)
Superior degree incomplete	4 (3.10%)
Superior degree complete	13 (10.08%)
Employment status n (%)	
Employee	23 (17.83%)
Unemployed	9 (6.98%)
Retired	97 (75.19%)

Table 2. Clinical characteristics of study subjects

Characteristic	Value
Mean Deviation (mean ± SD)	
Better eye	-5.27 ± 6.34
Worse eye	-11.32 ± 9.24
BCVA (mean ± SD)	
Better eye	0.32 ± 0.52
Worse eye	0.93 ± 0.99
Co-morbidity Index (mean ± SD)	1.19 ± 0.74
Advanced glaucoma in both eyes n (%)	
Yes	10 (7.75%)
Advanced glaucoma in one eye n (%)	
Yes	46 (35.66%)
Low Vision vision in both eyes n (%)	
Yes	9 (6.98%)
Low Vision vision in one eye n (%)	
Yes	32 (32.56%)
Depression and/or anxiety n (%)	
Yes	13 (10.08%)
Depression n (%)	
Yes	3 (2.33%)
Anxiety n (%)	
Yes	6 (4.65%)
Depression and anxiety n (%)	
Yes	4 (3.10%)

SD= standard deviation; MD= mean deviation; BVCA= best corrected logMAR visual acuity.

Table 3. Predictors of anxiety and/or depressive disorders from logistic regression

Predictors	Odds ratio	*p*-value
Age	1.00	0.851
Gender	**5.25**	**0.015**
Race	1.12	0.118
Marital status	0.68	0.430
Family Income	0.59	0.128
Level of Instruction	0.94	0.750
Employment status	0.85	0.584
Co-morbidity Index	**2.82**	**0.038**
Glaucoma eyedrops	0.91	0.704
Advanced Glaucoma in both eyes	2.45	0.292
Advanced Glaucoma in one eye	0.78	0.698
Low vision in both eyes	1.12	0.915
Low vision in one eye	0.91	0.885
MD Worse eye	0.99	0.843
BCVA Worse eye	0.98	0.950
Pseudophakia	0.38	0.160
Use of Beta-blocker	1.12	0.852

MD= mean deviation; BCVA= best corrected logMAR visual acuity.

with a larger number of associated co-morbidities were at greater risk for depression and/or anxiety disorders. To our knowledge, this is the first study to examine the association between glaucoma and anxiety/depression disorders in Brazil, as well as to investigate potential risk factors.

Glaucoma is a chronic degenerative disease and the leading cause of irreversible blindness worldwide[18]. Considering the asymptomatic nature of the disease and its potentially devastating outcomes, and likewise the economic impact related to the cost and side effects of antihypertensive medications used to control it, glaucoma might cause or aggravate pre-existing psychological burdens in this patient cohort[19]. Anxiety and depression are common psychological disorders that are important public health problems[20,21].

Previous studies have shown that patients with glaucoma are more likely to suffer from both anxiety and depression[7,22,23]. Our findings reveal that the prevalence of depression and/or anxiety in this patient cohort was 10.1%; 2.33% reported only depression, 4.65% reported only anxiety and 3.10% presented with both depression and anxiety. These findings are consistent with those reported previously that identified higher rates of depression and anxiety among glaucoma patients. Rezapour et al.[24] reported the prevalence of depression and anxiety among 293 glaucoma patients at 6.6% and 5.3%, respectively. Mabuchi et al.[1] found that, among 230 patients undergoing treatment for glaucoma, 13.0% and 10.9% of also experienced anxiety and depression, respectively.

It is also critical to consider these observations from the opposite perspective. It is also possible that the presence of depressive symptoms in patients with glaucoma may lead to poor compliance with the medication regimen[25,26]. As such, it will be critical to provide these patients with adequate psychological care not only to improve quality of life but also to ensure medication compliance[25]. In order to detect, prevent and treat anxiety and depression that may coexist among those with glaucoma, it is also important to have some comprehension of the risk factors associated with these psychological disorders. Our findings suggest that female gender and patients with a higher number of co-morbidities are at greater risk for a diagnosis of depression and/or anxiety.

We found that female patients had a 5.25-fold higher chance of succumbing to depression and/or anxiety disorders when compared to age-matched male patients

(p=0.015). Among the 55 women from our sample, 10 presented with anxiety and/or depression, while only 3 of 74 men were diagnosed with the same disorders. Lim et al.[22] also reported that female glaucoma patients were more likely to suffer from depression. Tastan et al.[27] also found that the risk of anxiety in women with glaucoma was 7.5 times higher than in men. Society-driven risk factors for anxiety and depression in women are likely have a biological origin; among these traits, we consider differences in physical strength and related personality traits[28].

Our study also demonstrated that patients with more co-morbidities were at higher risk for anxiety and/or depression (OR=2.82, p=0.038). The co-morbidity index was created using a simple summation score from questions regarding present conditions and/or history of conditions such as: diabetes mellitus, arthritis, high blood pressure, heart disease, depression, asthma, and cancer[5,17]. Our sample included 25 patients with no co-morbidities; no depression or anxiety were detected among members of this patient cohort. In the group of patients with one co-morbidity (49 patients), 5 patients (10.2%) were diagnosed with anxiety and/or depression. Finally, in the group with 2 or more co-morbidities (42 patients), 8 (19%) presented with anxiety and/or depression.

Previous studies have revealed that depressive disorders play important roles in the etiology, course, and outcomes associated with chronic diseases[20]. In fact, patients with chronic medical illnesses are also known to be at high risk for both depression and anxiety[20,21].

Interestingly, objective measures of visual acuity and severity of glaucoma as defined by the mean deviation from standard automated perimetry were not at all predictive of depression or anxiety disorders. This may be explained due to the fact that our sample did not include a large proportion of patients with low vision and advanced glaucoma. However, earlier studies have demonstrated that objective measures of visual function may not be directly associated with the prevalence of psychiatric disorders[4]. These results suggest that the association between glaucoma and depression or anxiety is complex and reflects the perceptions of patients and the subjective experiences of their illness rather than conventional objective measures, such as visual acuity or visual field.

We recognize that our study has several limitations. First, the study design is cross-sectional and there was no follow-up phase. Hence, we were not able to document the psychological changes that may become more or less evident over time. Second, our study did not include a control group which would have permitted us to determine whether the prevalence of psychiatric disorders is actually higher in the glaucoma group. We did not explore the duration of glaucoma in order to evaluate the possibility that length of disease might correlate with a higher prevalence of psychiatric disorders. Finally, although the HADS scale is easy and convenient for testing purposes, the questionnaire is not comparable to a formal psychiatric diagnosis from a mental health specialist.

In summary, this cross-sectional study revealed that a significant proportion of glaucoma patients also present with depression and/or anxiety disorders. We found that females and patients with co-morbidities were at greater risk for depression and or anxiety. Ophthalmologists should make an attempt to recognize these psychiatric disorders in patients with glaucoma and refer them to appropriate care; this will provide dramatic improvements in the patient's quality of life[26]. Ophthalmologists should also provide accurate and appropriate information about glaucoma to their patients in order to prevent the development of excessive and inappropriate anxiety and depression[29]. Furthermore, longitudinal studies should be conducted with a larger sample size and with reliable tools that were designed to assess psychological disorders. This might be accompanied by an investigation into whether the treatment of these psychiatric disorders may result in an improved the quality of life for patients with glaucoma and promote increased adherence to anti-glaucomatous treatment.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

Use of automated quantitative pupillometric evaluation for monitoring the severity of diabetic retinopathy

Uso da pupilometria quantitativa automatizada no monitoramento da severidade da retinopatia diabética

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ABSTRACT | Purpose: We aimed to evaluate the use of automated quantitative static and dynamic pupillometry in screening patients with type 2 diabetes mellitus and different stages of diabetic retinopathy. **Method:** 155 patients with type 2 diabetes mellitus (diabetes mellitus group) were included in this study and another 145 age- and sex-matched healthy individuals to serve as the control group. The diabetes mellitus group was divided into three subgroups: diabetes mellitus without diabetic retinopathy (No-diabetic retinopathy), nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy. Static and dynamic pupillometry were performed using a rotating Scheimpflug camera with a topography-based system. **Results:** In terms of pupil diameter in both static and dynamic pupillometry ($p<0.05$), statistically significant differences were observed between the diabetes mellitus and control groups and also between the subgroups No-diabetic retinopathy, nonproliferative diabetic retinopathy, and proliferative diabetic retinopathy subgroups. But it was noted that No-diabetic retinopathy and nonproliferative diabetic retinopathy groups have showed similarities in the findings derived from static pupillometry under mesopic and photopic conditions. The two groups also appeared similar at all points during the dynamic pupillometry ($p>0.05$). However, it could be concluded that the proliferative diabetic retinopathy group was significantly different from the rest of the subgroups, No-diabetic retinopathy and nonproliferative diabetic retinopathy groups, in terms of all the static pupillometry measurements ($p<0.05$). The average speed of dilation was also significantly different between the diabetes mellitus and control groups and among the diabetes mellitus subgroups ($p<0.001$). While weak to moderate significant correlations were found between all pupil diameters in static and dynamic pupillometry with the duration of diabetes mellitus ($p<0.05$ for all), the HbA1c values showed no statistically significant correlations with any of the investigated static and dynamic pupil diameters ($p>0.05$ for all). **Conclusion:** This study revealed that the measurements derived from automated pupillometry are altered in patients with type 2 diabetes mellitus. The presence of nonproliferative diabetic retinopathy does not have a negative effect on pupillometry findings, but with proliferative diabetic retinopathy, significant alterations were observed. These results suggest that using automated quantitative pupillometry may be useful in verifying the severity of diabetic retinopathy.

Keywords: Diabetic retinopathy; Diabetes mellitus; Diagnostic techniques, ophthalmological; Pupil; Reflex, pupillary

RESUMO | Objetivos: Procuramos avaliar o uso da pupilometria estática e dinâmica quantitativa automatizada na triagem de pacientes com *diabetes mellitus* tipo 2 e em diferentes estágios de retinopatia diabética. **Métodos:** Cento e cinquenta e cinco pacientes com *diabetes mellitus* tipo 2 (grupo com *diabetes mellitus*) foram incluídos neste estudo e outros 145 controles saudáveis pareados por idade e sexo para server como grupo controle. O grupo com *diabetes mellitus* foi dividido em três subgrupos: *diabetes mellitus* sem retinopatia diabética (retinopatia não diabética), retinopatia diabética não proliferativa e retinopatia diabética proliferativa. A pupilometria estática e dinâmica foi realizada utilizando uma camera rotative Scheimpflug com um

Submitted for publication: June 24, 2019
Accepted for publication: February 3, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Mustafa Kemal University (#18-2038).

sistema baseado em topografia. **Resultados:** Em termos de diâmetro da pupila, tanto na pupilometria estática quanto na dinâmica (p<0,05), foram observadas diferenças estatisticamente significantes entre os grupos *diabetes mellitus* e controle e também entre os subgrupos retinopatia não diabética, retinopatia diabética não proliferativa e retinopatia diabética proliferativa. Mas foi observado que os grupos de retinopatia não diabética e retinopatia diabética não proliferativa mostraram semelhanças nos achados derivados da pupilometria estática em condições mesópicas e fotópicas. Os dois grupos também pareciam semelhantes em todos os pontos durante a pupilometria dinâmica (p>0,05). No entanto, pode-se concluir que o grupo de retinopatia diabética proliferative foi sugnificativamente diferente do restante dos subgrupos, retinopatia não diabética e retinopatia diabética não proliferativa, em termos de todas as medidas de pupilometris estática (p<0,05). A velocidade média de dilatação também foi significativamente diferente entre os grupos *diabetes mellitus* e controle, e entre os subgrupos *diabetes mellitus* (p<0,001). Enquanto correlações significativas fracas a moderadas foram encontradas entre todos os diâmetros da pupila na pupilometria estática e dinâmica com a duração do *diabetes mellitus* (p<0,05 para todos), os valores de HbA1c não mostraram correlações estatisticamente significantes com nenhum dos diâmetros da pupila estática e dinâmica investigados (p>0,05 para todos). **Conclusão:** Este estudo revelou que as medidas derivadas da pupilometria automatizada estão alteradas em pacientes com *diabetes mellitus* tipo 2. A presença de retinopatia diabética não proliferativa não afeta negativamente os achados pupilométricos, mas com a retinopatia diabética proliferative, alterações significativas foram observadas. Estes resultados sugerem que o uso da pupilometria quantitativa automatizada pode ser útil na verificação gravidade da retinopatia diabética.

Descritores: Retinopatia diabética; Diabetes Mellitus; Técnicas de diagnóstico oftalmológico; Pupila; Reflexo pupilar

INTRODUCTION

The size and function of the pupils are directly controlled by the autonomic nervous system through the sphincter (circular) and dilatator (radial) muscles of the iris. The parasympathetic neuronal axons, originating from the Edinger-Westphal nucleus, synapse on the ciliary ganglion and innervate the sphincter muscle of the pupil. At the same time, the dilatator muscle of the pupil is innervated by sympathetic neuronal axons originating from the posterolateral hypothalamus that synapse on the intermediolateral cell column of C8 to T2 and the superior cervical ganglion. These muscles and nerves work in coordination, providing optimal retinal lightning and perfect depth of focus via optimal pupil size[1].

Diabetic retinopathy (DR), diabetic macular edema, and neovascular glaucoma are well-known ocular complications of diabetes mellitus (DM), but all the layers of the eye globe, from the precorneal tear film to the lamina cribrosa, are vulnerable to experiencing more manifestations of DM, which could lead to more complications than just these[2,3]. Diabetic autonomic neuropathy (DAN) is another common ophthalmological complication, but it is less studied and less understood than the aforementioned three. Smaller resting pupil diameter and reflex amplitudes are relatively well-recognized as early clinical manifestations of DAN, but pupil diameter in static pupillometry under scotopic, mesopic, and photopic conditions and dilation capacity and speed have not been described extensively in different stages of DR[4,5].

Examining the pupillomotor function is a useful method for screening for DAN, which can be incorporated in a wide range of techniques from simple scale measurements to infrared observation[6]. Although the best way to measure the pupil size has not been definitively determined, automated quantitative pupillometry is considered as the best modern method for improving the screening for autonomic dysfunction[7]. However, despite its objective, repeatable, and quantitative measurements on the pupillomotor function, automated pupillometry requires specific equipment, trained operators, and active patient participation.

In this study, we sought to evaluate the findings of automated quantitative static and dynamic pupillometry in type 2 DM patients with different stages of DR.

METHODS

This prospective study was carried out at an ophthalmology clinic of a university hospital, with approval granted by the local research ethics committee. The aims and methods of the study were explained to the selected participants in detail, and informed consent was obtained thereafter for each subject. All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki for human subjects.

Study subjects

In all eligible study participants, DM was previously detected by the corresponding internal medicine department. The status of DR was assessed by fundus photography and confirmed with fluorescein angiography and optical coherence tomography. Early Treatment of Diabetic Retinopathy Study criteria were utilized to define various stages of DR. Selected age- and sex-matched healthy controls (control group) had visited the ophthal-

mology clinic for a routine ocular examination and/or presbyopic complaints. Cases with any systemic disease in the control group were excluded from this study.

All subjects underwent detailed medical questioning and ophthalmological evaluation including manifest refraction, best-corrected visual acuity (BCVA) (all subjects had a 0.4 decimal or better BCVA finding with the Snellen chart), color vision, intraocular pressure measurement, slit-lamb biomicroscopy, and dilated fundus examination. Colored fundus photography, fundus fluorescein angiography, and/or optical coherence tomography were performed for the DM group by the same clinician (V. C.). The DM group was divided into three subgroups as follows: DM without DR (No-DR), nonproliferative DR (NPDR), and proliferative DR (PDR).[8] Moreover, the duration of DM and the glycosylated hemoglobin (HbA1c) values were recorded for the patients with DM.

However, we excluded individuals who had a history of ocular trauma, glaucoma, uveitis, hyperopia, myopia or astigmatism of more than 1.00 diopters (D), herpetic corneal diseases, iris, or pupil anomalies, pseudoexfoliation, grades 3 or 4 cataract, retinal diseases that may affect the pupil, optic neuropathies, color vision deficiencies, and use of chronic topical ophthalmic medications. Subjects with other systemic diseases, especially affecting the central nervous system or urinary system and/or who were using systemic medications, were also excluded. Any patient with proliferative retinopathy associated with systemic diseases or localized retinal vascular and/or ocular inflammatory diseases was excluded as well. For the DM subjects, additional exclusion criteria included those who have undergone panretinal laser photocoagulation at any time or focal laser photocoagulation or intravitreal injection in the last year, respectively.

Pupillometry

Automated pupillometry was performed by the same experienced clinician (V. C.) using a Sirius 3D Rotating Scheimpflug camera topography system with the software suite Phoenix v2.1 (Costruzione Strumenti Oftalmici, Scandicci, Italy). The examination was conducted in a completely dark room following dark adaptation for 20 minutes, and the measurements were obtained during the same hours each day (between 13:00 and 15:00 hours) to minimize the impact of circadian variation on pupillary response[9,10].

Static and dynamic pupillometry were evaluated under different illumination conditions. Static pupillometry was applied in three stages as follows: (1) scotopic measurement, in which the only visible light source was a light-emitting diode (LED) at 0.4 lux; (2) mesopic measurement, in which the disk was illuminated to bring the ambient light intensity to 4.0 lux; and (3) photopic measurement, in which the disc was illuminated to bring ambient intensity to 40.0 lux. The LED output had the following characteristics at T_A (ambient temperature) of 25°C: peak wavelength 660 nm, dominant wavelength 640 nm, spectral line half width 20 nm, capacitance 95 pF, forward voltage 1.85 V (typical), 2.5 V (maximum), and reverse current maximum of 10 μA. To prevent accommodative response, the subjects were advised to look straight ahead rather than at the LED source. The measurements of static and dynamic pupillometry were performed with capture started with the ring disc fully illuminated with 500 lux; the illumination was then switched off when capture started. Hereby, it could be possible to monitor dilation in conditions from photopic to scotopic and to evaluate the pupil diameter and offset instant by instant. After the measurements of dynamic pupillometry, the speed of change in pupil diameter was calculated using this formulation: $V_{average} = ([\Phi_t - \Phi_{t0}]/t)$; according to this formulation, average speed (mm/s) is equal to the difference in the pupil diameter (mm) between time (seconds) at sampling and at $t = 0$ divided by duration (seconds) between time at sampling and at $t = 0$[10,11].

Statistical analysis

The data of the study were analyzed using the Statistical Package for the Social Sciences version 24.0 for Windows software program (IBM Corp., Armonk, NY, USA). The data taken after examining the right eyes of the study subjects were subjected to statistical analysis. Descriptive data were presented as means ± standard deviations, minimums, and maximums, and the chi-square test was used to analyze these categorical variables. Normal distribution of the variables was checked by Kolmogorov-Smirnov test. Mahalanobis distance was reviewed for the variables that did not fit normal distribution, and then one-way analysis of variance and Student's parametric t-tests were used. Post hoc tests (Tukey's honestly significant difference) for pairwise comparisons were also performed. Meanwhile, Pearson correlation tests were used to investigate the correlations of pupil diameter

with the duration of the DM and the HbA1c level. Statistically significance was set at $p < 0.05$.

RESULTS

This study included 155 subjects in DM group and 145 age- and sex-matched subjects in the control group. Demographic characteristics of the two groups are summarized in table 1. There were 49 patients in the No-DR subgroup, 53 patients in the NPDR subgroup, and 53 patients in the PDR subgroup, respectively. No statistically significant differences in age or gender were noted among these subgroups ($p>0.05$ for all). The mean durations of DM were 8.26 ± 3.96 years in the No-DR subgroup, 14.05 ± 4.75 years in the NPDR subgroup, and 16.62 ± 4.92 years in the PDR subgroup ($p<0.001$ in No-DR vs. NPDR, $p<0.001$ in No-DR vs. PDR, and $p=0.144$ in NPDR vs. PDR). Demographic and clinical characteristics of the DM subgroups are summarized in table 2.

Upon analyzing the pupil diameter in static and dynamic pupillometry, there were statistically significant differences found between the DM and control groups ($p<0.05$ for all), as summarized in table 3.

The DM subgroup analysis revealed statistically significant differences between the No-DR, NPDR, and PDR subgroups ($p<0.001$ for all). Pupil diameter results from static and dynamic pupillometry of the DM subgroups are summarized in table 4. As per the findings of static pupillometry under the scotopic condition, the No-DR, NPDR, and PDR subgroups were statistically different from one another ($p=0.014$ in No-DR vs. NPDR, $p<0.001$ in No-DR vs. PDR, and $p<0.001$ in NPDR vs. PDR). However, the results of dynamic pupillometry and static pupillometry in the mesopic and photopic conditions showed otherwise: findings for the No-DR and NPDR subgroups were similar regarding these measurements ($p>0.05$ for all), while those of the PDR subgroup were statistically significantly different from either ($p<0.05$ for all).

The average speed of pupillary dilation, another important parameter of dynamic pupillometry, was also measured. Of note, differences between the DM and control groups ($p<0.001$ for all) were statistically significant, as demonstrated in figure 1. Among the DM subgroups, the results of the PDR subgroup were significantly different, while those of the No-DR and NPDR subgroups were similar; these are summarized in table 5 and figure 2.

In table 6, correlations between static and dynamic pupil diameters were presented, taking into consideration the duration of DM and HbA1c levels. There were weak to moderate significant correlations between all pupil diameters in static and dynamic pupillometry with the duration of DM ($p<0.05$ for all). On the other hand, HbA1c values showed no statistically significant correlations with any of the investigated static and dynamic pupil diameters ($p>0.05$ for all).

Table 1. Demographic characteristics of the DM and control groups

	DM group (n=155)	Control group (n=145)	p value*
Age (years), mean ± SD (range)	55.2 ± 8.9 (26-73)	55.6 ± 7.2 (36-70)	0.605
Gender (male/female)	85/70	80/65	0.954

DM= diabetes mellitus; SD= standard deviation; M= male; F= female.
*Student's t-test was used for age, and chi-square test was used for gender.

DISCUSSION

Resting pupil size is mainly controlled by the sympathetic nervous system, and a decrease in resting pupil diameter is considered as a result of diminishing sympathetic outflow to the pupillary dilatator muscle[12]. In the pupillary construction phase, changes in pupil dia-

Table 2. Demographic and clinical characteristics of the No-DR, NPDR, and PDR groups

	No-DR group (n=49) Mean ± SD (range)	NPDR group (n=53) Mean ± SD (range)	PDR group (n=53) Mean ± SD (range)	p value*
Age (years)	54.3 ± 10.1 (26-73)	56.2 ± 7.4 (28-70)	55.0 ± 9.2 (27-71)	0.556
Gender (M/F)	27/22	29/24	29/24	0.999
DM duration (years)	8.3 ± 4.0 (3-20)	14.1 ± 4.8 (5-26)	16.6 ± 4.9 (8-30)	**<0.001**[a]
HbA1c (%)	9.1 ± 2.5 (5.5-15.8)	9.5 ± 1.7 (6.0-13.4)	9.5 ± 2.2 (6.6-16.3)	0.553

DR= diabetic retinopathy; NPDR= nonproliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy; SD= standard deviation; M= male; F= female; DM= diabetes mellitus.
*Student's t-test was used for age and chi-square test was used for gender.
a= $p<0.001$ in No-DR vs. NPDR, $p<0.001$ in No-DR vs. PDR, and $p=0.144$ in NPDR vs. PDR

meter and the duration of pupil size change are related to the parasympathetic nervous system. Separately, in the postconstruction recovery phase, the sympathetic and parasympathetic nervous systems work in harmony with each other[13]. Ferrari et al.[14] stated that DM subjects have both sympathetic and parasympathetic dysfunctions, as evidenced by diminished amplitude reflexes and smaller pupil diameters. This study showed there are significant differences between DM and non-DM subjects in terms of pupil diameter in static and dynamic pupillometry and the average speed of pupillary dilation.

Some previous studies have suggested that pupillary parameters are altered in various groups of patients with DR. There is a very limited number of studies in literature in which DM subjects were grouped according to DR stages. Park et al.[11] studied the pupillary functions of 50 DM subjects who did not have DR or NPDR in several

Table 3. The results of pupil diameter in DM and control groups

		DM group (n=155) Mean ± SD (range)	Control group (n=145) Mean ± SD (range)	p value*
Static pupillometry	Scotopic (mm)	4.2 ± 0.8 (2.3-6.4)	4.9 ± 0.7 (3.4-6.9)	**<0.001**
	Mesopic (mm)	3.9 ± 0.7 (2.3-5.6)	4.4 ± 0.7 (2.5-6.3)	**<0.001**
	Photopic (mm)	3.3 ± 0.6 (2.2-4.7)	3.5 ± 0.6 (2.4-5.5)	**0.007**
Dynamic pupillometry	0th second (mm)	3.1 ± 0.6 (2.0-4.5)	3.3 ± 0.5 (2.3-5.0)	**0.005**
	1st second (mm)	3.6 ± 0.6 (2.3-5.1)	4.0 ± 0.6 (2.7-5.6)	**<0.001**
	2nd second (mm)	3.8 ± 0.7 (2.4-5.4)	4.3 ± 0.6 (3.0-5.9)	**<0.001**
	4th second (mm)	4.0 ± 0.8 (2.4-5.6)	4.6 ± 0.6 (3.0-6.3)	**<0.001**
	6th second (mm)	4.1 ± 0.8 (2.5-6.0)	4.8 ± 0.6 (3.3-6.6)	**<0.001**
	8th second (mm)	4.2 ± 0.8 (2.5-6.3)	4.9 ± 0.7 (3.4-6.7)	**<0.001**
	10th second (mm)	4.3 ± 0.8 (2.5-6.3)	4.9 ± 0.7 (3.5-6.8)	**<0.001**

DM= diabetes mellitus; SD= standard deviation.
*Student's t-test was used.

Table 4. The results of pupil diameter in No-DR, NPDR, and PDR groups

		No-DR group (n=49) Mean ± SD (range)	NPDR group (n=53) Mean ± SD (range)	PDR group (n=53) Mean ± SD (range)	p value*
Static pupillometry	Scotopic (mm)	4.7 ± 0.7 (3.4-6.4)	4.3 ± 0.6 (3.0-5.9)	3.6 ± 0.8 (2.3-5.9)	**<0.001**[a]
	Mesopic (mm)	4.2 ± 0.7 (3.0-5.6)	4.0 ± 0.6 (3.0-5.6)	3.4 ± 0.7 (2.3-5.4)	**<0.001**[b]
	Photopic (mm)	3.4 ± 0.6 (2.5-4.7)	3.4 ± 0.7 (2.5-4.7)	3.0 ± 0.6 (2.2-4.3)	**<0.001**[c]
Dynamic pupillometry	0th second (mm)	3.2 ± 0.5 (2.2-4.5)	3.3 ± 0.5 (2.5-4.4)	2.9 ± 0.5 (2.0-4.1)	**<0.001**[d]
	1st second (mm)	3.8 ± 0.6 (2.8-5.1)	3.8 ± 0.5 (2.9-5.0)	3.2 ± 0.6 (2.3-4.8)	**<0.001**[e]
	2nd second (mm)	4.0 ± 0.6 (2.9-5.2)	4.0 ± 0.6 (3.1-5.4)	3.3 ± 0.6 (2.4-5.2)	**<0.001**[f]
	4th second (mm)	4.3 ± 0.6 (3.1-5.6)	4.2 ± 0.6 (3.2-5.6)	3.4 ± 0.7 (2.4-5.5)	**<0.001**[g]
	6th second (mm)	4.5 ± 0.7 (3.1-6.0)	4.3 ± 0.6 (3.3-5.9)	3.5 ± 0.7 (2.5-5.7)	**<0.001**[h]
	8th second (mm)	4.6 ± 0.7 (3.2-6.3)	4.4 ± 0.7 (3.4-6.0)	3.6 ± 0.8 (2.5-5.7)	**<0.001**[i]
	10th second (mm)	4.7 ± 0.7 (3.2-6.3)	4.5 ± 0.6 (3.5-6.1)	3.6 ± 0.8 (2.5-5.8)	**<0.001**[j]

DR= diabetic retinopathy; NPDR= nonproliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy; SD= standard deviation*One-way analysis of variance was useda: p=0.014 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
b: p=0.232 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
c: p=0.800 in No-DR vs. NPDR, p=0.015 in No-DR vs. PDR, and p=0.002 in NPDR vs. PDR.**
d: p=0.773 in No-DR vs. NPDR, p=0.005 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
e: p=0.936 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
f: p=0.790 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
g: p=0.537 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
h: p=0.467 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
i: p=0.386 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
j: p=0.323 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
**Tukey post hoc test was used.

stages and 25 healthy control subjects. They stated that the mean baseline pupil diameters of all NPDR groups in the dark were smaller than that in the control group. Additionally, the moderate-severe NPDR group was separated from the no NPDR and mild NPDR groups according to many other parameters[11]. Jain et al.[15] studied cases containing either no DR, mild NPDR, moderate NPDR, severe NPDR, or PDR. They concluded that pupillary dynamics are abnormal in the early stages of DR and progress with increasing DR severity. They further investigated pupillary function with another technique; however, their study included both eyes of subjects, and they did not exclude type 1 DM[15]. Meanwhile in this study, patients were divided into categories No-DR, NPDR, and PDR. Firstly, it showed that pupil diameter is altered in patients with DM. Second, the pupillometry measurements are similar in DM patients without DR and with NPDR. In other words, the presence of NPDR does not provoke a significant difference in pupillometry measurements according to this study. Also, pupillometry measurements are more altered in DM patients with PDR. The most important finding of this study is that the characteristics of PDR differ significantly from other stages of DR.

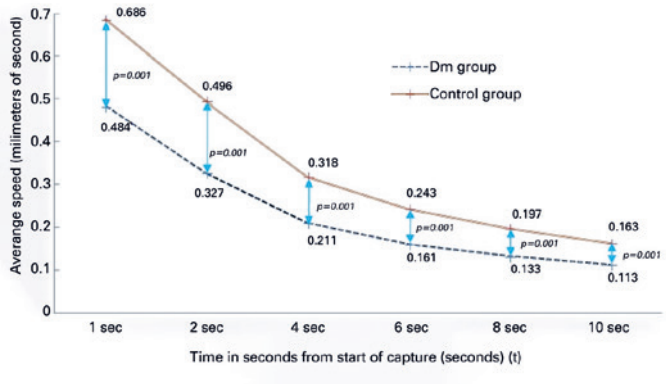

Figure 1. Demonstration of the average speeds of the DM and control groups.

Ortube et al.[16] showed a statistically significant alteration in constriction velocity of moderate to severe NPDR cases when compared with a control group. According to their report, these values were highly correlated with the severity of the DR but not with the duration of the DM[16]. Interestingly, our study showed different results from this previous study. In our study, a weak to moderate significant relationship was found between all investigated pupil diameters with the duration of DM. This difference can be explained by the use of infrared pupillometry and the small subject group size. In addition, a relationship between pupillary function and DM duration was also determined. DR is a microangiopathy involving hypoxia in neuronal cells and the main pathophysiological mechanism of DM-related neuropathy[17]. The duration of DM is related to increased nerve fiber influences and changes in pupillary functions. With the extension of the duration of DM, more and more nerve fibers are affected, and pupillary functions are increasingly altered. Similar results were found by Cahill et al.[18] with infrared pupillometry.

Table 5. Average speed of pupillary dilation in No-DR, NPDR, and PDR groups

	No-DR group (n=49) Mean ± SD (range)	NPDR group (n=53) Mean ± SD (range)	PDR group (n=53) Mean ± SD (range)	p value*
1st second (mm/s)	0.6 ± 0.2 (0.4-0.8)	0.5 ± 0.2 (0.4-0.7)	0.4 ± 0.2 (0.3-0.5)	<0.001a
2nd second (mm/s)	0.4 ± 0.2 (0.3-0.6)	0.3 ± 0.1 (0.2-0.4)	0.2 ± 0.1 (0.2-0.3)	<0.001b
4th second (mm/s)	0.3 ± 0.2 (0.2-0.4)	0.2 ± 0.1 (0.2-0.3)	0.1 ± 0.1 (0.1-0.2)	<0.001c
6th second (mm/s)	0.2 ± 0.1 (0.1-0.3)	0.2 ± 0.1 (0.1-0.3)	0.1 ± 0.1 (0.1-0.2)	<0.001d
8th second (mm/s)	0.2 ± 0.1 (0.1-0.2)	0.1 ± 0.1 (0.1-0.2)	0.1 ± 0.1 (0.1-0.1)	<0.001e
10th second (mm/s)	0.2 ± 0.1 (0.1-0.2)	0.1 ± 0.1 (0.1-0.2)	0.1 ± 0.1 (0.1-0.1)	<0.001f

DR= diabetic retinopathy; NPDR= nonproliferative diabetic retinopathy; PDR= proliferative diabetic retinopathy; SD= standard deviation*One-way analysis of variance was useda: p=0.334 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p <0.001 in NPDR vs. PDR.**
b: p=0.298 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
c: p=0.246 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
d: p=0.202 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
e: p=0.182 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
f: p=0.190 in No-DR vs. NPDR, p<0.001 in No-DR vs. PDR, and p<0.001 in NPDR vs. PDR.**
**Tukey post hoc test was used.

In pediatric patients with DM, Karavanaki et al.[19] studied pupillary adaptation to darkness using a portable pupillometer and found that the mean pupil size was negatively correlated with HbA1c level. In contrast to their study, we did not find any correlations between HbA1c values and pupil diameter in static and dynamic pupillometry. However, there are many methodological differences between the two studies, with the most important one being the categorization of numerical values. Karavanaki et al.[19] separated the DM patients as having either poor-, moderate-, or good-controlled HbA1c, and this differed from the uniformly high HbA1c levels observed in the present study.

Pittasch et al.[4] and Cahill et al.[18] in their respective investigations evaluated pupillary function using pharmacological manipulations. Ferrari et al.[14] used a pupil stimulator and response recorder that document pupillary responses with a video camera after stimulating with white bright and infrared LEDs. Similarly, Park et al.[11], Jain et al.[15], and Yang et al.[20] employed a pupillography system including an infrared-sensitive video camera and a luminometer. Prakash et al.[10] measured pupil responses in normal subjects using a modern Scheimpflug-based automatic pupillometry system. This device could measure pupillary responses via either scotopic, mesopic, or photopic static pupillometry or dynamic pupillometry, yielding information about the behavior of the pupil under decreasing illumination conditions. Here, we measured pupil responses in DM subjects. Therefore, to our knowledge, our study is the first study that evaluated the pupillary function of DM patients by Scheimpflug-based automated pupillometry. Also, our study contains one of the largest sample sizes for this subject to date in literature (specifically, 300 subjects, with 155 having type 2 DM without or with DR in several stages).

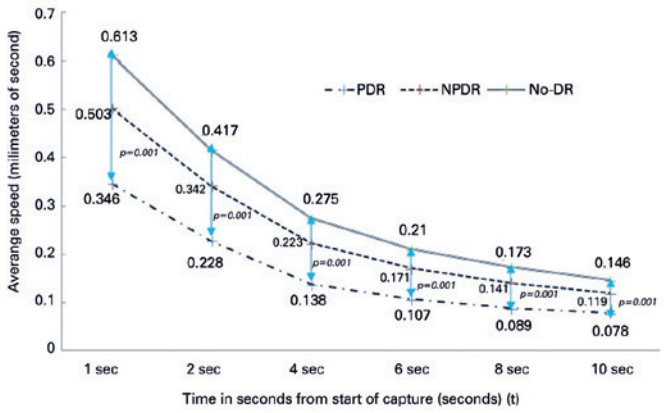

Figure 2. Demonstration of the average speeds of the diabetic subgroups

We applied great care on elucidating the differences between the types of DM in our patients and evaluated patients with type 2 DM. Separating DM subjects is vital in the study because we know different pupillary responses can be observed in patients with type 1 versus type 2 DM[18]. In addition, the most important part of our study involved subjects with PDR. We included subjects with PDR from among newly diagnosed, previously untreated patients to exclude any effects of laser treatment on pupil responses, because it has been shown that panretinal laser photocoagulation may significantly affect pupil diameter; however, focal/grid laser photo-

Table 6. The correlations between pupil diameter with DM duration and HbA1c level

		DM duration (years)		HbA1c (%)	
		r value	p value*	r value	p value*
Static pupillometry	Scotopic (mm)	-0.480	**<0.001**	-0.100	0.214
	Mesopic (mm)	-0.375	**<0.001**	-0.079	0.328
	Photopic (mm)	-0.191	**<0.001**	-0.052	0.524
Dynamic pupillometry	0th second (mm)	-0.212	**<0.001**	-0.086	0.410
	1st second (mm)	-0.377	**<0.001**	-0.074	0.359
	2nd second (mm)	-0.446	**<0.001**	-0.079	0.329
	4th second (mm)	-0.487	**<0.001**	-0.074	0.360
	6th second (mm)	-0.507	**<0.001**	-0.085	0.293
	8th second (mm)	-0.504	**<0.001**	-0.083	0.302
	10th second (mm)	-0.502	**<0.001**	-0.077	0.341

DM= diabetes mellitus.
*Pearson correlation coefficient test was used.

coagulation may not[21]. Park et al.[11] in their research did not include patients who had undergone panretinal laser photocoagulation, and we designed our study with reference to their method. Thus, we excluded the effects of generalized retinal cell death on pupillary function. In this regard, our study includes a homogeneous DM group as well as a large sample size.

The main goal of this study was to extensively investigate pupillary function in patients with type 2 DM, and it can be deemed different from the previous studies in terms of its design, methods, and results; nevertheless, this study also has several limitations. Systemic diseases, use of insulin or oral antidiabetics, and previous ocular treatments may affect pupillary measurements in DM patients, and it is utopian to think completely excluding these factors. Additionally, ultrastructure abnormalities in iris specimens, including sphincter and dilatator pupil muscle nerve endings, were observed in DM patients, but we did not study how these might affect pupillometry measurements[22]. These are possible topics that should be delved into in future research.

In conclusion, this study shows that static and dynamic pupillometry measurements are altered in patients with type 2 DM and that this alteration progresses as the duration of DM increases. The presence of NPDR does not have a negative effect on pupillometry findings, but it is more altered in the co-presence of PDR. These results suggest that automated quantitative pupillometry may be useful to verify the severity of DR.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

Codeine plus acetaminophen improve sleep quality, daily activity level, and food intake in the early postoperative period after photorefractive keratectomy: a secondary analysis

Melhora da qualidade do sono e das atividades diárias pós PRK imediato utilizando codeína com paracetamol: análise secundária de um ensaio clínico randomizado, duplo-cego e placebo-controlado

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ABSTRACT | Purpose: To determine whether codeine plus acetaminophen after photorefractive keratectomy (PRK) have beneficial effects on sleep quality, activity levels, and food intake, beyond their effect of pain relief. **Methods:** We enrolled 40 patients (80 eyes) in this randomized, double-blind, paired-eye, placebo-controlled, add-on trial. Each eye was treated 2 weeks apart, and the patients were randomly allocated to receive either the placebo or the intervention (30 mg codeine and 500 mg acetaminophen) (4 times a day for 4 days). Outcomes were sleep quality, daily activity level, and food intake within 24-72 h post-photorefractive keratectomy, as measured by the McGill Pain Questionnaire. **Results:** Sleep quality and daily activity level were inversely associated with pain scores within the first 48 h post-photorefractive keratectomy. During the intervention, patients were significantly more likely to score their sleep quality as good at 24 h (relative risk=2.5; 95% confidence interval 1.48-4.21, p<0.001) and 48 h compared to during placebo (relative risk=1.37; 95% confidence interval: 1.03-1.84, p=0.023). The probability of reporting good daily activity level at 24 and 72 hours post-photorefractive keratectomy was three times higher when patients received the intervention compared to the placebo (relative risk=3.0; 95% confidence interval: 1.49-6.15, p=0.006 and relative risk=1.31; 95% confidence interval: 1.02-1.67, p=0.021, respectively). No difference was observed in food intake. **Conclusion:** The oral combination of codeine and acetaminophen significantly improves sleep quality and daily activity level within the first 24-72 h post-photorefractive keratectomy compared to a placebo.

Keywords: Codeine; Photorefractive keratectomy; McGill Pain Questionnaire; Pain; Acetaminophen; Sleep; Activities of daily living

ClinicalTrials.gov number: NCT02625753

RESUMO | Objetivo: Determinar se codeína (30 mg) mais paracetamol (500 mg) após ceratectomia fotorrefrativa fornece efeitos benéficos sobre a qualidade do sono, níveis de atividade e ingestão de alimentos além de seu efeito analgésico. **Métodos:** Quarenta pacientes (80 olhos) foram incluídos neste estudo randomizado, duplo-cego, pareado, placebo-controlado, *add-on*. Cada olho foi tratado com 2 semanas de intervalo, sendo aleatoriamente alocado para placebo ou intervenção (4x/dia durante 4 dias). Os resultados incluíram a qualidade do sono, atividade diária e ingestão de alimentos dentro de 24-72 horas de pós-operatório, conforme medido pelo McGill Pain Questionnaire. **Resultados:** A qualidade do sono e os níveis de atividade foram inversamente associados aos escores de dor nas primeiras 48 horas após o ceratectomia fotorrefrativa. Durante a intervenção, os pacientes foram significativamente mais propensos a classificar seu sono como bom em 24 horas (risco relativo=2,5, intervalo de confiança de 95%: 1,48-4,21, p<0,001) e 48 horas comparado ao placebo (risco relativo=1,37, intervalo de confiança de 95%: 1,03-1,84, p=0,023). A probabilidade de relatar bons níveis de atividade em 24 e 72 horas após ceratectomia fotorrefrativa também foi significativamente maior durante a intervenção em comparação com placebo (risco relativo=3,0, intervalo de confiança de 95%: 1,49-6,15, p=0,006 e risco relativo=1,31, intervalo de confiança de 95%: 1,02 -1,67, p=0,021, respectivamente). Nenhuma diferença foi observada

Submitted for publication: August 13, 2019
Accepted for publication: January 16, 2020

Funding: This study received no specific financial support. Latinofarma partially funded the drugs used in this study.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (CAAE: 91428718.1.0000.0068).

entre a intervenção e placebo em relação à alimentação oral. **Conclusão:** A combinação de codeína e paracetamol melhorou significativamente a qualidade do sono e atividades diárias nas primeiras 24-72 horas após o ceratectomia fotorrefrativa em comparação com placebo.

Descritores: Codeina; Ceratectomia fotorrefrativa; McGill Pain Questionnaire; Dor; Acetaminofen; Sono; Atividades cotidianas

ClinicalTrials.gov number: NCT02625753

INTRODUCTION

Excimer laser photorefractive keratectomy (PRK) is a surgical procedure commonly performed for correcting mild-to-moderate refractive errors[1,2]. It is a preferred approach to treating special cases, such as a thin cornea, moderate dry eye, and subtle topographic irregularities, and patients who underwent previous eye surgeries[3,4]. However, despite its effectiveness and safety, PRK usually involves a high level of postoperative pain and discomfort[5], which not only adversely affects the patient's overall satisfaction with the procedure but also reduces his or her willingness to undergo the procedure again[6,7]. Therefore, improvement of patient care during the immediate PRK postoperative period has become a major clinical challenge for ophthalmologists[8-12].

We recently demonstrated that adding an oral combination of codeine and acetaminophen to a standardized postoperative pain regimen is an effective and safe therapeutic strategy to alleviate post-PRK pain[8]. This approach provides significantly greater pain relief compared to a placebo without affecting corneal wound healing or having serious adverse effects. However, whether this therapeutic strategy also leads to improvement in subjective indexes of health and well-being in the early PRK postoperative period is unclear. It is conceivable that improvements in personal, social, and daily activity-related contexts post-PRK might potentially lead to better patient satisfaction and clinical outcomes, ultimately having profound implications for PRK's popularity and acceptability[7]. Surprisingly, to the best of our knowledge, no clinical trial has specifically performed a multidimensional analysis of how a pain management strategy affects health-related quality of life outcomes post-PRK.

In light of the limited data on the benefits of systemic opioids on improving patient care post-PRK, we performed a post-hoc secondary analysis based on our previous randomized clinical trial in order assess whether, compared to a placebo, the oral combination of codeine and acetaminophen provides beneficial effects on sleep quality, daily activity level, and food intake in patients post-PRK. This study will provide a more detailed assessment of the feasibility of using this therapeutic strategy in clinical practice.

METHODS

Study design, participants, and outcomes

The trial design, eligibility criteria, outcomes, and postoperative pain protocol have been reported previously[8]. Briefly, we performed a randomized, double-blind, paired-eye, placebo-controlled, add-on trial (ClinicalTrials.gov number: NCT02625753). We assessed the efficacy and safety of the oral combination of codeine and acetaminophen compared to a matching placebo for pain reduction post-PRK. Between November 2014 and June 2015, 228 patients were admitted to the Hospital das Clínicas, Universidade de São Paulo, São Paulo, Brazil, between November 2014 and June 2015 for PRK. We excluded pregnant or lactating women and patients with hypersensitivity or allergy to oral medications, active allergic disease, inflammatory, or infectious conditions, a history of ocular disease or trauma, best-corrected visual acuity ≤20/25, autoimmune diseases or immunosuppression, or type I/II diabetes. Inclusion criteria were as follows: patients scheduled for myopic excimer laser PRK, age ≥20 years, eyes with a spherical component between -1.00 and -5.00 diopters (D) with or without astigmatism, cylindrical component ≤1.5 D, spherical anisometropia ≤0.75 D, cylindrical anisometropia ≤0.5 D, and documented refractive stability over the previous 12 months. Therefore, 41 patients (82 eyes) met all eligibility criteria. Of them, 1 patient who had recurrent vomiting after the first surgery and was found to have celiac disease was excluded. Thus, a total of 40 patients (80 eyes) participated in the trial, of which 27 (67%) were women and most were white (57%).

The original primary outcome was a difference in pain levels between codeine+acetaminophen-treated eyes and placebo-treated eyes, as measured on a 0-10 pain visual analog scale (VAS) obtained 24 h post-PRK. A detailed list of all secondary outcomes is available in our previous publication.

The trial was approved by the local ethics committee and adhered to the Declaration of Helsinki. All participants provided written informed consent.

PRK, procedures, and drug administration

All surgeries were performed by the same surgeon. The unit of analysis was the eye. All patients underwent

bilateral PRK, but each eye was treated 2 weeks apart. Patients were randomly administered either the intervention or the placebo in the form of indistinguishable capsules containing either 30 mg of codeine and 500 mg or acetaminophen or the placebo (1:1 ratio). Blinding and allocation concealment were maintained by the use of identical, coded medication bottles prepared by an independent pharmacist. Randomization was controlled by the dispensing pharmacy that dispensed either the intervention or the placebo using computer-generated random numbers. Treatment was given orally 4 times a day for 4 days post-PRK.

In addition, all patients received standard care as per the hospital protocol: a regimen of 200 mg of celecoxib twice a day for 4 days started 1 h before PRK, and a drop each of 0.5% moxifloxacin and 0.1% dexamethasone immediately post-PRK but before receiving an Acuvue II therapeutic contact lens (Johnson & Johnson, New Brunswick, NJ, USA). Patients were instructed to use 0.5% moxifloxacin and 0.1% dexamethasone ophthalmic drops every 4 h for 7 days, 1 mg/mL of nepafenac ophthalmic suspension every 6 h for 3 days, and artificial tears, as needed, without any concurrent medications for 72 h post-PRK. One week post-PRK, patients received 1 mg/mL of fluorometholone eye drops every 8 h for 7 days, with increasing dose intervals: every 12 h in week 3 and once per day in week 4.

Outcomes in secondary analysis

Findings for patient-reported outcomes were reported on the basis of three domains of the McGill Pain Questionnaire: sleep quality, daily activity level, and food intake. Sleep quality was measured on a 3-point Likert scale (good, fitful, or can't sleep). Both daily activity level and food intake were operationalized on a 4-point Likert scale (good, some, little, none), as previously described[13].

Statistical analysis

Data were presented as mean (95% confidence intervals [CIs]) or counts (percentage). To test the effects of the intervention compared to the placebo, we constructed multinomial logistic and multiple linear regression models (adjusted for age, gender, and race). These models explicitly incorporated the paired-eye design using a robust estimator of the variance, which took into account the correlation between pairs of eyes. Relative risks [RRs] and 95% CIs were calculated, as described previously[14]. All analyses were performed using Stata 14 (Stata Corp, College Station, TX, USA). P was two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

A description of the patient population has been reported previously[8] and will be briefly summarized here. The mean age of the patients was 30 years (min-max=22-52 years). The mean spherical equivalent was -2.18 (0.66) in the right eye and -2.16 (0.63) in the left eye.

Sleep quality

Post-PRK sleep quality assessment revealed an inverse association between pain scores and sleep quality within the first 24 h post-PRK (Table 1); the higher the pain levels at 24 h, the lower the sleep quality (p for trend=0.008). However, we did not observe robust and statistically significant correlations between pain levels and sleep quality at 48 and 72 h post-PRK (Table 1). Remarkably, at 24 and 48 h post-PRK, patients receiving the intervention were significantly more likely to score their sleep as good compared to patients receiving the placebo (58% vs. 25%; $p<0.001$ and 82% vs. 60%; p=0.02, respectively) (Table 2).

Daily activity level

Analysis of the daily activity level post-PRK indicated that higher pain levels are associated with less activity within the first 48 h post-PRK (p for trend=0.039 and 0.018 at 24 and 48 h, respectively) (Table 1). The probability of reporting good daily activity levels at 48 h post-PRK was three times higher when patients received the intervention compared to the placebo (RR=3.0; 95% CI=1.5-6.1; p=0.006). In addition, although at 48 and 72 h, the effect sizes were smaller, the results were qualitatively analogous (RR=1.6; 95% CI=0.9-3.2; p=0.10 and RR=1.31; 95% CI=1.0-1.7; p=0.021, respectively) (Table 2).

Food Intake

The patients' food intake was not associated with pain levels post-PRK (Table 1). When questioned about their food intake post-PRK, all patients reported adequate food intake throughout the 72 h period post-PRK (Table 2).

DISCUSSION

Main findings

The addition of an oral combination of codeine and acetaminophen to the post-PRK pain control protocol

Table 1. Association between subjective indexes of health, personal and social contexts, and pain levels

Time point	Category	Eyes (*n*=80)	Pain levels (cm), mean (95% CI)	*P* (overall)	*P* (trend)	β in cm (95% CI)	*P* (coefficient)
Sleep quality							
24h	Good	33 (41)	4.60 (3.85,5.35)	0.003	0.008	Reference	
	Fitful	38 (47)	6.52 (5.74,7.30)			1.92 (0.85,2.98)	0.001
	Can't sleep	9 (11)	6.29 (4.67,7.91)			1.69 (-0.11,3.48)	0.06
48h	Good	57 (71)	2.19 (1.71,2.67)	0.37	0.37	Reference	
	Fitful	23 (29)	2.61 (1.90,3.31)			0.41 (-0.51,1.34)	0.37
	Can't sleep	0	-			-	-
72h	Good	75 (93)	0.53 (0.30,0.76)	0.85	0.63	Reference	
	Fitful	4 (5)	0.63 (0.00,1.60)			0.10 (0.00,1.13)	0.85
	Can't sleep	1 (1)	0			-	-
Daily activities							
24h	Good	10 (13)	4.48 (2.99,5.96)	0.16	0.04	Reference	
	Some	6 (7)	5.18 (4.22,6.15)			0.70 (-0.75,2.16)	0.33
	Little	25 (31)	5.25 (4.43,6.07)			0.77 (-0.94,2.49)	0.37
	None	39 (49)	6.38 (5.39,7.37)			1.90 (0.05,3.75)	0.04
48h	Good	24 (30)	2.01 (1.25,2.77)	0.05	0.018	Reference	
	Some	24 (30)	2.01 (1.35,2.67)			0 (-1.03,1.03)	0.99
	Little	26 (33)	2.49 (1.98,3.01)			0.48 (-0.50,1.46)	0.32
	None	6 (7)	3.93 (2.65,5.21)			1.92 (0.49,3.34)	0.01
72h	Good	53 (66)	0.46 (0.19,0.72)	0.56	0.58	Reference	
	Some	15 (19)	0.77 (0.30,1.25)			0.32 (-0.22,0.85)	0.24
	Little	11 (14)	0.56 (0.06,1.06)			0.11 (-0.48,0.69)	0.72
	None	1 (1)	0.14 (0.00,0.82)			-0.31 (-0.93,0.30)	0.31
Oral feeding							
24h	Good	40 (50)	5.43 (4.56,6.30)	0.30	0.18	Reference	
	Some	14 (17)	5.39 (4.03,6.75)			-0.04 (-1.79,1.70)	0.96
	Little	26 (33)	6.28 (5.31,7.26)			0.85 (-0.38,2.09)	0.17
	None	0	-			-	-
48h	Good	61 (76)	2.16 (1.72,2.60)	0.26	0.14	Reference	
	Some	13 (16)	2.91 (2.12,3.70)			0.75 (-0.18,1.68)	0.11
	Little	6 (7)	2.58 (1.43,3.72)			0.42 (-0.82,1.65)	0.50
	None	0	-				
72h	Good	73 (91)	0.55 (0.32,0.78)	0.09	0.64	Reference	
	Some	5 (6)	0.06 (0.00,0.45)			-0.49 (-0.97,-0.02)	0.04
	Little	2 (3)	0.65 (0.00,2.26)			0.10 (-1.54,1.73)	0.90
	None	0	-			-	-

Pain levels are from 0 to 10 VAS (cm).
β is the mean difference comparing a specific category to the reference group (in cm).
All results are adjusted for race, age, gender, and treatment (1=codeine with acetaminophen; 0=placebo) and take into account the correlation between pairs of eyes. *P* (overall): ANOVA-like test that examines whether there is any difference between groups. *P* (trend): tests the linear trend in the mean over categories (sleep quality: 0=good; 1=fitful; 2=can't sleep; daily activities and food intake: 0=good; 1=some; 2=little; 3=none). *P* (coefficient): examines whether specific categories differ from the reference category.
CI= confidence intervals; VAS= visual analog scale; ANOVA= analysis of variance.

might improve the patient's quality of life in the early recovery period post-PRK (24-48 h). Together with its efficacy in alleviating acute postoperative pain[8], this therapeutic strategy might lead to a higher postoperative quality of life and is likely to positively affect the patient's perception of PRK.

Comparison with previous investigations

Postoperative pain management in PRK has been explored by many researchers in recent years[5,8-12,15,16]. However, subjective indexes of health and well-being that take place outside the clinical encounter have been rarely investigated and are typically disregarded in

Table 2. Effect of the intervention (codeine and acetaminophen) compared to the placebo on subjective indexes of health and personal and social contexts

		Intervention		Placebo			
Time point	**Category**	***N***	**%**	***N***	**%**	**RR (95% CI)**	***P***
Sleep quality							
24h	Good	23	58	10	25	2.50 (1.48-4.21)	<0.001
	Fitful	16	40	22	55	0.63 (0.46-0.87)	0.002
	Can't sleep	1	2	8	20	0.25 (0.13-0.51)	0.009
48h	Good	33	82	24	60	1.37(1.03-1.84)	0.02
	Fitful	7	19	16	40	0.44(0.20-0.95)	0.02
	Can't sleep	0	0	0	0	NE	NE
72h	Good	40	100	35	88	1.05 (0.93-1.18)	0.44
	Fitful	0	0	4	10	0.25 (0.03-2.28)	0.29
	Can't sleep	0	0	1	2	NE	NE
Daily activities							
24h	Good	6	15	4	10	3.03 (1.49-6.15)	0.006
	Some	5	12	1	2	2.32 (1.29-4.14)	0.005
	Little	16	40	9	23	1.44 (1.04-1.99)	0.02
	None	13	33	26	65	0.54 (0.36-0.81)	0.001
48h	Good	15	38	9	22	1.66 (0.86-3.22)	0.10
	Some	15	38	9	22	1.66 (0.85-3.27)	0.11
	Little	8	20	18	45	0.44 (0.23-0.88)	0.006
	None	2	5	4	10	0.50 (0.12-2.03)	0.32
72h	Good	30	75	23	58	1.31 (1.02-1.67)	0.02
	Some	6	15	9	23	0.65 (0.42-1.01)	0.06
	Little	4	10	7	17	0.50 (0.26-0.94)	0.02
	None	0	0	1	2	0.44 (0.21-0.91)	0.03
Oral feeding							
24h	Good	23	58	17	42	1.35 (0.91-2.00)	0.13
	Some	10	25	4	10	2.50 (0.85-7.32)	0.09
	Little	7	17	19	48	0.37 (0.17-0.77)	0.008
	None	0	0	0	0	NE	NE
48h	Good	32	80	29	73	1.13 (0.91-1.38)	0.25
	Some	7	18	6	15	0.71 (0.39-1.29)	0.26
	Little	1	2	5	12	0.62 (0.27- 1.42)	0.26
	None	0	0	0	0	NE	NE
72h	Good	39	98	34	85	1.15 (1.01- 1.30)	0.03
	Some	1	2	4	10	0.17 (0.03-0.98)	0.05
	Little	0	0	2	5	0.14 (0.02-0.84)	0.03
	None	0	0	0	0	NE	NE

CI= confidence interval; RR= relative risk; NE= not estimated (due to sparse data).

clinical practice by ophthalmologists. Indeed, although the early postoperative period post-PRK should be evaluated as a multidimensional concept[7], no studies have specifically addressed health-related quality of life outcomes post-PRK.

Even though many factors alter sleep architecture and sleep quality, pain is a major cause of postoperative sleep disturbance in several medical specialties[17]. Notably, sleep disturbance might adversely affect postoperative recovery. In fact, sleep disturbance, commonly experienced by patients in the early PRK postoperative period, is associated with compromised patient recovery, longer hospitalization[18], and reduced quality of life in non-ophthalmologic surgeries[19]. In addition, even short-term impaired sleep quality might modify the patient's sensitivity to nociceptive stimuli[20], increasing pain perception[21], which can exacerbate sleep disturbance. A previous observational study showed that poor sleep

quality might increase the risk of dry eye[22] and exacerbate or prolong highly prevalent transient ocular surface disease[6,23,24]. Therefore, therapeutic strategies, such as the combination of codeine and acetaminophen, capable of improving sleep, can optimize the early postoperative PRK recovery period and likely result in improved clinical outcomes and greater patient satisfaction.

We are not aware of any randomized trials that have compared the effects of pain reduction strategies on a patient's activities post-PRK. However, the higher daily activity level during intervention, compared to the placebo, could be explained, at least in part, by decreased pain levels and better sleep quality. In fact, both pain levels and sleep quality strongly affects the patient's daily activity level[25,26].

Limitations

This trial had a few limitations. First, the analysis was limited by a relatively low statistical power to detect small to moderate effects. Second, the Likert-based component of the McGill Pain Questionnaire does not capture the complex multidimensionality of the patient's quality of life. Other health-related quality of life instruments, such as SF-12/36[27], might evaluate a range of different health domains and are likely to be more suitable for further, more comprehensive investigations.

The oral combination of codeine and acetaminophen significantly improves sleep quality and the daily activity level within the first 24-72 hours post-PRK compared to a placebo, which reinforces the feasibility of this therapeutic strategy for use in post-PRK pain management. Our findings highlight the importance of both patient-reported outcomes and patient-centered type of care post-PRK to increase the popularity and acceptability of this common laser vision correction procedure.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

Impact of a mobile unit on access to eye care in São Paulo, Brazil

Impacto do uso de unidade móvel no acesso à saúde ocular em São Paulo, Brasil

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ABSTRACT | Purpose: The goal of this study was to determine the impact of a mobile eye health unit on access to eye care and to generate a profile of the population requiring ophthalmic care by age, nature of their ophthalmic diseases, and optimal management. **Methods:** The study was conducted in 14 cities in the southwest region of São Paulo, Brazil. Subjects included individuals who participate in the Brazilian Unified Health System who were in need of eye care. There were no restrictions on age, gender or socioeconomic status. Data was transferred to an Excel table for statistical analyses. **Results:** We evaluated 6,878 participants in this survey with mean age of 44 years (range 4 months to 96 years); 65.5% were female. Among the diagnoses, 78.6% presented with refractive errors, 9.6% presented with cataracts and 8.3% presented with pterygium. New corrective lenses were prescribed for 60.9% of the participants; 10% retained their existing lenses, ~28% required counseling only and18.1% of the participants were referred to a tertiary facility for specialized exams and/or surgical procedures. Of the participants who required outside referrals, 36.4% required oculoplastic/external eye surgery and 31.8% required cataract surgery. **Conclusion:** The vast majority of patients presenting to a mobile eye health unit required prescriptions for corrective lenses. The rate of detection of ocular disorders was relatively high and the mobile unit provided effective treatment of refractive errors and referrals for specialized ophthalmic examinations and procedures. A mobile eye health unit can be an effective alternative method for improving access to basic eye care, for promoting eye health education and preventing blindness.

Keywords: Mobile health units; Eye health; Vision disorders; Refractive errors; Eyeglasses; Blindness/prevention & control

RESUMO | Objetivo: Determinar o impacto do uso de unidade móvel no acesso à saúde ocular e avaliar o perfil da população que necessita de cuidados oftalmológicos, as doenças oculares mais frequentes e o tratamento. **Métodos:** Estudo transversal realizado em 14 municípios da região sudoeste do Estado de São Paulo utilizando uma unidade móvel oftalmológica. Os participantes eram usuários do Sistema Único de Saúde que procuraram atendimento oftalmológico, sem restrição quanto a idade, gênero ou condição socioeconômica. Os dados foram transferidos para a tabela Excel para análise estatística. **Resultados:** Participaram do estudo 6.878 pessoas, com média de idade de 44 anos (variação de 4 meses a 96 anos) e 65,5% eram mulheres. Erros refrativos estavam presentes em 78,6% dos participantes, catarata em 9,6% e pterígio em 8,3%. Para 60% foram prescritos óculos, para 10% foi mantida a correção óptica em uso e para 28% foram necessárias apenas orientações. Exames especializados ou procedimentos cirúrgicos foram indicados para 18,1% dos casos que foram encaminhados para tratamento em serviço terciário. Dentre os pacientes referenciados, 36,4% necessitavam de cirurgia oculoplástica ou para tratar afecções externas do olho e 31,8%, de cirurgia de catarata. **Conclusão:** A grande maioria dos pacientes que procurou atendimento na unidade móvel necessitava de prescrição de óculos. A unidade móvel oftalmológica possui alto grau de resolutividade para os problemas oculares, com oportunidade de tratar os erros refrativos e referenciar os pacientes que necessitam de atendimento especializado, geralmente relacionado a condições cirúrgicas. Unidades móveis podem ser uma alternativa aos cuidados oftalmológicos básicos, melhorando o acesso, atuando na promoção da saúde ocular e prevenindo a cegueira.

Submitted for publication: July 26, 2018
Accepted for publication: December 22, 2019

Funding: This study was supported by FAPESP (Convenio FAPESP – CNPq SUS - processo 2009/53281-1).

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Universidade Estadual Paulista Protocolo 4001-2011.

Descritores: Unidades móveis de saúde; Saúde ocular; Transtornos da visão; Erros de refração; Óculos; Cegueira/prevenção & controle

INTRODUCTION

Globally, there are 253 million visually-impaired individuals of whom 217 million experience moderate to severe dysfunction; 36 million individuals are legally blind[1]. It is estimated that 80% of the cases of visual impairment and blindness are caused by disorders that are either curable or preventable[2,3].

The prevalence of visual impairment has decreased in the past 20 years, although the absolute number of cases has increased due to population growth and aging[4]. In Brazil, 18.8% of the population is visually impaired, including almost 50% of individuals over 65 years of age[5]; ~0.4 to 0.5% of the Brazilian population suffers from blindness[6].

One key measure to reduce visual impairment and blindness is to provide effective access to eye care services[2]. Although the number of ophthalmologists has increased in Brazil to a level that is currently considered to be sufficient, availability and access to ophthalmic services are vastly different in different regions and do not meet the needs of all communities; this is mainly due to economic difficulties, poor distribution of resources and limited infrastructure[7-9]. This is of particular concern given that aging is clearly associated with a significant increase in the incidence of ophthalmic disorders[4,7,8].

While eighty percent of the Brazilian population depends on public health care provided by the Unified Health System (SUS), only 25% of the practicing ophthalmologists participate in this system. As such, those who rely on the public system currently do not have effective access to eye care services[10]. Even when ophthalmic care is available, other factors can hinder access to eye care[6], including inadequate transportation, limited social support and the comparatively high cost of evaluation and treatment[11].

Brazilians have no access to eye care[12]. Mobile units represent a feasible alternative for those living in small municipalities and at the periphery of large cities and/or for providing coverage for specific target populations. The mobile units can be equipped for basic ophthalmic examinations and should be capable of screening for more complex eye diseases and generating appropriate referrals for treatment[13,14].

The model of mobile units was originally conceived in the United States early in the 20th century and were put into practice as Community Mobile Eye Clinics; this model was ultimately used as a means to provide other medical services in addition to basic eye examinations[15]. These units were used primarily by those who had limited access to basic health care, primarily in resource-poor regions with inadequate physical infrastructure[16].

Several countries are currently using mobile eye health units to improve access to eye care and have collected epidemiological data and generated screening programs in impoverished areas and among segments of the population who have limited access to health care[17]. Primary eye care provided by mobile units is typically more efficient at providing care for the population at large than a traditional practice[14]. However, the impact of mobile units on ocular health is difficult to evaluate quantitatively as there are substantial geographic and socioeconomic variations among those in the population to be served and likewise among the services offered[17].

The purpose of this study was to determine the impact of a mobile eye health unit on access to eye care and evaluate the profile of the population requiring ophthalmic consultation in São Paulo, Brazil. We also identified the main ocular diseases in the community and their appropriate management in this setting.

METHODS

This research was approved by the Ethics and Research Committee of the Faculty of Medicine of Botucatu, São Paulo State, Brazil and the study adhered to the tenets of the Declaration of Helsinki. All subjects underwent a thorough informed consent procedure and were required to sign an informed consent form prior to participation in the study.

The study was conducted in 2011 in the urban areas within 14 municipalities from the southwest region of São Paulo State, Brazil, and enrolled participants who spontaneously requested services from a mobile eye health unit in their municipality. Individuals of any age, gender or socioeconomic status were included as participants in the study. Individuals who refused to participate were excluded from this study.

The mobile eye health unit was a bus adapted for ophthalmic care (Figure 1). This bus was equipped with an auto lensometer (AL 500 Reichert, NY, USA), an auto refractor (Accuref K Shinn Nippon, Tokyo, Japan), a manual refractor, a retinoscope, skiascopic rulers, 'E' charts, a direct ophthalmoscope (Welch Allyn Inc., NY,

USA), 78 diopter lenses (Volk Optical Inc., Ohio, USA), slit lamp (Shinn Nippon, Tokyo, Japan), a pneumo-tonometer (CT-60, Topcon, Tokyo, Japan) and an applanation tonometer (Goldmann tonometer Haag Streit, Switzerland).

Standardized eye examinations were performed by a trained team that included two ophthalmologists, three ophthalmology residents and four technicians who provided support services, including filling out forms, arranging patient flow, instilling eye drops and providing general information.

The order of the examination was determined by a specific protocol using demographic data, specific eye complaints, self-reported systemic or ocular diseases and a family history of eye problems. The ocular exam was divided into stations as follows: pre-consultation, visual acuity, pneumatic intraocular pressure, automatic objective refraction, pupillary dilation and/or cycloplegia, biomicroscopy and fundoscopy.

Uncorrected visual acuity for distance was evaluated for each eye using an illiterate 'E' chart placed six meters from the participant; a second test was performed with eyeglasses if in use. If the patient was unable to see the top line of the chart at six meters, the vision was tested and recorded as counting fingers, hand movements, light perception or no light perception. Children who were pre-verbal were evaluated by preferred gaze or light tracking. Based on the results of this preliminary examination, subjective refraction was performed for those with ocular complaints of reduced visual acuity or symptoms of asthenopia. If the participants were less than 40 years old, they underwent a cycloplegic refraction 30 minutes after instillation of cyclopentolate (Cicloplegic®, Allergan, Guarulhos/SP, Brazil). Biomicroscopic exam after instillation of three drops of mydriatic eye drops (Mydriacyl®, Alcon, São Paulo/SP, Brazil) within an interval of five minutes, and examination after 30 minutes was done to identify causes of low vision which did not improve with a refractive correction. Goldmann tonometry was performed for individuals >40 years old, in individuals with a family history of glaucoma, and in those with suspected glaucoma. Fundoscopic examination under mydriasis was performed for patients with hypertension, diabetes mellitus, visual impairment without improvement with refraction and for patients with high refractive errors.

The dDefinition of visual impairment and blindness was adopted from the tenth edition of the international code of diseases by World Health Organization (WHO) based on visual acuity (VA) as follows: moderate visual impairment >0.1 VA <0.3; severe visual impairment, >0.05 VA <0.1 and blindness VA <0.05[18]. The measure of VA was based on the results from the better of the two eyes after refraction.

After completion of the ophthalmic examination, an ophthalmologist determined whether corrective lenses were required and/or whether any additional clinical/surgical treatments were warranted and required referral to a regional tertiary hospital.

The data were transferred to an Excel table for statistical analyses; $p<0.05$ was considered as statistically significant.

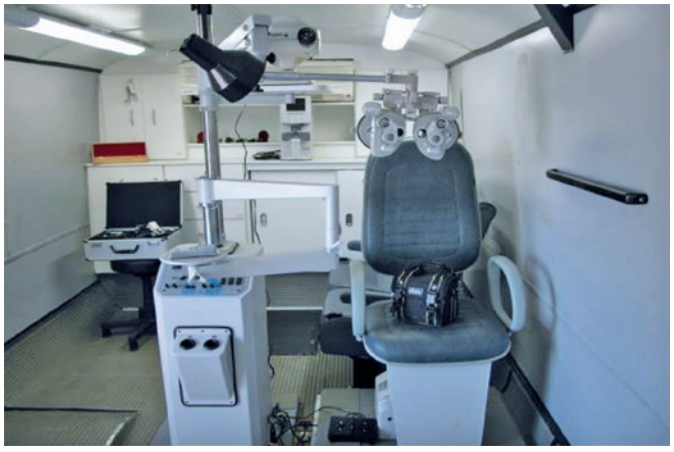

Figure 1. Mobile eye health unit: a bus that has been adapted to provide eye care.

RESULTS

The specific cities, their characteristics, and the number of study participants from each municipality are presented in table 1.

The study included 6,878 participants. The mean age was 44 years old (range 4 months to 96 years). Of these, 4,508 (65.5%) were female.

The most common ocular complaints were reduced near VA which presented in 4,151(60.4%) of the participants followed by reduced far VA presented by 3,851 (56%) of the participants (Table 2).

Based on participant response, 4,359 (63.4%) of the individuals were otherwise healthy; 2,151 (31.3%) had been diagnosed with hypertension and 797 (11.6%) with diabetes mellitus. Corrective lenses had been prescribed previously for 2,350 (34.2%); 341 (5%) had undergone

cataract surgery, 271(3.9%) had undergone pterygium resection, 96 (1.4%) reported glaucoma and 84 (1.2%) reported previous ocular trauma.

The best corrected VA was within normal limits for 6,290 participants, or 92.4% of the study population. Another 349 participants (5.2%) had moderate and severe visual impairment and 134 (2%) were blind. There were 132 (1.9%) participants who were unable to report VA; this group included primarily pre-verbal children.

Visual impairment and blindness was significantly more common among individuals over 70 years old ($p<0.001$).

Ametropias were diagnosed in 5,406 (78.6%) of the individuals who were evaluated by the mobile eye health unit; 660 (9.6%) were diagnosed with cataract and 483 (7%) with pterygium; 247 (3.6%) of the participants had a fully normal exam. Corrective lenses were prescribed for 4,101 (60.9%) of the participants, while 718 (10%) did not require a change in lens prescription; 1908 individuals (28.4%) required only counseling at the time of the visit.

A full 81.7% (5,619 patients) were treated successfully in the mobile eye health unit. Successful treatment was significantly higher among females (83.5%) than among males (78.8%; $p=0.03$); 1,245 of the participants (18.1%) required referral to a tertiary eye center (Figure 2). Likewise, participants older than 60 years of age were more likely to require referral ($p<0.001$). Most of re-

Table 1. Characteristics of the cities served by the mobile eye health units and and number of participants

City	Location[a] Latitude Longitude	Distance to Botucatu[a] (km)	IDHM[b]	Population[c]	Number of ophthalmologists[d] SUS	Number of participants
Águas de Santa Bárbara	22°52' 49°15'	108	0.757	5,601	0 0	456
Assis	22°39"42' 50°24"44'	250	0.805	95,144	10 6	1,444
Barra Bonita	22°29"41' 50°24"44'	59.9	0.788	35,246	4 4	233
Bernardino de Campos	23°00"47' 49°28"27'	137	0.734	10,775	1 1	335
Botucatu	22°53"09' 48°26"42'	0	0.800	127,328	15 9/35*	1,222
Brotas	22°1"72' 48°7"37'	92,6	0.740	21,580	3 0	561
Dois Córregos	22°21"58' 48°22"49'	81.2	0.725	24,761	0 0	218
Maracaí	22°36"39' 50°40"1'	277	0.771	13,332	0 0	309
Óleo	22°56"29' 49°20"31'	128	0.730	2,673	0 0	355
Pratânia	22°48"30' 48°39"58'	38.4	0.701	4,599	0 0	208
Promissão	21°32"12' 49°51"29'	222	0.743	35.674	0 0	233
Taquarituba	23°31"59' 49°14"40'	138	0.701	22,291	1 1	799
Tarumã	22°44"48' 50°34"38'	271	0.753	12,885	0 0	208
Torrinha	22°25"34' 48°10"09'	73,5	0.744	9,330	0 0	297

*number including ophthalmologists of Ophthalmology Service of Botucatu Medical School

[a]= Google Earth Mapas [Internet]. [citado 2018 Abr 15]. Disponível em]: https://www.google.com/earth/

[b]= Atlas do desenvolvimento humano no Brasil 2013 [Internet]. Programa das Nações Unidas para o Desenvolvimento; 2013.[citado 2018 Abr 15]. Disponível em: http://www.atlasbrasil.org.br/2013/

[c]= Instituto Brasileiro de Geografia e Estatística(IBGE) [Internet]. Rio de Janeiro: IBGE; 2015 [citado 2018 Abr 15]. Disponível em: http://www.ibge.gov.br/home/estatistica/populacao/censo2010/tabelas_pdf/Brasil_tab_1_14.pdf

[d]= Brasil. Ministério da Saúde. Departamento de Informática do Sistema Único de Saúde – DATASUS - Cadastro Nacional dos Estabelecimentos de Saúde do Brasil – CNES [Internet]. Brasília (DF): CNES; 2015 [citado 2018 Abr 15]. Disponível em: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?cnes/cnv/prid02sp.def.

ferrals were for oculoplastics/external eye or cataract surgery (Figure 3).

Logistic regression analysis revealed that defects in VA correlated with gender (females were more likely to have visual impairment), age (more visual impairment was detected among the elderly), presence of comorbidities (visual impairment was more likely among patients with more comorbidities) and locality of residence (visual impairment was more likely among those living far from specialized centers; Table 3).

Table 2. Main ocular complaints of the participants

Ocular complaint	Number of participants	%
Near visual difficulty	4,151	60.4
Far visual difficulty	3,851	56.0
Headache	1,836	26.7
Ocular pain	1,071	15.6
Pruritus	446	6.5
Hyperemia	365	5.3
Tearing/photophobia	212	3.1
Foreign body sensation	177	2.6
No complaint	176	2.6
Cataracts	106	1.6
Pterygium	82	1.2
Floaters/scotomata	70	1.0
Strabismus	24	0.4
Diplopia	17	0.2
Wounds and injuries	14	0.2
Secretions	12	0.2
Glaucoma	8	0.1
Edema	8	0.1
Blepharospasm	4	0.1
Color vision disturbances	4	0.1

*The same patient may have reported more than one complaint.

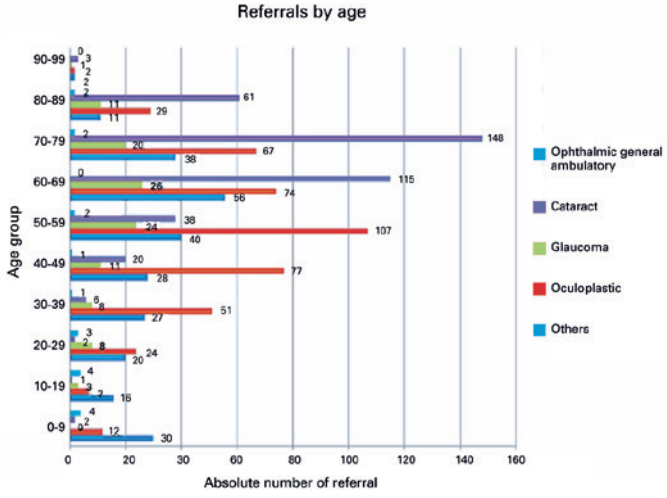

Figure 2. Distribution of referrals to a tertiary hospital for ophthalmic assistance after eye examination in a mobile eye health unit stratified by age

DISCUSSION

In the present study, the majority of participants were female. This observation concurs with previous studies from Brazil[19,20]. However, this outcome may be different in countries with socio-cultural and economic limitations that reduce women's access to health care[4,21].

There was no age restriction for participation in this study. As such, we were able to identify characteristics of individuals who required ophthalmic care in the general population. Similar to other surveys, the most common ocular complaints were those related to refractive errors[19,22,23]. Other complaints such as headache, pain, hyperemia, tearing and burning sensations can be manifestations of asthenopia; if included as such, this would further increase the complaints related to refractive errors.

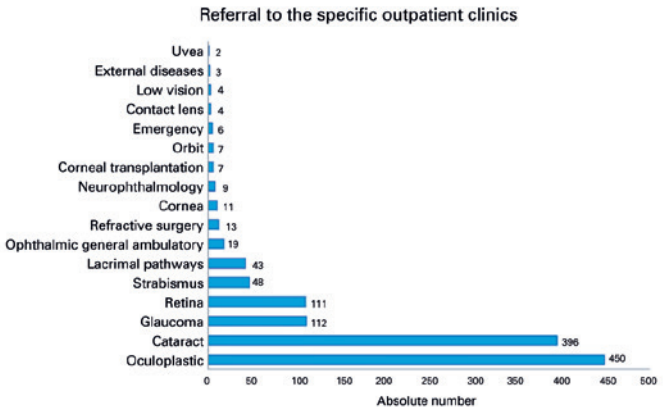

Figure 3. Distribution of ophthalmic subspecialty referrals to a tertiary hospital after eye examination in a mobile eye health unit.

Table 3. Multiple logistic regression according to gender, age, presence of comorbidity, and residence of each of the participants

Variable	Coefficient (error)	*P*-value	OR	IC (95%)
Sex	-0.3600 (0.0717)	<0.001	0.697	(0.606;0.803)
Age (years)	0.0490 (0.0022)	<0.001	1.050	(1.046;1.055)
Comorbidities	0.0953 (0.0481)	0.047	1.100	(1.001;1.209)
Residence locality	0.0258 (0.0081)	0.002	1.026	(1.010;1.043)

Hypertension and diabetes mellitus were the most common comorbidities in this population. However, it is critical to note that these conditions were self-reported condition. The majority of the participants had never presented with eye problems but for those with a previous ocular history, refractive error predominated.

The current study was conducted in the state of São Paulo, which is economically the most developed region in Brazil and has the highest concentration of ophthalmologists[9]. Surprisingly, the burden of untreated visual impairment was quite high and similar to that reported in regions with little to no access to health care[4,6]. This outcome may relate to the fact that we enrolled individuals who were seeking eye care from the mobile unit; this may have resulted in an overestimation of visual impairment and blindness compared to those members of the community who have routine access to eye care. Hence, our findings may not accurately represent the absolute prevalence of visual impairment and blindness in São Paulo as a whole.

There was a significant increase in the number of blind and visually impaired among the elderly, a finding that confirms those from previous reports[2-4] and clearly reflects the ophthalmic problems related to aging[24,25]. These observations indicate the necessity of providing additional assistance to the elderly who require monitoring and ophthalmic care.

Refractive error was the most common condition and was diagnosed in 78.6% of the participants. This outcome also confirms those in previous reports[10,19,20]. In the current study, 60.9% of the participants needed a prescription for corrective lenses; these results suggest that these regions require more dispensaries that prepare and fit eyeglasses [23]. Eyeglasses are more common in subjects older than 50 years primarily due to presbyopia[13].

The mobile eye health unit is an efficient method for providing eye care; we found that 81.7% of the participants had their issues resolved in a single visit. In a similar study[20] the resolution rate was 91.1% and the main reason for referral was surgery, similar to the results obtained here. Another, more qualitative study reported a resolution rate of 85.9% as part of a secondary referral service[26], although Covolo et al. reported resolution of only 44.8% of cases in a single visit[19]. The differences may relate to different needs that are unique to a specific region and/or issues secondary to the health care infrastructure.

The 18.1% of participants who required referrals were primarily those who needed surgery or additional examination with specialized equipment. The evaluation in the mobile eye health unit in these cases could be considered an important screening service which provided critical referrals to specific outpatient clinics.

The need for referrals to the tertiary service varied between genders. Although the majority of participants were female, the need for referral was statistically higher for males. This finding may indicate males seeking ophthalmic care tend to be those who have more serious pathology; it is certainly possible cultural influences are such that men seek for medical attention only when the pathology is more severe.

The logistic regression analysis revealed that an increased risk of visual impairment was directly correlated with aging, the presence of more comorbidities and distance resided from a tertiary care hospital; any efforts made toward preventive measures should take these factors into consideration. Mobile eye health units working in cooperation with the local health services can be an even more effective screening tool and referral framework if they can focus on overcome these specific barriers[27].

The vast majority of patients presenting to a mobile eye health unit required a prescription for corrective lenses. Mobile eye clinics are highly efficient for managing eye problems; they can prescribe corrective lenses for under-diagnosed refractive errors and refer patients to specialized ophthalmic services as needed. Taken together, our results indicate that mobile eye health units can be used as an effective, alternative method to deliver eye care as they can improve access, provide public health education and ultimately reduce visual impairment and prevent blindness in largely under-served populations.

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ORIGINAL ARTICLE

Arquivos Brasileiros de Oftalmologia

Firearm-associated ocular injuries: analysis of national trauma data

Lesões oculares relacionadas a armas de fogo: análise de dados nacionais de traumas nos EUA

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ABSTRACT | Purpose: The United States of America has the highest gun ownership rate of all high-income nations, and firearms have been identified as a leading cause of ocular trauma and visual impairment. The purpose of this study was to characterize firearm-associated ocular injury and identify at-risk groups. **Methods:** Patients admitted with firearm-associated ocular injury were identified from the National Trauma Data Bank (2008-2014) using the International Classification of Diseases, Ninth Revision, Clinical Modification diagnostic codes and E-codes for external causes. Statistical analysis was performed using the SPSS 24 software. Significance was set at $p<0.05$. **Results:** Of the 235,254 patients, 8,715 (3.7%) admitted with firearm-associated trauma had ocular injuries. Mean (standard deviation) age was 33.8 (16.9) years. Most were males (85.7%), White (46.6%), and from the South (42.9%). Black patients comprised 35% of cases. Common injuries were orbital fractures (38.6%) and open globe injuries (34.7%). Frequent locations of injury were at home (43.8%) and on the street (21.4%). Black patients had the highest risk of experiencing assault (odds ratio [OR]: 9.0; 95% confidence interval [CI]: 8.02-10.11; $p<0.001$) and street location of injury (OR: 3.05; 95% CI: 2.74-3.39; $p<0.001$), while White patients had the highest risk of self-inflicted injury (OR: 10.53; 95% CI: 9.39-11.81; $p<0.001$) and home location of injury (OR: 3.64; 95% CI: 3.33-3.98; $p<0.001$). There was a steadily increasing risk of self-inflicted injuries with age peaking in those >80 years (OR: 12.01; 95% CI: 7.49-19.23; $p<0.001$). Mean (standard deviation) Glasgow Coma Scale and injury severity scores were 10 (5.5) and 18.6 (13.0), respectively. Most injuries (53.1%) were classified as severe or very severe injury, 64.6% had traumatic brain injury, and mortality occurred in 16% of cases. **Conclusion:** Most firearm-associated ocular injuries occurred in young, male, White, and Southern patients. Blacks were disproportionally affected. Most firearm-associated ocular injuries were sight-threatening and associated with traumatic brain injury. The majority survived, with potential long-term disabilities. The demographic differences identified in this study may represent potential targets for prevention.

Keywords: Eye injuries; Firearms; Database; demographic disparity

RESUMO | Objetivo: Os Estados Unidos têm a maior taxa de posse de armas de fogo de todos os países de alta renda e essas armas foram identificados como uma das maiores causas de trauma ocular e deficiência visual. O objetivo deste estudo foi caracterizar as lesões oculares associadas a armas de fogo e identificar grupos de risco. **Métodos:** Foram identificados pacientes hospitalizados com lesões oculares associadas a armas de fogo no período de 2008 a 2014, a partir do Banco de Dados Nacional de Trauma (*National Trauma Data Bank*), usando os códigos de diagnósticos da CID9MC e códigos "E" para causas externas. A análise estatística foi efetuada usando o programa SPSS. O nível de significância considerado foi de $p<0,05$. **Resultados:** De um total de 235.254 pacientes hospitalizados com trauma associado

Submitted for publication: October 8, 2019
Accepted for publication: January 29, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Albert Einstein College of Medicine (project # 2015-4769).

a armas de fogo, 8.715 (3,7%) tinham lesões oculares. A média de idade foi de 33,8 (DP 16,9) anos. A maioria foi de homens (85,7%), brancos (46,6%) e da região Sul (42,9%); 35% dos pacientes eram negros. As lesões mais comuns foram fraturas de órbita (38,6%) e lesões de globo aberto (34,7%). Os locais mais frequentes foram a residência (43,8%) e a rua (21,4%). Pacientes negros tiveram maior probabilidade de sofrer agressões (RP=9,0, IC 95%=8,02-10,11; p<0,001) e da ocorrência ser na rua (RP=3,05, IC 95%=2,74-3,39; p<0,001), enquanto pacientes brancos tiveram maior probabilidade de lesões autoprovocadas (RP=10,53, IC 95%=9,39-11,81; p<0,001) e da ocorrência ser na residência (RP=3,64, IC 95%=3,33-3,98; p<0,001). A probabilidade de lesões autoprovocadas aumentou com a idade de forma consistente, atingindo o máximo em pacientes com mais de 80 anos (RP=12,01, IC 95%=7,49-19,23; p<0,001). A pontuação média na escala de coma de Glasgow foi 10 (DP 5,5) e na escala de severidade da lesão foi 18,6 (DP 13,0). A maioria das lesões (53,1%) foi classificada como severa ou muito severa. Dentre os pacientes, 64,6% tiveram lesão cerebral traumática e 16% evoluíram a óbito. **Conclusão:** A maior parte das lesões oculares relacionadas a armas de fogo ocorreu em pacientes jovens, do sexo masculino, brancos e sulistas. Negros foram afetados desproporcionalmente. A maior parte das lesões oculares relacionadas a armas de fogo apresentou riscos à visão e foi associada a lesões cerebrais traumáticas. A maioria dos pacientes sobreviveu, mas com potencial para invalidez no longo prazo. As diferenças demográficas identificadas podem ser potencialmente alvos de ações preventivas.

Descritores: Traumatismos oculares; Ferimentos por armas de fogo; Banco de dados

INTRODUCTION

The United States of America (USA) has firearm-associated injuries that far outnumber those of other affluent nations. In a cross-sectional analysis of high-income countries, the USA was found to contribute 80% of all firearm-associated deaths[1] with a crude rate of 11.1 per 100,000 individuals in 2015[2]. A retrospective survey of firearm-associated injuries (2006-2014) estimated that the combined financial burden of emergency room visits, hospitalization, and lost wages was $45.6 billion per year[3]. Ocular trauma is a leading cause of monocular blindness in the USA and second only to cataracts as the most frequent cause of visual impairment[4]. Firearm injuries are a leading cause of ocular trauma, often resulting in permanently impaired vision and blindness[5-11].

Firearm injuries, especially those afflicting the face and head, are associated with significant morbidity and mortality[10-13]. Fahimi et al.[13] found that, even when compared with victims of motor vehicle accidents and assault not related to gunshot wounds, patients who survived firearm violence had a five-fold higher hazard of death in their first year after discharge. In one of very few studies of firearm-associated ocular injury (FAOI), Chopra et al.[9] found that 44% of patients from two New York City hospitals who survived firearm injury suffered long-term visual disability, highlighting the impact of firearms on vision. Research focusing on FAOI on a national scale is limited. Thus, we utilized a large national database to characterize FAOIs by describing the circumstances and spectrum of ocular injuries and identify at-risk demographic groups.

METHODS

This retrospective analysis of patient records from the National Trauma Data Bank (NTDB) between 2008 and 2014 was approved by the Institutional Review Board at the Montefiore Medical Center/Albert Einstein College of Medicine (Bronx, NY, USA). The NTDB, an American College of Surgeons-maintained database, aggregates de-identified patient data from >900 trauma centers to form one of the world's largest trauma registries. These data provide nationally representative estimates of hospitalized patients with trauma.

Subjects and methodology

We included all patients who were admitted, expired upon arrival, or expired after an initial evaluation who had International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 800.00-959.9. Patients who had ocular trauma resulting from a firearm mechanism were identified. Ocular injuries included all sub-categories of superficial injury of the eye and adnexa (918.0-918.2, 918.9), burn to the eye and adnexa (940.0-940.5, 940.9), contusion of the eye and adnexa (921.0-921.4, 921.9, 364.0-364.1, 364.3), foreign body on the ocular surface (930.0-930.2, 930.8-930.9), foreign body inside the eye (871.5-871.6, 360.59-360.69), orbital injuries (802.6-802.9, 376.32-376.33), open wound of the eyeball (871.0-871.7, 871.9), open wound of the ocular adnexa (870.0-870.9), optic nerve injury and/or visual pathways (950.0-950.3, 950.9), and cranial nerve injury other than optic nerve (951.0-951.4, 951.9). For other cranial nerves, we focused on those commonly observed in neuro-ophthalmic injuries comprising oculomotor, trochlear, abducens, trigeminal, and facial nerves. All types of firearms, including handguns, automatic shotguns, hunting rifles, and military firearms, for all intentions were identified using ICD-9 E-codes: unintentional (922.0-922.9), self-inflicted

(955.0-955.9), assault (965.0-965.4), undetermined intent (985.0-985.4), and legal intervention (970.0).

From the selected patients, we documented demographic data, including age, gender, race and ethnicity, type of injuries, location, intent of injury, length of hospital stay, medical insurance, disposition upon discharge, trauma center designation level (I-IV), and USA geographic census region (Northeast, South, Midwest, West). Emergency department-determined Injury Severity Score (ISS) and Glasgow Coma Scale (GCS) were documented and used as indices of injury severity. ISS (1-75) is a scoring system that designates severity with increasing scores based on the degree and anatomical site of injury. GCS (0-15) is a common measure of the level of consciousness; low scores are assigned to greater traumatic brain injury (TBI). ISS ≥15 is designated major trauma and GCS ≤8 is considered severe TBI. The Center for Disease Control criteria were used to guide the identification of patients with TBI, using ICD-9-CM codes for skull fracture (800.0-801.9, 803.0-804.9), injury to the optic chiasm, optic pathway or visual cortex (950.1-950.3), intracranial injury (850.0-854.1), and head injury not otherwise specified (959.01). The mortality rate was determined by assessing the types of discharge and included deaths on arrival and after admission.

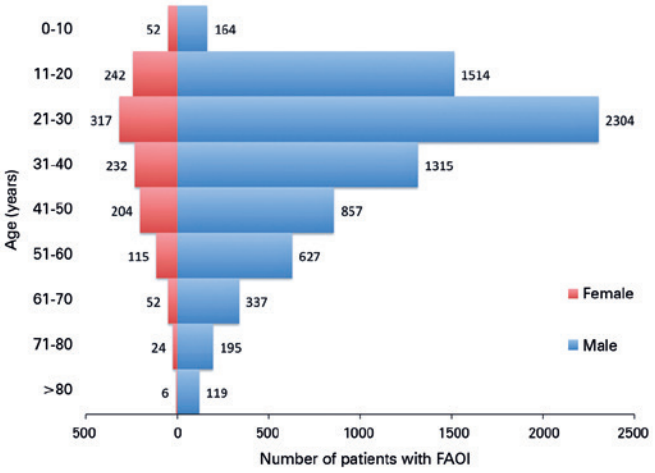
Statistical analysis

Analysis was conducted using the SPSS software (Statistical Package for Social Science, version 24; IBM Corp., Armonk, NY, USA). For all continuous variables, mean, standard deviation, median, and interquartile range values were calculated. For the logistic regression analysis, ages were stratified into decade groups. Similarly, ISS and GCS were grouped according to NTDB sub-classifications. For ISS, the grouping was as follows: minor (ISS: 1-8), moderate (ISS: 9-15), severe (ISS: 16-24), and very severe (ISS >24) injury. For GCS, the grouping was as follows: mild (GCS: 13-15), moderate (GCS: 9-12), and severe (GCS ≤8) brain injury. Associations between variables were analyzed using the paired Student's t-test, chi-squared test, and logistic regression analysis. Charts and tables were generated using Microsoft Excel (Microsoft Corp, Redmond, WA, USA). Data points classified under "undetermined," "not applicable", or "unknown" were excluded from comparative analyses.

RESULTS

A total of 235,254 patients with firearm-associated trauma were admitted between 2008 and 2014, and 8,715 (3.7%) of those resulted in FAOI. This represented 2.75% of all ocular injuries (316,485) during this time period. When stratified by year of admission, the frequency of injuries was relatively stable, with an average of 1,245 per year (range: 1,173-1,351). The mean (standard deviation [SD]) age was 33.8 (16.9) years, with 22.6%, 70%, and 6.2% of cases classified in the pediatric (≤20 years), adult (21-65 years), and elderly (≥65 years) age groups, respectively. Males had similar mean (SD) age to women: 33.8 (17) and 33.7 (16) years, respectively. However, they had higher overall rates of FAOI (85.7% vs. 14.3%, respectively). In all age groups, males outnumbered women (Figure 1). Of all cases, Whites represented 46.6%, Blacks, 35%, and all other races, 18.4%. Hispanic ethnicity comprised 13.7%. Common locations of injury were at home (43.8%) and on the street (21.4%). Most cases were from the Southern (42.9%) and Northeast (21.5%) regions (Table 1).

Orbital injuries (28.6%), open globe wounds (34.7%), and contusions to the globe/adnexa (15.7%) were the most common FAOI. Associated TBI occurred in 64.6% of cases. Visual pathway injuries occurred in 7.92% of the patients. The optic nerve was most frequently affected (87.7%). The mean (SD) GCS score was 10 (5.5), and 38.1% of injuries were classified as severe brain injury (GCS ≤8). Similarly, the mean (SD) ISS was 18.6 (13.0), and 33.8% were classified as very severe injuries (ISS >24). Intention of injuries were assault (56.8%), self-inflicted (30.1%), and unintentional (9.3%). Most patients



SD= standard deviation; NTDB= National Trauma Data Bank.
Figure 1. Age distribution of patients with firearm-associated ocular injury by age and gender, NTDB (2008-2014). Mean (SD) age of patients was 23.8 (16.9) years (range: 0-110 years). For both genders, >50% of patients were aged 11-40 years.

Table 1. Descriptive findings and demographic data of firearm-associated ocular injuries, National Trauma Data Bank, 2008-2014

Characteristic	Number	%	Characteristic	Number	%	Mean (SD)	Median (IQR)
Year			Age (years)			23.8 (16.9)	29 (21-44)
2008	1,173	13.5	0-10	216	2.5		
2009	1,244	14.3	11-20	1,756	20.1		
2010	1,198	13.7	21-30	2,621	30.1		
2011	1,178	13.5	31-40	1,547	17.8		
2012	1,274	14.6	41-50	1,061	12.2		
2013	1,297	14.9	51-60	742	8.5		
2014	1,351	15.5	61-70	389	4.5		
Total	8,715	100.0	71-80	219	2.5		
			>80	125	1.4		
Gender							
Male	7,469	85.7					
Female	1,246	14.3	Hospital stay (days)			9.8 (14.6)	4 (1-13)
			1	2,450	28.1		
Race			2-3	1,639	18.8		
Black	3,050	35.0	4-6	1,178	13.5		
White	4,065	46.6	>6	3,416	39.2		
Other	1,600	18.4	Unknown	32	0.4		
Hispanic	1,193	13.7					
			ISS			18.6 (13.0)	18 (9-26)
Hospital			1-8	2,026	23.2		
Level I	3,915	44.9	-9-15	1,639	18.8		
Level II	1,378	15.8	16-24	1,685	19.3		
Level III	68	0.8	>24	2,948	33.8		
Level IV	14	0.2					
Not applicable	3,340	38.3					
			GCS			10.4 (5.3)	14 (3-15)
Locations			≤8	3,321	38.1		
Home	3,815	43.8	9-12	418	4.8		
Street	1,868	21.4	13-15	4,347	49.9		
Public building	376	4.3	Unknown	629	7.2		
Recreation	153	1.8					
Residential Institution	23	0.3					
Industry							
Farm	17	0.2	TBI	5,634	64.6		
Other	719	8.2					
Unspecified	1,333	15.3	Mortality	1,409	16.2		
Unknown	370	4.3					
US regions			Intention				
Midwest	1,872	21.5	Assault	4,954	56.8		
Northeast	1,142	13.1	Self-inflicted	2,619	30.1		
South	3,742	42.9	Unintentional	808	9.3		
West	1,805	20.7	Other	1	0.0		
Not applicable	31	0.4	Undetermined	333	3.8		
Unknown	123	1.4	Unknown	0	0.0		

SD= standard deviation; IQR= interquartile range; ISS= injury severity score; GCS= Glasgow Coma Scale; TBI= traumatic brain injury.

(48.8%) were discharged home and fewer patients (20.5%) were transferred to another facility. Mean (SD) hospital stay was 9.8 (14.6) days and the mortality rate was 16.2% (Table 1).

Comparative analyses

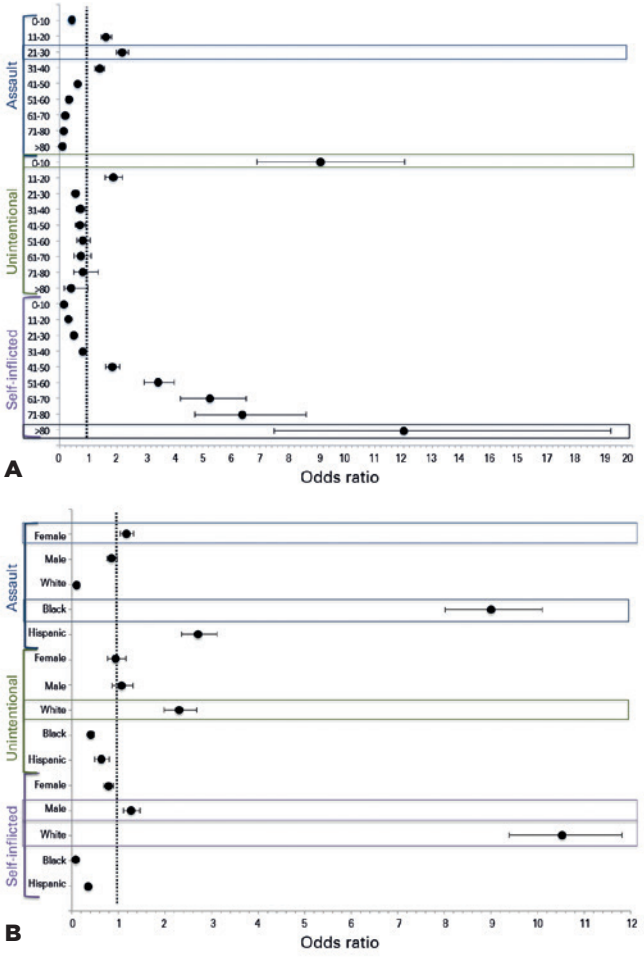
Age and gender differences

Across all age groups, injuries occurred most frequently at home, with the highest risk observed in the two extreme age groups. Patients aged 0-10 years had a 2.87-fold higher risk (95% confidence interval [CI]: 2.15-3.84; p<0.001) of injury at home than elsewhere; those aged >80 years had the highest risk of injury at home (odds ratio [OR]: 5.84; 95% CI: 3.71-9.91; p<0.001) compared with other locations. The street was the most likely site in those aged 21-30 years (OR: 1.56; 95% CI: 1.49-1.74; p<0.001). The 11-20-year group had the highest risk of firearm injury in a recreational facility than other locations (OR: 1.61; 95% CI: 1.13-2.28; p=0.008), followed closely by the street (OR: 1.44; 95% CI: 1.28-1.63; p<0.001).

Patients aged between 0-10 years had a 9.11-fold higher risk (95% CI: 6.89-12.04; p<0.001) of sustaining FAOI due to unintentional injury. Meanwhile, teens and young adults had an increased risk of injury due to assault, with the 21-30-year group having the highest risk (OR: 2.19; 95% CI: 1.99-2.42; p<0.001). There was steadily increasing risk of self-inflicted injury from the 41-50 year group (OR: 1.85; 95% CI: 1.62-2.11; p<0.001) to a peak in the >80 year group (OR: 12.01; 95% CI: 7.4919.23; p<0.001) (Figure 2A). Males were at a higher risk of self-inflicted injury (OR: 1.27; 95% CI: 1.11-1.46; p<0.001) than other intentions. Males were also at a higher risk of injuries occurring in a recreational facility (OR: 1.81; 95% CI: 1.02-3.21; p=0.039), while females had the highest risk of assault (OR: 1.17; 95% CI: 1.06-1.33; p=0.01) and a higher likelihood of injury at home (OR: 1.63; 95% CI: 1.45-1.84; p<0.001) than other locations.

Race and ethnic differences

Hispanics and Blacks suffering injuries were more likely to be in the 11-20-year group (OR: 1.62; 95% CI: 1.41-1.86; p<0.001) and 21-30-year group (OR: 1.93; 95% CI: 1.76-2.12; p<0.001), respectively. On the other hand, Whites were the most elderly, with the highest risk of injury noted in the 71-80-year group (OR: 8.5; 95% CI: 5.67-12.75; p<0.001). Whites were at a higher risk of injury at home than other common locations (OR: 3.64; 95% CI: 3.33-3.98; p<0.001), while Blacks (OR: 3.05; 95% CI: 2.75-3.39; p<0.001) and Hispanics (OR: 1.62; 95% CI: 1.41-1.86; p<0.001) were at a higher risk of injury on the street.



NTDB= National Trauma Data Bank; SD= standard deviation; OR= odds ratio.

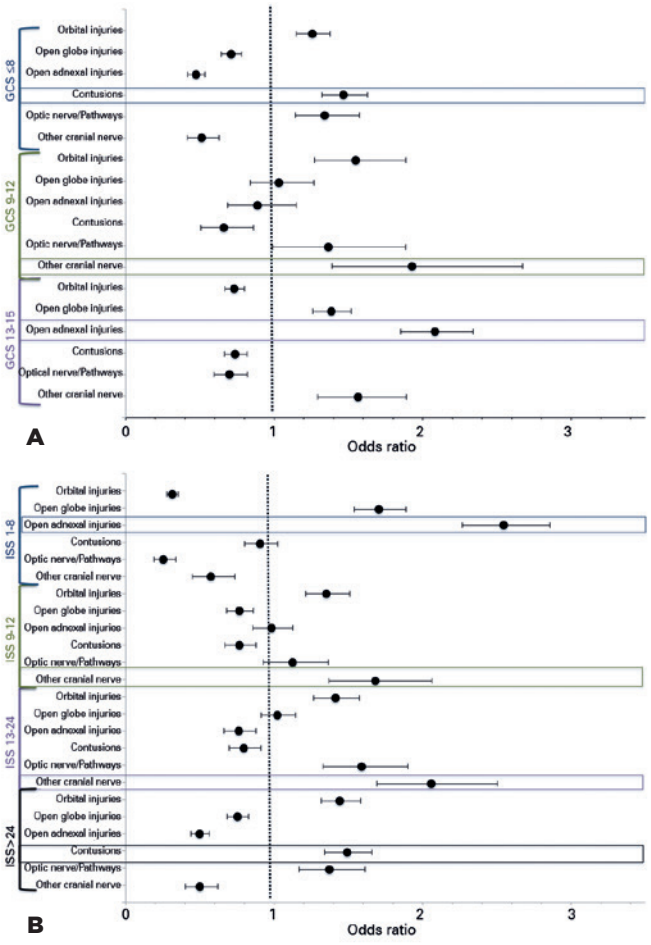
Figure 2. A) Simple logistic regression of intent of injury and age in patients with firearm-associated ocular injuries, NTDB (2008-2014). Summary of simple logistic regression with odds ratio and 95% confidence intervals analysis of intent of injury amongst different age groups with firearm-associated ocular injuries. Unintentional injury showed a strong association with the youngest age strata, 0-10 years with a 9-fold higher risk; p<0.001. including 9.1 odds of association with 0-10 years. Self-inflicted was most associated with the oldest age strata, >80 years with 12 -fold higher risk of association; p<0.001. Assault showed a strong association with strata between -20-30 years with a 2-fold higher risk of association; p<0.001. Boxed plots represent categories with the highest odds ratio. B) Simple logistic regression of intent of injury and gender, race, and ethnicity in firearm-associated ocular injuries, NTDB (2008-2014). Summary of simple logistic regression with odds ratio and 95% confidence intervals analysis of intent of injury and gender, race, and ethnicity in firearm-associated ocular injury. Assault was associated with female gender (OR: 1.2; p<0.001), and 9.0-fold and 2.7-fold odds of association with Blacks (p<0.001) and Hispanics (p<0.001), respectively. Unintentional injury had 2.3-fold odds of being associated with Whites (p<0.001) without significant gender association. Self-inflicted injury had an associated 10.5-fold odds of association with Whites (p<0.001) and 1.2-fold odds with males (p<0.001). Boxed plots represent categories with the highest odds ratio.

With respect to intention, Blacks had a 9.0-fold increased risk (95% CI: 8.02-10.11; p<0.001) of injury due to assault than other intentions. Similarly, Hispanics were at the highest risk of assault (OR: 2.71; 95% CI: 2.36-3.12; p<0.001). Whites were more likely to suffer from self-inflicted injuries (OR: 10.53; 95% CI: 9.39-11.81; p<0.001) than other intentions (Figure 2B). The South was associated with the highest risk of FAOI compared with the other regions (OR: 1.29; 95% CI: 1.24-1.36; p<0.001). However, analysis based on racial/ethnic groups showed that Whites (OR: 1.20; 95% CI: 1.08-1.33; p=-0.001) and Hispanics (OR: 4.18; 95% CI: 3.67-4.75; p<0.001) were at the highest risk of FAOI in the West and Blacks in the Mid-West (OR: 1.69; 95% CI: 1.53-1.88; p<0.001) than other regions.

Role of intention

Intention was found to be associated with the types of ocular injury, injury severity, and levels of TBI. Open globe (OR: 1.88; 95% CI: 1.52-2.17; p<0.001) and open adnexal wound injuries (OR: 1.72; 95% CI: 1.47-2.03; p<0.001) exhibited the highest likelihood of occurring in unintentional firearm injuries. Of note, other non-visual pathway cranial nerve injuries (OR: 1.78; 95% CI: 1.47-2.16; p<0.001) and open adnexal wounds (OR: 1.43; 95% CI: 1.29-1.5; p<0.001) were most likely to occur after assault injuries. Self-inflicted firearm injury was most associated with orbital injuries (OR: 1.79; 95% CI: 1.63-1.96; p<0.001), and optic nerve and visual pathway injuries (OR: 1.82; 95% CI: 1.56-2.14; p<0.001).

TBI (64.6%) was most likely to occur following self-inflicted FAOI (OR: 5.37; 95% CI: 4.74-6.08; p<0.001). Figures 3A and 3B illustrate the relative associations of ocular injuries with GCS (TBI) and ISS. Severe FAOI associated with low GCS (<8) (OR: 22.91; 95% CI: 18.85-27.84; p<0.001) and high ISS (>24) (OR: 14.88; 95% CI: 12.73-17.38; p<0.001) were associated with the highest risk of mortality. When analyzed based on intention, unintentional firearm injuries were linked to minor TBI (OR: 2.40; 95% CI: 2.03-2.83; p<0.001) and ISS (OR: 3.73; 95% CI: 3.21-4.33; p<0.001), while self-inflicted injuries were associated with severe TBI (OR: 5.34; 95% CI: 4.82-5.93; p<0.001) and very severe ISS (OR: 2.99; 95% CI: 2.71-3.29; p<0.001). Consequently, self-inflicted injuries were linked to the highest risk of mortality (OR: 3.60; CI: 3.20-4.04; p<0.001). Assault injuries were most associated with a risk of mild or intermediate injury severity compared with the other intentions; GCS: 13-15 (OR:3.16, 95% CI: 2.88-3.46; p<0.001) and ISS: 9-15 (OR: 1.70, 95% CI: 1.52-1.90; p<0.001).



NTDB= National Trauma Data Bank; GCS= Glasgow Coma Scale; OR= odds ratio; TBI= traumatic brain injury; ISS= Injury Severity Score; OR= odds ratio.
Figure 3. A) Simple logistic regression of ocular injuries and Glasgow Coma Scale in firearm-associated ocular injuries, NTDB (2008-2014). Summary of simple logistic regression with odds ratio and 95% confidence intervals analysis of injury type and injury severity (GCS) in firearm-associated ocular injury. Contusions (OR: 1.63, p<0.001), optic nerve and pathway (OR: 1.57; p<0.001), and orbital injuries (OR: 1.26; p<0.001) were associated with GCS scores <8 (severe TBI). Other cranial nerve (OR: 1.93; p<0.001) and orbital (OR: 1.55; p<0.001) were associated with GCS scores of 9-12 (moderate TBI). Open adnexal (OR: 2.08; p<0.001), open globe (OR:1.39; p<0.001), and other cranial nerve injuries (OR: 1.56; p<0.001) were associated with GCS scores of 13-15 (mild TBI). Boxed plots represent categories with the highest odds ratio. B) Simple logistic regression of ocular injuries and injury severity score in firearm-associated ocular injuries, NTDB (2008-2014). Summary of simple logistic regression with odds ratio and 95% confidence intervals analysis of injury type and injury severity (ISS) in firearm-associated ocular injury. Open adnexal (OR: 2.55; p<0.001) and open globe injuries (OR: 1.71; p<0.001) were associated with ISS (1-8: minor); other cranial nerve (OR: 1.68; p<0.001) and orbital (OR: 1.35; p<0.001) of ISS (9-12: moderate). Optic nerve and pathway (OR: 1.59; p<0.001) and orbital injuries (OR: 1.41, p<0.001) were associated with ISS (16-24: severe); contusions (OR: 1.49; p<0.001), orbital (OR: 1.44; p<0.001), and optic nerve and pathways of ISS >24, or the most severe injuries. Boxed plots represent categories with the highest odds ratio.

DISCUSSION

The current dearth of literature addressing firearm injuries is incommensurate with the gravity of this public health issue in the USA. Ophthalmologists manage these patients frequently as patients with major trauma, admitted with multiple injuries. This study evaluated a national database to determine the scope of ophthalmic injuries incurred following firearm-associated injuries. Although we affirmed the common finding of trauma occurring most frequently in young males, additional findings revealed that FAOI were more strongly associated with older age groups (>40 years) and self-inflicted injury in Whites, while Blacks and Hispanics tended to be younger and victims of assault (Figures 2A and 2B). Furthermore, Blacks were disproportionately affected overall. Blacks represent only 13% of the USA population[14] but account for 35% of all FAOI victims. Our study confirms the conclusions from other firearm trauma reports in the USA indicating that this demographic group represents an at-risk sub-population[5,15]. Intention of injury was also associated with different types of firearm-related injuries. Open globe and adnexal wound injuries were mostly associated with unintentional trauma, other non-visual pathway cranial nerve injuries were associated with assault and optic nerve/visual pathway, and orbital injuries were associated with self-inflicted injury. Self-inflicted injury exhibited the strongest association with TBI and mortality.

Most reports of FAOI have concentrated on non-powder firearm injuries from air, paintball, pellet, and nail guns.[16,17] with very few reports including handguns, shotguns, and rifles[6,9]. McGwin et al. investigated the epidemiology of both air gun (BB, pellet, paint, and rifles) and firearm (all powder guns) trauma using the National Electronic Injury Surveillance System (NEISS) and reported similar demographic findings to those of our study[6]. They found that young males were at the highest risk of injury; Blacks were more likely to be injured by firearms and assault, while Whites were more likely to be injured by air guns and unintentional injury. Fowler et al. utilized the National Vital Statistics and NEISS to describe fatal and nonfatal firearm-associated injuries in the USA, and reported similar demographic patterns[15]. Notably, they also identified intention as a predictor of injuries; homicides were more frequent in adolescents and young adults, while firearm suicide tended to increase with age. Their findings are consistent with those observed in this study. In a small regional analysis of two New York City hospitals, Chopra et al.[9] also found similar patterns, with 3% of firearm injuries involving the eyes; assault and self-inflicted were the most common (64%) and least common (7%) intentions, respectively. They recorded a mean (SD) ISS and GCS score of 14.15 (9.69) and 12.85 (4.16), respectively. Although the rate of assault noted in the present study was comparable (56.8%), we observed a higher rate of suicide injuries (30.1%), which may account for the greater severity of injuries reported in our study. These differences highlight difficulties in comparing data from one setting with data from a large, inclusive national trauma database. Despite the differences, there appears to be consensus between studies identifying young, male, and minority populations as particularly vulnerable to firearm-associated injury[6,7,13,15]. Understanding these demographic patterns is crucial for identifying those who are most likely to benefit from future, targeted prevention programs.

In a retrospective, multicenter study, Shackford et al. investigated the association between firearm-associated injuries to the face and morbidity/mortality[12]. As expected, there was a high mortality rate, with 97% of deaths associated with brain injury. Ocular sequelae were frequent complications in those with non-fatal injuries. We found that more than a third of patients had GCS and ISS scores consistent with severe brain injury and very severe injury. Specifically, orbital injury, contusions, and optic nerve injuries were associated with higher severity scores. We also observed a high incidence of brain injury; nearly 65% of patients admitted for FAOI suffered TBI. All degrees of TBI can lead to short and long-term disruption of visual processing that includes, but is not limited to, abnormal saccades and smooth pursuit, convergence insufficiency, diplopia, and accommodative dysfunction[18,19].

In a study of the United States Eye Injury Registry, Kuhn et al.[20] found that 6% of all severe eye traumas were caused by firearms. Furthermore, they found that 28.5% of patients sustained bilateral injuries in firearm-associated injuries and 58% of eyes with FAOI remained blind after 6 months. Although our data did not include ophthalmic clinical details and visual outcomes, we know that most patients survived their injuries albeit with high rates of TBI. This suggests that survivors may experience complicated rehabilitation when considering the neurocognitive consequences of TBI. With this knowledge, healthcare providers managing patients with FAOI should consider coordinating ophthalmic and neurologic care, during a long-term follow-up beyond the post-operative period, to optimize visual outcomes[21-23].

Our study identified self-inflicted injury or suicide as a major cause of FAOI in Whites and older adults. This intention also exhibited the strongest association with TBI, greater ISS, and mortality than other intensions. In an analysis of a World Health Organization mortality database, Richardson et al. found that 80% of all firearm-related deaths occurred in the USA. Despite having a 30% lower suicide rate than other high-income countries, the USA had a 5.8-fold higher rate of firearm-associated suicide[1]. Through the Center for Disease Control questionnaire data (2000-2002), Miller et al. found that with every 1% increase in firearm ownership, the rate of firearm-related suicide increased by 3.5%[24]. They concluded that since firearms are implicated in >50% of suicides in the USA, reductions in firearm ownership would drastically reduce the rate of firearm-related suicide. With the progressive aging of the USA population, there exists a growing need to develop strategies for identifying these high-risk elderly patients[1,25,26]. Although effective worthy treatment algorithms have been developed to restore appearance and functionality in patients maxillofacial and ocular injuries after failed suicide attempts[27], associated residual visual compromise and the high rate of TBI and mortality in elderly individuals warrants the creation of targeted prevention strategies.

In a recent study investigating pediatric FAOI, Weiss et al.[28] found that this group represented 22.6% of all cases, with 62.9%, 17.5%, and 13.1% caused by assault, unintentional injury, and self-inflicted injury, respectively. Most injuries (38.6%) occurred at home. When considering preventive strategies in the pediatric group, Barkin et al.[29] found that >40% of homes had ≥1 unlocked firearm and deduced that >1.7 million children aged <18 years are living in homes in which loaded and unlocked firearms are present. Through a randomized controlled trial, they showed that office-based violence-prevention discussions led to increased firearm storage and decreased child media usage, factors that they suggest contribute to firearm-associated injuries. The recent establishment of hospital-based violence intervention programs to target high-risk, injured patients, has been found to be cost-effective and reduce recidivism. These programs aim at reducing obstacles to services and improve behavior that decreases exposure to violence[30]. We identified assault and self-harm injuries as major intentions at both ends of the age spectrum that led to the most severe injuries and an increased susceptibility to TBI. Ophthalmologists could play an important role in the initial surgical intervention and subsequent TBI management, as well as in reducing the incidence of future firearm-related injuries by engaging patients in similar violence prevention strategies or by appropriately referring them to available services.

The main limitation of this study was its retrospective design. Although extensive, NTDB data were not submitted by ophthalmologists, but rather by trauma/emergency room personnel who may have underestimated ophthalmic injuries. Also, ophthalmic clinical details and long-term visual outcomes were not available. ICD-9-CM codes were used during this period and do not describe injuries with the same degree of accuracy as ICD-10-CM codes. Furthermore, we evaluated patients admitted with major trauma, which likely skewed the data towards more severely injured patients. However, given the severity of firearm-associated injuries and the wide reach of the NTDB, the general patterns elucidated herein may provide valuable insight and a sound foundation for further investigation.

In conclusion, we found that FAOI were often sight-threatening and associated with TBI. Intentions were associated with age groups, gender, race and ethnicity as well as injury severity and the degree of TBI. Further ICD10-CM NTDB analysis needs to be conducted to confirm the present findings and enhance our knowledge in this field.

ACKNOWLEDGEMENTS

The authors would like to thank John McNelis (MD, FACS, FCCM, MHCM, Chairman, Department of Surgery), Melvin E Stone Jr (MD, Associate Director of Trauma Services & Surgical Critical Care, Department of Surgery), and James Meltzer (MD, Department of Pediatrics) at Jacobi Medical Center (Bronx, NY, USA) for their contributions and support, as well as for providing access to the NTDB database.

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Arquivos Brasileiros de
Oftalmologia

ORIGINAL ARTICLE

High glucose induces pyroptosis of retinal microglia through NLPR3 inflammasome signaling

Altos níveis de glicose induzem piroptose da micróglia da retina por sinalização de inflamassomas NLPR3

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ABSTRACT | Purpose: Diabetic retinopathy is currently considered a chronic inflammatory disease involving NOD-like receptor family pyrin domain containing 3 inflammasome activation and retinal microglial pyroptosis. In this study, we aimed to investigate whether NOD-like receptor family pyrin domain containing 3 inflammasome signaling induces pyroptotic death of retinal microglia under high-glucose conditions. **Methods:** Retinal microglia were stimulated by high glucose levels for 24 h. Cell viability, lactate dehydrogenase release, and caspase-1 activity were detected *in vitro*. The expression of pro-inflammatory cytokine (interleukin-1β, activated microglia marker ionized calcium-binding adapter molecule-1), NOD-like receptor family pyrin domain containing 3, cleaved caspase-1, and cleaved gasdermin D were examined. Subsequently, retinal microglia were pretreated with the inhibitors of NOD-like receptor family pyrin domain containing 3 inflammasome signaling prior to stimulation with high glucose, and their molecular and functional changes were evaluated. **Results:** High-glucose (25, 50, or 100 mM) stimulation decreased cell viability, but enhanced lactate dehydrogenase release and caspase-1 activity in a dose-dependent manner. Moreover, high glucose upregulated the protein expression of interleukin-1β, ionized calcium-binding adapter molecule-1, NOD-like receptor family pyrin domain containing 3, cleaved caspase-1, and cleaved gasdermin D. However, pretreatment with the inhibitors of NOD-like receptor family pyrin domain containing 3 inflammasome signaling inhibited high glucose (25 mM)-induced cytotoxicity, NOD-like receptor family pyrin domain containing 3 inflammasome activation, and pyroptosis of retinal microglia. **Conclusions:** NOD-like receptor family pyrin domain containing 3 inflammasome signaling may modulate retinal microglia-related inflammation and pyroptosis under high-glucose conditions.

Keywords: Diabetic retinopathy; Microglia; NLRP3 inflammasome; Pyroptosis; Gasdermin D

RESUMO | Objetivo: Atualmente, a retinopatia diabética é considerada uma doença inflamatória crônica envolvendo a ativação de inflamassomas NLRP3 e piroptose da micróglia da retina. Neste estudo, objetivamos investigar se a sinalização de inflamassomas NLRP3 induz a morte da micróglia da retina sob condições de alta glicose. **Métodos:** A micróglia da retina foi estimulada por altos níveis de glicose durante 24 horas. A viabilidade celular, a liberação de LDH e a atividade da caspase1 foram analisadas *in vitro*. Avaliou-se a expressão de citocina pró-inflamatória (IL1β), de marcador de micróglia ativado (Iba1), de NLRP3, de caspase1 clivada e de GSDMD clivada. Subsequentemente, a micróglia da retina foi pré-tratada com inibidores da sinalização de inflamassomas NLRP3 antes da estimulação com altos níveis de glicose e suas alterações moleculares e funcionais foram avaliadas. **Resultados:** A estimulação com altos níveis de glicose (25 mM, 50 mM ou 100 mM) diminuiu a viabilidade celular, mas aumentou a liberação de LDH e a atividade da caspase1 de forma dependente da dose. Além disso, os altos níveis de glicose aumentaram a expressão das proteínas lL1β, lba1, NLRP3, caspase1 clivada e GSDMD clivada. No entanto, o pré-tratamento com inibidores da sinalização de inflamassomas NLRP3 e a posterior estimulação com altos níveis de glicose (25 mM) induziu citotoxicidade, a ativação de inflamassomas NLRP3 e a piroptose da micróglia da retina. **Conclusão:** A sinalização de inflamassomas NLRP3 pode modular a inflamação e a piroptose da micróglia da retina na presença de altos níveis de glicose.

Descritores: Retinopatia diabética; Microglia; NLRP3 Inflammassomos; Piroptose; Gasdermin D

Submitted for publication: July 22, 2019
Accepted for publication: December 22, 2019

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: The First Affiliated Hospital of Fujian Medical University (#2016-YK-163).

INTRODUCTION

Diabetic retinopathy (DR), the major ocular complication of diabetes mellitus, is the leading cause of blindness in working-age populations[1]. Numerous studies have documented the effectiveness of routine DR screening and early treatment[2-3], while current therapies are unable to reverse the vision loss in the advanced background or proliferative stage of DR.

The exact mechanisms of DR remain unclear. Although DR has been traditionally described as a microvascular disorder, recent evidence demonstrated that early DR is linked to retinal inflammation associated with microglia activation[4-5]. Over-activated microglia (M1 phenotype) induce the release of inflammatory factors, contribute to the development of neurovascular unit lesions, and eventually lead to irreversible retinal dysfunction[6-7].

The NOD-like receptor family pyrin domain containing 3 (NLRP3) inflammasome, one of the key sensors in microglial plasma, plays a critical role in inflammation mediated by inflammatory cytokines, such as interleukin-1β (IL-1β), from microglia[8]. NLRP3 recognizes different endogenous and exogenous stimuli, and combines with the adaptor apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC) and pro-caspase-1. Accordingly, they are assembled to a multiprotein complex[9]. Activation of the NLPR3 inflammasome activates pro-caspase-1 cleavage, facilitates IL-1β secretion, and subsequently triggers a highly inflammatory type of programmed cell death termed pyroptosis[10]. Gasdermin D (GSDMD) is a membrane pore-forming protein involved in pyroptosis[11]. The NLPR3 inflammasome could cleave GSDMD to generate the N-terminal fragment of GSDMD, cause cell rupture, and increase the release of IL-1β[12].

It has been reported that NLRP3 inflammasome signaling is involved in the pathogenesis of various eye diseases[13-15]. Some studies have demonstrated that caspase-1 activity and IL-1β production were significantly increased in microglia *in vitro* following exposure to hyperglycemic conditions[16-17], suggesting that microglial pyroptosis is a crucial factor in the pathogenesis of DR. A recent study found that NLRP3 gene knockout downregulated the expression of caspase-1 and proinflammatory cytokines, and alleviated retinal ganglion cell death following optic nerve crush injury[18]. Moreover, high glucose could trigger pyroptosis of retinal microvascular endothelial cells via the NLRP3 inflammasome signaling pathway[19-20]. However, it remains poorly understood whether the activation of the NLRP3 inflammasome causes pyroptosis of retinal microglia in DR.

In the present study, we constructed an *in vitro* model to determine the role of NLRP3 inflammasome signaling in modulating retinal microglial pyroptosis under high-glucose conditions. Additionally, we intended to interpret the pathogenesis of DR in terms of microglia pyroptosis and related inflammation.

METHODS

Primary retinal microglia culture

All animal procedures were approved by the Animal Care and Use Committee of the First Affiliated Hospital of Fujian Medical University (Fuzhou, China) (Approval No. 2016-YK-163), and conformed to the Association for Research in Vision and Ophthalmology Statement on the Use of Animals in Ophthalmic and Vision Research.

The primary microglial culture was performed as previously described[21]. In brief, retinas of healthy newborn C57BL/6 mice (Shanghai SLAC Laboratory Animal Co. Ltd., Shanghai, China) were digested with 0.125% trypsin for 30 min at 37°C to generate a single-cell suspension. Subsequently, the cells were resuspended in Dulbecco's modified Eagle's medium/F-12 culture medium containing 10% fetal bovine serum, 1% microglia growth supplement (Sciencell, USA), 100 U/mL penicillin, and 100 μg/mL streptomycin, plated onto 75 cm^2 culture flasks, and incubated at 37°C in a humidified atmosphere containing 5% CO_2. The culture medium was changed at 24 h. After 2 weeks, mixed glial cells were purified by shaking at 200 rpm for 1 h. The supernatant containing microglia were harvested and used in the following experiments. The purity of microglia was determined through flow cytometry using fluorescein isothiocyanate-conjugated rabbit anti-CD11b and isotype immunoglobulin G2b control antibodies (Abcam, Cambridge, UK).

Cell treatment

Microglia were incubated with D-glucose 5.5 (control), 25, 50, and 100 mM (Sigma-Aldrich, St. Louis, MO, USA) for 24 h. The cells were pretreated with the NLRP3 inhibitor MCC950 (10 μM) or caspase-1 inhibitor Z-Tyr-Val-Ala-Asp(OMe) fluoromethyl ketone (Z-YVAD-FMK; 10 μM) (all from Sigma-Aldrich) for 30 min prior to treatment with high glucose to suppress NLRP3 inflammasome signaling.

Cell viability

Cell viability was detected using the Cell Counting Kit-8 (CCK-8; Beyotime), according to the instructions provided by the manufacturer. After the indicated treatments, CCK-8 solution (10 μL) was added to each well and treated for 2 h at 37°C. The optical density was measured at 450 and 690 nm.

Cytotoxicity assay

The levels of lactate dehydrogenase (LDH) in supernatants were determined using the LDH Cytotoxicity Assay Kit (Beyotime) as previously described[22]. Cytotoxicity (%) was calculated as follows: 100 × (experimental LDH - spontaneous LDH)/(maximum LDH release - spontaneous LDH).

Caspase-1 activity analysis

After the indicated treatments, microglia were disintegrated and centrifuged to obtain cell lysates. Caspase-1 activity was detected using the Caspase-1 Activity Assay Kit (Beyotime) according to the instructions provided by the manufacturer.

Evaluation of IL-1β secretion in the supernatants

The concentration of IL-1β in the culture supernatants was determined using enzyme-linked immunosorbent assay kits (R&D Systems, MN, USA), based on the instructions provided by the manufacturer.

Western blotting analysis

Total protein was extracted from the cells, and the concentration was determined using a bicinchoninic acid kit (Pierce, Rockford, IL, USA). The proteins were separated by electrophoresis on a 10% sodium dodecyl sulfate-polyacrylamide gel and transferred to a high-quality polyvinylidene difluoride membrane. After blocking with 5% nonfat milk in tris-buffered saline with Tween 20 solution, the membranes were incubated with primary antibodies overnight at 4°C. The following antibodies were used: rabbit anti-Iba-1 (1:200; Abcam); rabbit anti-NLRP3 (1:500; Abcam); rabbit anti-cleaved caspase-1 (1:500; Cell Signaling Technology, Danvers, MA, USA); rabbit anti-cleaved GSDMD (1:500; Cell Signaling Technology); and rabbit anti-glyceraldehyde-3-phosphate dehydrogenase (anti-GAPDH: 1:1,000; Santa Cruz Biotechnology, Santa Cruz, CA, USA). After washing, each blot was incubated with horseradish peroxidase-conjugated secondary antibody (goat anti-rabbit immunoglobulin G-horseradish peroxidase; Santa Cruz Biotechnology, Santa Cruz, CA, USA) for 1 h, and visualized with enhanced chemiluminescence. The quantitation of each band was performed using the Quantity One software 4.6 (Bio-Rad Laboratories, Hercules, CA, USA) using GAPDH as an internal control.

Statistical analysis

Data are expressed as the mean ± standard deviation. Statistical analysis was performed using one-way analysis of variance with the Tukey-Kramer multiple comparison test (GraphPad Prism, version 5.01; GraphPad, La Jolla, CA, USA). Statistical significance was set at $p<0.05$. Error bars indicate standard deviation.

RESULTS

Characterization and identification of retinal microglia *in vitro*

Primary retinal microglia showed either rounded, bipolar, or multipolar shapes (Figure 1A). The purity of retinal microglia was 80.18 ± 4.38%, determined through flow cytometry using a CD11b antibody (Figure 1B).

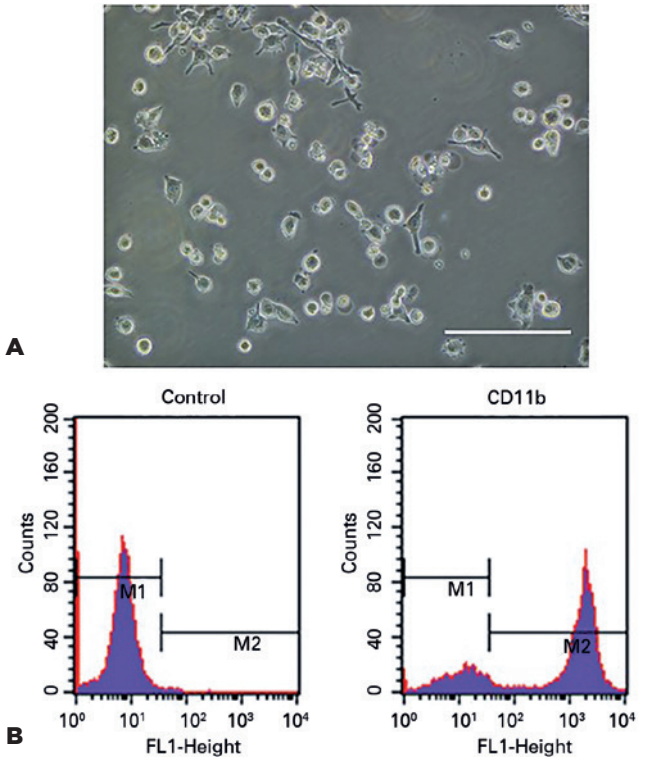


Figure 1. Morphology and identification of retinal microglia in culture. Primary retinal microglia appeared in either rounded, bipolar, or multipolar shapes (A). The surface expression rate of CD11b was 80.18 ± 4.38%. Six batches of microglia were analyzed using flow cytometry (B). Scale bars indicate 100 μm.

High glucose affected the viability of retinal microglia *in vitro*

As shown by the CCK-8 assay, incubation with high glucose (25, 50, or 100 mM) resulted in a remarkable decline in cell viability in a dose-dependent manner compared with the control ($p<0.05$) (Figure 2).

High glucose activated retinal microglia *in vitro*

Treatment with high glucose (25, 50, or 100 mM) upregulated the protein expression of Iba-1, which is a specific marker for activated microglia, compared with the control ($p<0.05$) (Figure 3). Western blotting analysis did not reveal significant differences among the groups treated with different concentrations of high glucose ($p>0.05$).

High glucose induced the activation of NLRP3 inflammasome signaling and pyroptosis of retinal microglia

LDH release and caspase-1 activity in the high glucose-treated group (25, 50, or 100 mM) were higher than those measured in the control group ($p<0.05$) (Figure 4A, B), showing a dose-dependent effect.

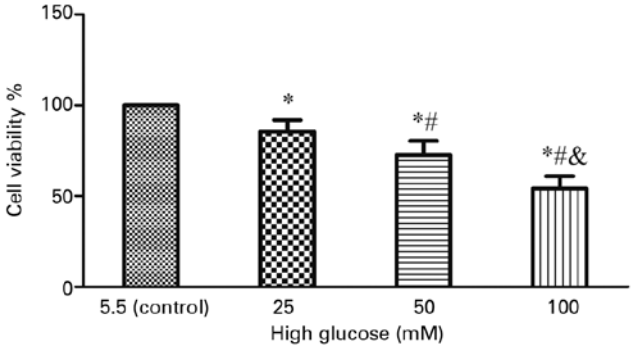
The enzyme-linked immunosorbent assay showed that high glucose (25, 50, or 100 mM) significantly increased the secretion of IL-1β compared with the control ($p<0.05$) (Figure 4C). However, IL-1β secretion was not significantly different among the groups treated with different concentrations of high glucose ($p>0.05$).

Moreover, western blotting analysis indicated that high glucose upregulated the protein expression of NLRP3, cleaved caspase-1 and cleaved GSDMD in retinal microglia ($p<0.05$) (Figure 4D). There were no significant differences observed among the groups treated with different concentrations of high glucose ($p>0.05$).

NLRP3 inflammasome signaling mediated high glucose-induced pyroptosis in retinal microglia

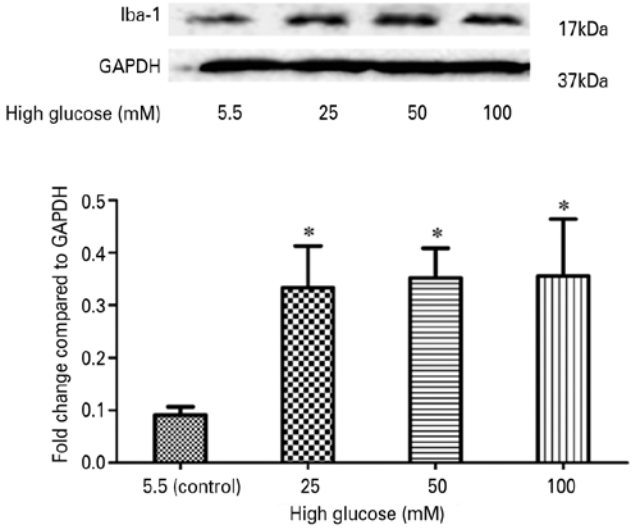
MCC950 or Z-YVAD-FMK were used to inhibit NLRP3 or caspase-1 for evaluating the effect of NLRP3 inflammasome signaling in high glucose-induced pyroptosis. As the degree of retinal microglia activation did not exhibit significant differences among the groups treated with different concentrations of high glucose, stimulation with the minimum concentration of high glucose (25 mM) was performed in subsequent experiments.

As shown in figure 5, either MCC950 or Z-YVAD-FMK could suppress LDH release, caspase-1 activity, and IL-1β secretion in retinal microglia stimulated with high glucose (25 mM) ($p<0.05$). Additionally, western blotting analysis confirmed that the protein expression of NLRP3, cleaved caspase-1, and cleaved GSDMD was downregulated in retinal microglia ($p<0.05$).



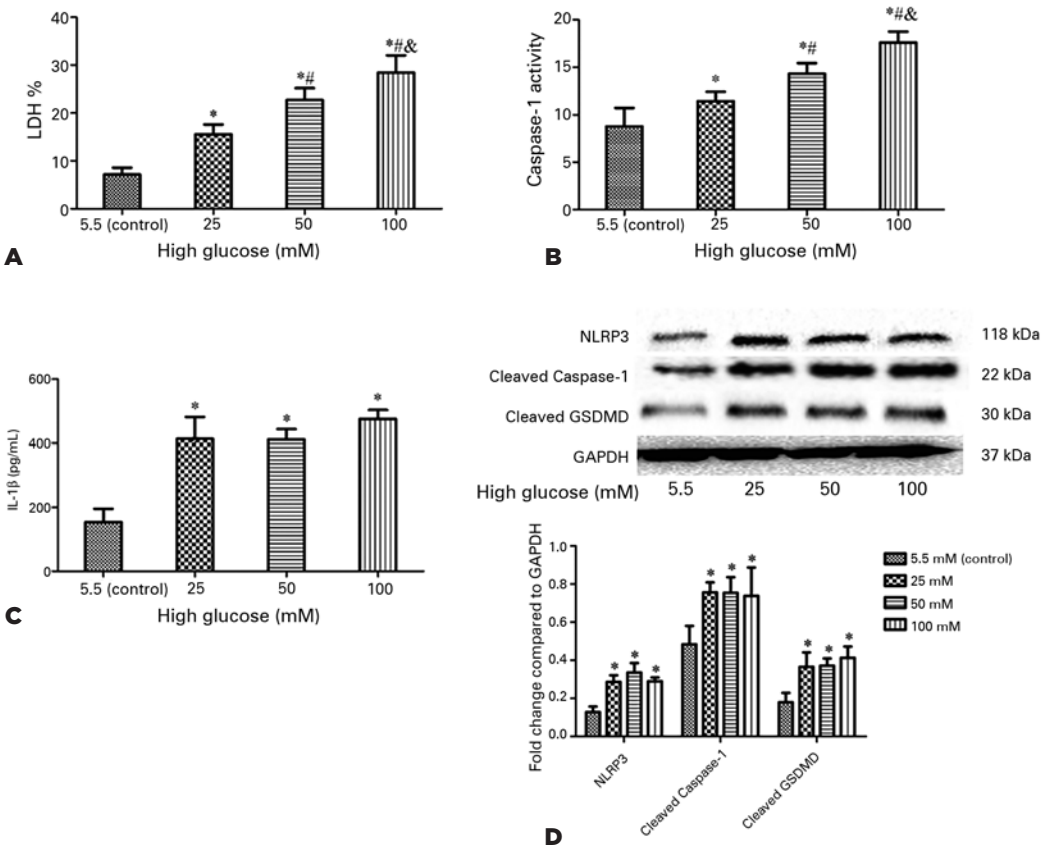
*p<0.05 versus the control group; #p<0.05 versus the 25 mM high glucose-treated group; &p<0.05 versus the 50 mM high glucose-treated group. CCK-8= Cell Counting Kit-8; SD= standard deviation.

Figure 2. High glucose reduced the viability of retinal microglia *in vitro*. Retinal microglia were stimulated by different concentrations of high glucose (25, 50, and 100 mM). The cell viability was measured using the CCK-8 kit, which revealed a marked decline in a dose-dependent manner. Values are expressed as the mean ± SD. n=6.



Values are expressed as the mean ± SD. n=3; *p<0.05 versus the control group. Iba-1= ionized calcium-binding adapter molecule-1; SD= standard deviation; GAPDH= glyceraldehyde-3-phosphate dehydrogenase.

Figure 3. High glucose activated retinal microglia *in vitro*. Western blotting analysis indicated that treatment with high glucose upregulated the protein expression of Iba-1 in retinal microglia. There were no significant differences observed among the groups treated with different concentrations of high glucose (25, 50, and 100 mM).



Values are expressed as the mean ± SD. n=3; *p<0.05 versus the control group; #p<0.05 versus the 25 mM high glucose-treated group; &p<0.05 versus the 50 mM high glucose-treated group.
NLRP3= NOD-like receptor family pyrin domain containing 3; LDH= lactate dehydrogenase; ELISA= enzyme-linked immunosorbent assay; IL-1β= interleukin-1β; GSDMD= gasdermin D; SD= standard deviation; GAPDH= glyceraldehyde-3-phosphate dehydrogenase.

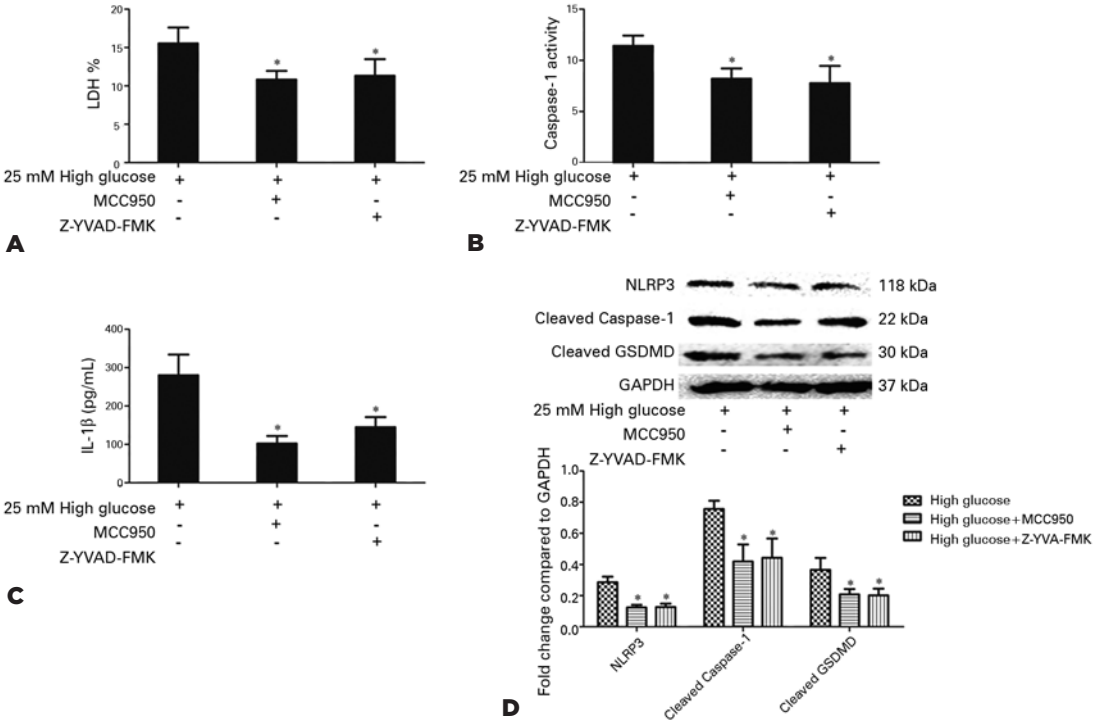
Figure 4. High glucose triggered NLRP3 inflammasome signaling and pyroptosis in retinal microglia. Treatment with high glucose (25, 50, and 100 mM) increased LDH release (A) and caspase-1 activity (B) in retinal microglia in a dose-dependent manner. Detection with ELISA showed that high glucose increased the release of IL-1β (C). Moreover, western blotting analysis indicated that high glucose enhanced the protein expression of NLRP3, cleaved caspase-1, and cleaved GSDMD (D).

DISCUSSION

The mechanisms triggering pyroptotic cell death during the development of DR are intricate and not fully understood[23]. In this study, we demonstrated that NLRP3 inflammasome signaling could modulate retinal microglial pyroptosis under high-glucose conditions and induce microglia-related inflammation in the retina.

As the crucial immunoregulatory cells in the retina, microglia play a pivotal role in the maintenance of homeostasis in the retinal microvasculature, and are involved in various retinal diseases (especially DR)[7,24]. Metabolic abnormalities may initially give rise to microglial dysfunction[25]. The treatment of DR with microglia to alleviate retinal inflammation has been widely investigated[26-27]. Our results are in line with the current evidence[28] that high glucose could decrease cell viability and activate retinal microglia *in vitro*. Iba-1, a calcium-binding protein, participates in the migration and phagocytosis of activated microglia[29]. The present study showed that there are no significant differences in Iba-1 expression among the groups treated with different concentrations of high glucose. We hypothesized that the migratory and phagocytic capability of activated retinal microglia may have already peaked after stimulation with 25 mM high glucose.

Upon excess activation, retinal microglia shifted to the M1 phenotype[30], promoted the release of pro-inflammatory factors (e.g., IL-1β), and may subsequently result in the activation of pyroptosis to rupture microglia and further aggravate inflammatory responses in the retina[31]. We demonstrated that IL-1β secretion by retinal microglia was upregulated under high-glucose



Values are expressed as the mean ± SD. n=3; *p<0.05 versus the control group.
NLRP3= NOD-like receptor family pyrin domain containing 3; Z-YVAD-FMK= Z-Tyr-Val-Ala-Asp(OMe) fluoromethyl ketone; LDH, lactate dehydrogenase; IL-1β= interleukin-1β; GSDMD= gasdermin D; SD= standard deviation; GAPDH= glyceraldehyde-3-phosphate dehydrogenase.

Figure 5. NLRP3 inflammasome signaling modulated high glucose-induced pyroptosis in retinal microglia. Retinal microglia were pretreated with the NLRP3 inhibitor MCC950 or caspase-1 inhibitor Z-YVAD-FMK prior to incubation with high glucose (25 mM). LDH release (A), caspase-1 activity (B), and IL-1β secretion (C) by retinal microglia were inhibited, along with the decrease of the protein expression of NLRP3, cleaved caspase-1, and cleaved GSDMD (D).

conditions, suggesting that hyperglycemia may induce phenotypic polarization of retinal microglia to generate proinflammatory effects *in vitro*. Moreover, high glucose increased LDH release and cleaved caspase-1/cleaved GSDMD expression, which could form cell membrane pores and accordingly lead to pyroptosis of retinal microglia to induce damage of the neurovascular unit in DR.

NLRP3 inflammasome signaling is closely related to the maturation of downstream caspase-1[32]. Activation of the NLRP3 inflammasome mediates the induction of pyroptosis to further secrete IL-1β[33]. Some studies have revealed that the activity of the NLRP3/caspase-1/IL-1β axis was enhanced in microglia located in the central nervous system of patients with Parkinson's disease[34-35]. In the present study, we determined that high glucose could activate NLRP3 inflammasome signaling in retinal microglia, and subsequently trigger pyroptosis. Furthermore, pretreatment with the inhibitors of NLRP3 inflammasome signaling significantly attenuated the high glucose-induced cytotoxicity, activation of the NLRP3 inflammasome, IL-1β secretion, and pyroptosis. These results confirmed that pyroptosis of retinal microglia was due to high glucose-induced activation of NLRP3 inflammasome signaling. Nevertheless, further studies are warranted to assess whether other signaling pathways are involved in the regulation of pyroptosis in retinal microglia in DR.

In conclusion, treatment with high glucose induced NLRP3 inflammasome-dependent pyroptosis in retinal microglia. This may be one of the main mechanisms resulting in retinal inflammation that initiates or promotes the pathophysiologic progression of DR. Our present findings may provide new potential targets and direction for the therapy of DR.

ACKNOWLEDGEMENTS

This study was supported by grants from the Startup Fund for Scientific Research of Fujian Medical University (Grant number: 2016QH041), and Fund for Young and Middle-aged University Teachers' Educational Research of Fujian Province (Grant number: JT180188).

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Nodular anterior scleritis associated with Berger's disease

Esclerite anterior nodular associada à doença de Berger

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ABSTRACT | A 45-year-old female patient presented with a complaint of right eye redness and pain for 7 days. She was under investigation for urinary abnormalities and reported a previous history of recurrent oral ulcers and ocular hyperemia in both eyes. Best-corrected visual acuity was 20/30 and 20/20 in the right and left eyes, respectively. Slit-lamp biomicroscopy of the ocular surface of the right eye revealed nasal scleral hyperemia that persisted after instillation of topical phenylephrine 10%, reinforcing the diagnosis of anterior scleritis. Renal biopsy showed immunoglobulin A immune complexes and confirmed the suspected diagnosis of Berger's disease. Maintenance immunosuppressive therapy with azathioprine following a 6-month induction of remission with cyclophosphamide was necessary after pulse therapy with methylprednisolone. Scleritis is usually related to systemic autoimmune diseases, such as rheumatoid arthritis, and polyangiitis. Herein, we describe a rare case of unilateral anterior scleritis associated with Berger's disease.

Keywords: Glomerulonephritis; Immunoglobulin A; Scleritis; Azathioprine; Cyclophosphamide; Case report

RESUMO | Paciente de 45 anos, sexo feminino queixava-se de hiperemia e dor no olho direito há sete dias. Encontrava-se sob investigação de alterações urinárias e relatou história pregressa de úlceras orais e hiperemia ocular bilateral recorrentes. A acuidade visual corrigida era de 20/30 no olho direito e 20/20 no esquerdo. A biomicroscopia da superfície ocular do olho direito revelou intensa hiperemia escleral em região nasal que persistiu após a instilação de fenilefrina tópica a 10%, reforçando o diagnóstico clínico de esclerite anterior unilateral. A biópsia renal revelou a presença de imunocomplexos de IgA e confirmou a hipótese de doença de Berger. Uma terapia imunossupressora de manutenção com azatioprina após 6 meses de indução de remissão com ciclofosfamida foi necessária após pulsoterapia com metilprednisolona. A esclerite geralmente está relacionada a doenças autoimunes sistêmicas, como artrite reumatoide e poliangeite. Descrevemos aqui um caso raro de esclerite anterior unilateral associada à doença de Berger.

Descritores: Glomerulonefrite; Imunoglobulina; Esclerite; Azatioprina; Ciclofosfamida; Relatos de casos

INTRODUCTION

Immunoglobulin A nephropathy (IgAN), also termed Berger's disease, is one of the most common primary glomerulopathies worldwide. This immune complex-mediated disease typically affects males, in the second and third decades of life, and may be asymptomatic or manifest with hematuria and/or proteinuria. Renal biopsy is essential for its diagnosis, taking into account that IgA deposits may be observed even in patients without evidence of kidney disease. Systemic manifestations may frequently include arterial hypertension and chronic renal failure in the late stages of the disease, although it rarely affects the eye[1].

Scleritis is an immune-mediated lesion characterized by painful inflammation of the sclera[2]. Although it can occur independently, up to 50% of patients present an underlying disease, such as connective tissue disorders, infectious agents, or previous history of trauma[2,3]. Rheumatoid arthritis, granulomatous polyangiitis, and

Submitted for publication: August 16, 2019
Accepted for publication: February 7, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Hospital Universitário Cassiano Antonio Moraes (CAAE 17460819.6.0000.5071).

 http://dx.doi.org/10.5935/0004-2749.20210011

systemic lupus erythematosus are the most common systemic disorders associated with scleritis. Commonly reported infectious agents include *Mycobacterium tuberculosis*, varicella-zoster virus, *Treponema pallidum*, and *Borrelia burgdorferi*[3,4].

Ocular involvement in IgAN is uncommon, and few reports described its association with anterior scleritis[5-9]. Herein, we describe a rare case of unilateral nodular anterior scleritis in a patient with IgAN and highlight the importance of routine urinary laboratory investigation in patients with scleral inflammation.

CASE REPORT

A 45-year-old female complained of redness and ocular pain in right eye for 7 days. She reported previous episodes of ocular hyperemia in both eyes, recurrent oral ulcers, systemic arterial hypertension, non-nephrotic proteinuria, hematuria without erythrocyte dysmorphism and normal renal function (under investigation by the Rheumatology and Nephrology Service).

On ocular examination, best-corrected visual acuity was 20/30 in the right eye (OD) and 20/20 in the left eye. Pupillary reactions, slit-lamp biomicroscopy of the anterior segment, intraocular pressure, and fundus examination were normal. Slit-lamp biomicroscopy of the ocular surface revealed intense nasal scleral hyperemia (Figure 1) that persisted after instillation of topical phenylephrine 10%, which, together with the painful eye, confirmed our diagnosis of unilateral anterior nodular scleritis. Owing to its hypothesized association with Behçet's disease, spondyloarthritis, systemic lupus erythematosus, or IgAN, pulse therapy with methylprednisolone (1 g/day for 3 days) followed by an oral corticosteroid-tapering regimen was prescribed after ruling out the presence of infectious diseases.

Laboratory tests revealed the following: a normal complete blood count, serum creatinine, blood urea nitrogen, C-reactive protein, erythrocyte sedimentation rate, and complement levels; negative antinuclear antibodies, anti-double stranded DNA, anti-Smith, anti-ribonucleoprotein, anti-human leukocyte antigen-B27, anti-human immunodeficiency virus-1 and -2, Venereal Disease Research Laboratory test, and purified protein derivative test; negative anti-Toxoplasma IgM and positive IgG. A 24-h urine analysis revealed non-nephrotic proteinuria, urinary casts, and hematuria without dysmorphic erythrocytes. Finally, renal biopsy showed mild and focal mesangial proliferation and expansion, glomerular synechiae, and normal vessels, without atrophy or fibrosis. Immunofluorescence evidenced granular deposits of IgA in a mesangial pattern with low intensity and confirmed the diagnosis of IgAN (Figure 2).

There was no significant improvement of the scleritis immediately after three consecutive daily intravenous methylprednisolone pulses of 1 g (Figures 3A, 3B). However, 40 days after pulse therapy, the best-corrected visual acuity improved to 20/20 in both eyes and the scleral inflammation completely resolved without sequelae (Figures 3C, 3D). Immunosuppression with cyclophosphamide (0.75 g/m^2 of body surface area/month) for 6 months and maintenance treatment with azathioprine was initiated due to the severity of the disease, the inherent risk of new episodes of scleritis, and the late response to pulse therapy with methylprednisolone. At

Figure 1. Image of both eyes showing nodular anterior scleritis in the nasal region of the right eye.

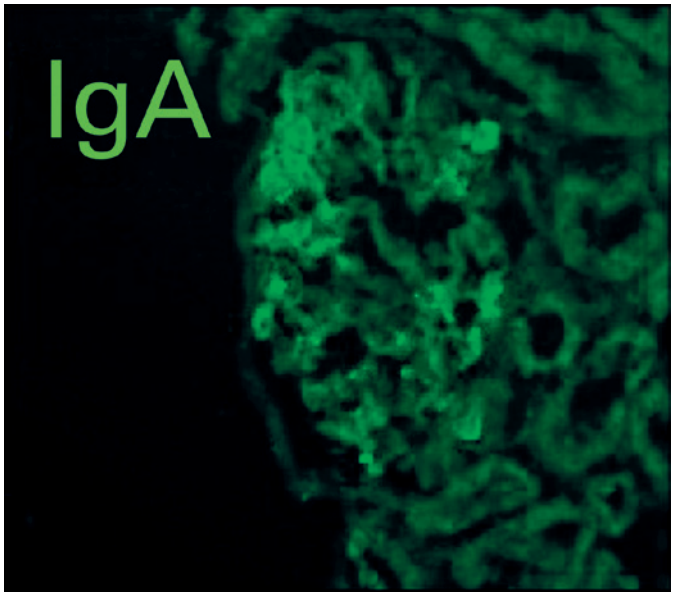

Figure 2. Renal biopsy with immunofluorescence staining showing granular deposition of immunoglobulin A (IgA) in a mesangial pattern with low intensity (1 of 3 points).

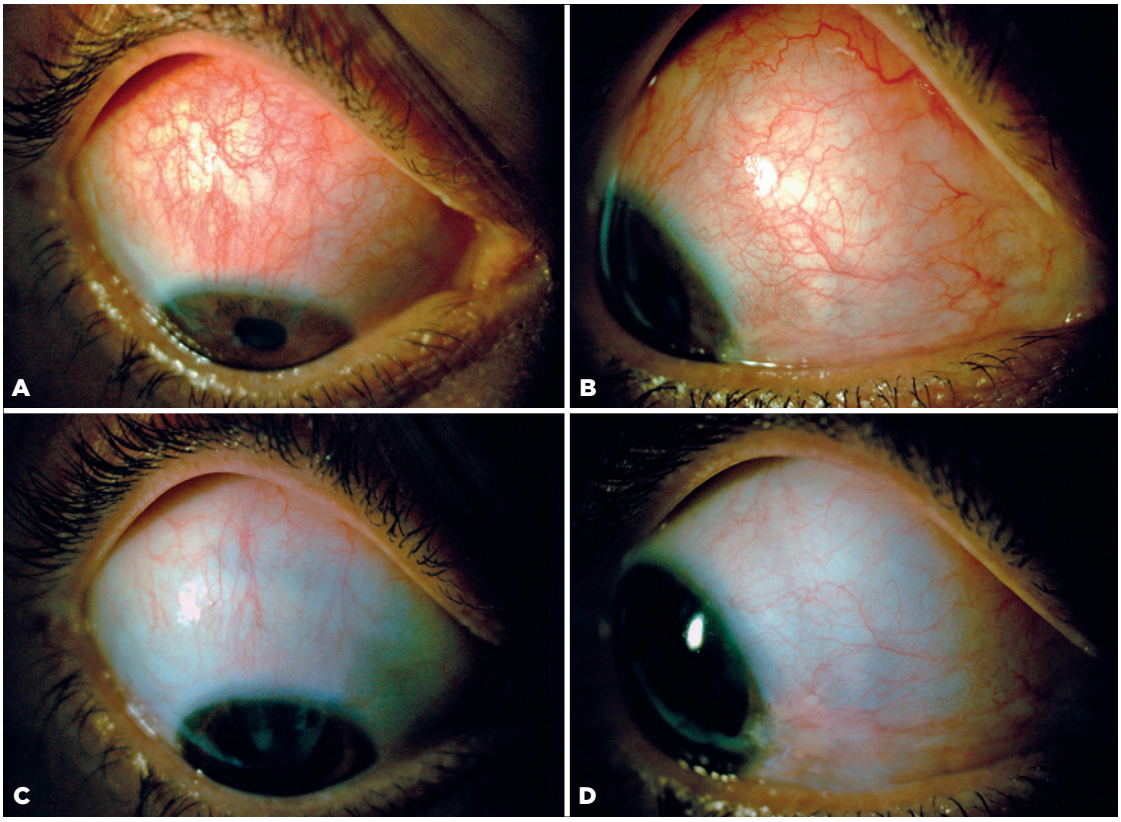

Figure 3. (A, B) Slit-lamp biomicroscopy of the right eye showing superior and nasal scleritis 3 days after pulse therapy with methylprednisolone. (C, D) At 40 days after pulse therapy, with complete improvement of nasal and superior inflammation of the right eye.

14 months of follow-up, the patient did not show recurrence after therapy with azathioprine.

DISCUSSION

Berger's disease (IgAN) is the most frequent occurring primary glomerulonephritis[1]. However, the disease is usually asymptomatic in the early phases. In most cases, IgAN is restricted to the kidney and rarely affects the eye. A large proportion of patients with scleritis present an underlying disease[2,3]. Therefore, systemic investigation of connective tissue disorders and infectious disease is mandatory. In our case, the presence of scleritis in a patient with recurrent oral ulcers and normal renal function associated with non-nephrotic proteinuria led us to the differential diagnoses of Behçet's disease, spondylarthritis, and systemic lupus erythematosus.

Ocular involvement in IgAN is uncommon. A systematic literature review showed episcleritis as the main ocular manifestation of IgAN[4] and the association of Berger's disease with anterior scleritis has been rarely described[5-9]. In this case, laboratory examinations ruled out numerous infectious and non-infectious causes of anterior scleritis. However, urinalysis played a pivotal role in guiding the etiological investigation of glomerular disease, due to the presence of non-nephrotic proteinuria, urinary casts, and hematuria without dysmorphic erythrocytes. The immunofluorescent evaluation of renal biopsy was decisive to reach a definitive diagnosis. In a patient with scleritis, IgAN should be considered even in the absence of urinary symptoms[8].

Complement activation through alternative and lectin pathways plays a key role in the pathogenesis of IgAN, leading to systemic circulation of immune complexes and locally in the kidneys[10]. The exact pathophysiology of the relationship between IgAN and scleritis is uncertain[4]. An episcleral biopsy in a patient with IgAN and episcleritis revealed dimeric IgA-secreting plasma cells, suggesting that ocular surface immunity may be involved in ocular manifestations in this nephropathy[11]. Ocular IgA may also be related to the development of scleritis in IgAN. However, further investigations are warranted.

Systemic medications for the treatment of scleritis are frequently required to reduce inflammation and ocular damage. Corticosteroids with or without other immunosuppressive drugs should be considered in patients with associated autoimmune disease[12]. Thus far, there is no optimal treatment for the ocular manifestations of IgAN. In our case report, scleral inflammation was only reduced 40 days after three consecutive daily pulse therapy sessions with methylprednisolone followed by an oral corticosteroid-tapering regimen. Furthermore, considering the severity of inflammation, the inherent risk of new episodes of scleritis, and the poor response to intravenous corticotherapy, the introduction of a stronger immunosuppressive agent is recommended for a long disease remission[13]. Further studies are warranted to evaluate the ocular involvement in Berger's disease and whether IgAN-related scleritis is associated with a poor response to treatment with immunomodulators.

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Lacrimal gland atrophy and dry eye related to isotretinoin, androgen, and prolactin: differential diagnosis for Sjögren's syndrome

Atrofia das glândulas lacrimais e olho seco relacionados aisotretinoína, androgênio e prolactina: diagnóstico diferencial com a síndrome de Sjögren

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ABSTRACT | This report is of three cases of sicca syndrome, initially suspected to be Sjögren's syndrome, which was ruled out by clinical and laboratory investigations. The patients were a 24-year-old woman, a 32-year-old man, and a 77-year-old woman with chronic symptoms of sicca syndrome, including dry eye syndrome. The first case was associated with the use of isotretinoin, a retinoic acid. The second was associated with the use of anabolic androgenic steroids, and the third was related to a prolactin- secreting pituitary adenoma. All cases manifested sicca, including dry eye syndrome, after those events, and the manifestations persisted. Magnetic resonance imaging revealed bilateral atrophy of the lacrimal gland. The medical history, ocular examinations, laboratory exams, and magnetic resonance images confirmed dry eye syndrome; however, the exams were all negative for Sjögren's syndrome. The lacrimal gland was absent on magnetic resonance imaging in all three cases. The clinical history revealed that the signs and symptoms appeared after chronic exposure to retinoic acid, anabolic androgenic steroids, and a prolactin-secreting pituitary adenoma, respectively. Chronic isotretinoin, anabolic androgenic steroids, and prolactin-secreting pituitary adenoma or, in this last case, its inhibitory treatment, can cause lacrimal gland atrophy, sicca syndrome, and dry eye syndrome, and a differential diagnosis of Sjögren's syndrome. Further studies on doses, time, and other susceptibilities to the long-lasting adverse effects of retinoic acid, anabolic androgenic steroids, and the repercussions of prolactin-secreting pituitary adenoma are necessary to confirm and expand upon these associations.

Keywords: Testosterone congeners; Isotretinoin; Dry eye syndrome; Lacrimal glands; Magnetic resonance imaging; Pituitary neoplasms; Adenoma; Prolactin; Sjögren's syndrome

RESUMO | O relato descreve três casos de síndrome de sicca, inicialmente suspeitos de serem a síndrome de Sjögren, que foram negados pela investigação clínica e laboratorial. O primeiro associado ao uso de isotretinoína, um ácido retinóico, o segundo ao uso de esteroides androgênicos anabolizantes e o terceiro relacionado ao adenoma da hipófise secretora da prolactina, todos manifestaram sicca, incluindo a síndrome do olho seco após esses eventos e as manifestações persistem. A ressonância magnética revelou atrofia bilateral da glândula lacrimal. Eles eram uma mulher de 24 anos, um homem de 32 anos e uma mulher de 77 anos com sintomas crônicos da síndrome de sicca, incluindo a síndrome do olho seco. A história médica, o exame ocular, os exames laboratoriais e a ressonância magnética foram confirmados como síndrome do olho seco, no entanto, todos os exames foram negativos para a síndrome de Sjögren. A glândula lacrimal estava ausente na ressonância magnética nos três casos. A história clínica revelou que sinais e sintomas se manifestaram após exposição crônica ao ácido retinóico, esteróides anabolizantes androgênicos e adenoma secretivo da prolactina hipofisária, respectivamente. Isotretinoína crônica, esteroides anabólicos androgênicos e adenoma hipofisário secretor de prolactina ou, neste último caso, seu tratamento inibitório pode ser a causa da atrofia da glândula lacrimal, síndrome da sicca e síndrome do olho seco e diagnóstico diferencial da síndrome de Sjögren. Estudos adicionais sobre doses, duração e outras suscetibilidades aos efeitos adversos duradouros do ácido retinóico, esteroides androgênicos anabólicos e repercussões do adenoma da hipófise

Submitted for publication: August 12, 2019
Accepted for publication: February 18, 2020

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Approved by the following research ethics committee: Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto - USP (CAAE: 16187119.0.0000.5440).

 http://dx.doi.org/10.5935/0004-2749.20210012

secretora da prolactina são necessários para confirmar e detalhar essas associações.

Descritores: Congêneres da testosterona; Isotretinoína; Síndromes do olho seco; Glândulas lacrimais; Imagem por ressonância magnética; Neoplasias hipofisárias; Adenoma; Prolactina; Síndrome de Sjögren

INTRODUCTION

Retinoic acid (RA), anabolic androgen steroids (AAS), and prolactin (PRL) act on the main lacrimal gland (LG), meibomian glands (MG), and the ocular surface (OS) epithelia. Therefore, that they have physiological effects on these tissues' homeostasis and a potential therapeutic effect on dry eye syndrome (DES)[1-4]. Conversely, genetic predisposition, hormone interactions, and excessive exposure to those hormones can induce paradoxical effects in the OS or other exocrine tissues, as previously reported for RA, AAS, and PRL[1,4-8].

In conditions associated with LG or salivary gland (SG) dysfunction, including Sjögren's syndrome (SS), observing the exocrine glands in magnetic resonance imaging (MRI) revealed correlations with volumetric reduction, lower fluid secretion, and other changes[9].

Our objective was to describe three cases of bilateral LG atrophy. The sicca manifestations led to an SS hypothesis; however, the only SS clinically relevant fact identified was the prior chronic use of isotretinoin (an isoform of RA), treatment with AAS in a recreational athlete, and a prolactinoma treated with a dopamine agonist, respectively. The SS investigation was negative in all the three cases, according to the American-European criteria[10].

CASES REPORT

Case 1

A 24-year-old white woman presented with DES over the last three years without dry mouth. She reported no comorbidities and no use of medications, except for treatment of acne with RA at 14 and 20 years of age, lasting for six months on both occasions. The ophthalmological examination demonstrated a visual acuity of 1.0 in both eyes (OU); a tear film break-up time (TFBUT) of 2 s in the right eye (OD) and 1 sin the left eye (OS); a grade 5 corneal fluorescein staining in OD and grade 3 in OS, with filamentary keratitis; and a Schirmer test (ST) showed absent tear flow (zero mm) in OU. Moderate MG dysfunction (MGD) with less than 30% of gland drop out, light expressibility, and cloudy oil secretion were observed. The ocular surface disease index (OSDI) was 70.45%, and the whole saliva flow was 0.13 ml/min (normal value, >0.1 ml/min). Serological tests for autoimmune and viral systemic diseases, including anti-Ro/SSA, anti-La/SSB, anti-dsDNA, anti-SM, anti-RNP, antinuclear antibody (ANA), and rheumatoid factor, were negative. A biopsy of her minor lip SG revealed a focus score of zero. MRI revealed the absence of the LG bilaterally (Figure 1A). The average normal LG volume is 0,580 cm^3.

Case 2

A 32-year-old white man presented with DES and dry mouth for 18 months. Prior to the visit, he received hydroxychloroquine sulfate, corticosteroids, topical cyclosporine, eyedrops, and punctual occlusion for presumed DES secondary to SS, without improvement. His only remarkable previous history was the use of AAS for bodybuilding, as follows: durateston (a solution of four molecules of synthetic testosterone, composed of propionate, fempropionate, isocaproate, and decanoate of testosterone at 30, 60, 60, and 100 mg of each compound per ml, respectively) at one intramuscular injection per week; and stanzonolol (100 mg) via intramuscular injection twice a week. Both were used, as mentioned above, for eight consecutive weeks, two months before the onset of symptoms. No other medications or diseases were reported. The ophthalmological examination demonstrated a visual acuity of 1.0 OU; a TFBUT of 8 s OU; no corneal fluorescein staining; and an ST of 40 mm OU. Examinations of MG and lid margins were normal, but the tarsal conjunctiva exhibited hyperemic and conjunctiva concretions (Figure 2). The OSDI was 90%, and the whole saliva flow was 0.20 ml/min. Serological tests for autoimmune and viral systemic diseases, including anti-Ro/SSA, anti-La/SSB, anti-dsDNA, anti-SM, anti-RNP, ANA, and rheumatoid factor, in addition to blood hormonal assays, were normal. A biopsy of his minor lip SG revealed a focus score of zero. The MRI evidenced that both LGs and the parotid SGs were absent (Figure 2A and B).

Case 3

A 77-year-old female presented with DES for five years, which had worsened 12 months before the visit and was attributed to emotional problems. She was using artificial tears and lacrimal punctal plug occlusion. She mentioned a diagnosis of prolactinoma 30 years prior to

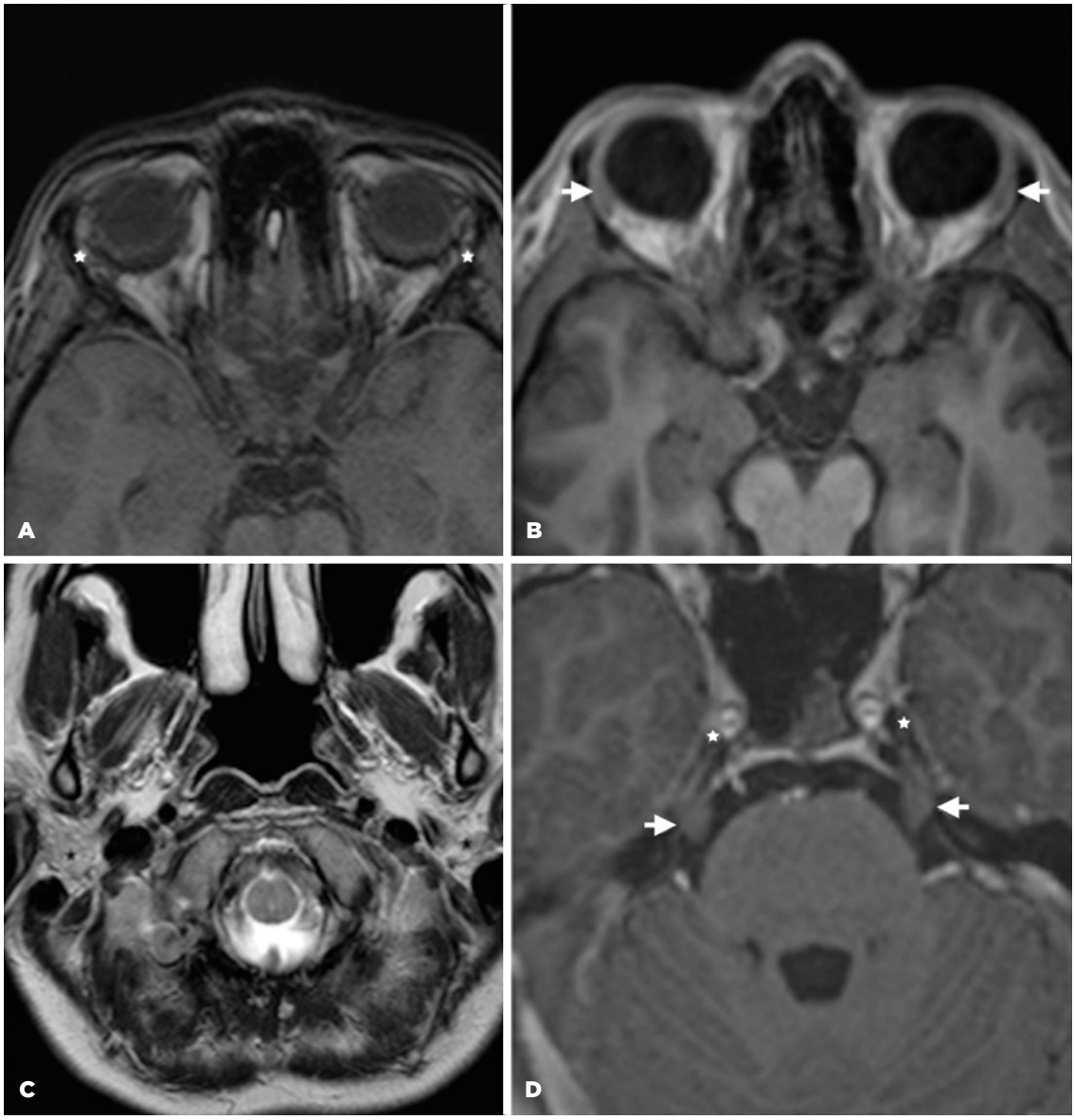

Figure 1. Case 1. A. Axial T1-weigthed magnetic resonance (MR) image, of the upper level of orbits shows the absence of the lacrimal glands (asterisk). B. Axial T1-weighted image, at the same level, in a normal subject (for comparison) shows the usual pattern of the lacrimal glands (white arrows). C. Axial T2-weigthed image shows a normal appearance of the parotid glands of this sequence, with high signal (asterisk). The asymmetry between the right and left sides is due to a slight rotation in the transverse plane. D. T1 axial oblique plane shows the cisternal portion of the trigeminal nerve (arrows) and Meckel's cave (asterisks).

this visit, which manifested initially with galactorrhea, further confirmed by laboratory and imaging exams. She had been using carbegoline since that diagnosis. Thyroidectomy and systemic arterial hypertension were treated with Puran T4 and hydroclortiazide, respectively. Her physical exam was not remarkable. Her ocular exam was positive for mild bilateral blepharospasm and mild punctate keratitis. The TFBUT was 30 s and the ST was 5 mm OU. Mild MGD with 20% of gland drop out, light expressibility, and cloudy oil secretion were observed. No changes in the eyelid margin, mucocutaneous junction, or gland orifices were observed. The whole salivary flow was 0.02 ml/min. The laboratory exams were normal, including the prolactin and thyroid stimulating hormone (TSH) levels. The anti-Ro/SSA, anti-La/SSB levels were negative. A biopsy of the lip SG revealed moderate acinar atrophy and mild diffuse lymphocytic infiltration, but no focus score. The MRI analysis revea-

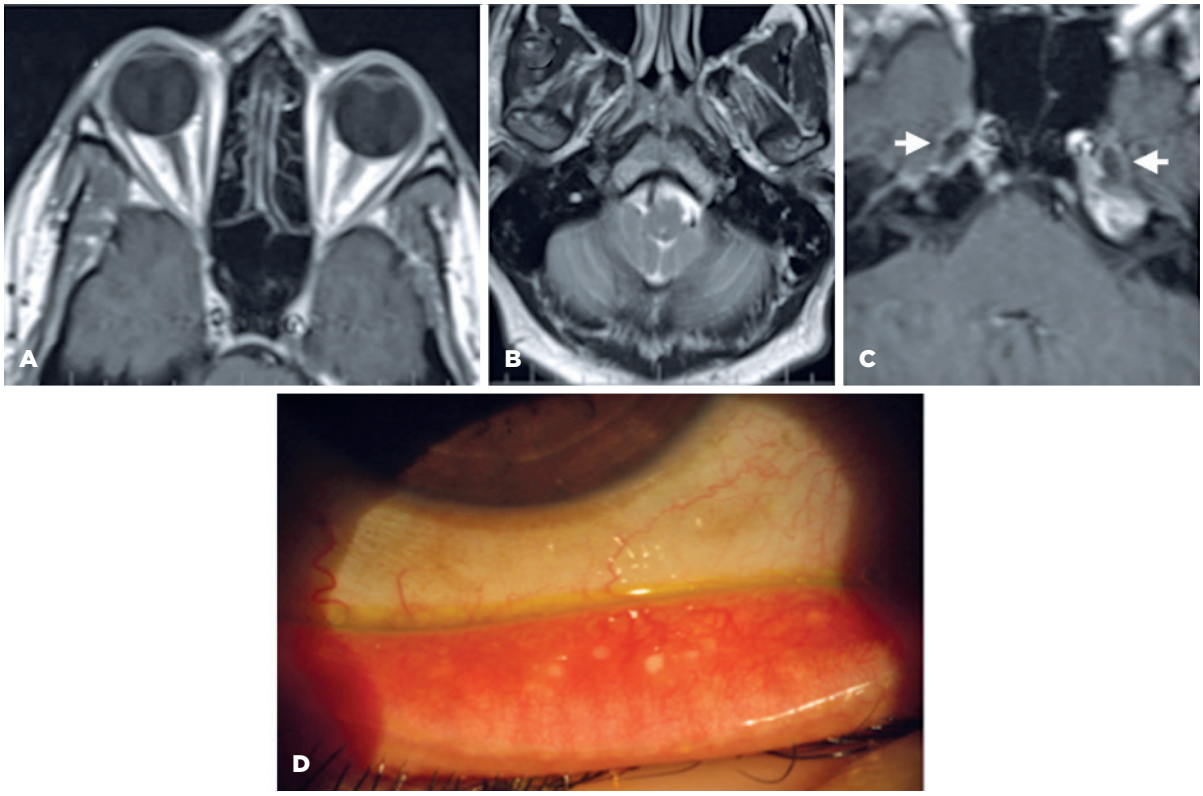

Figure 2. Case 2. A. Axial T1-weigthed magnetic resonance (MR) image at the upper level of the orbits shows the absence of the lacrimal glands. B. Axial T2-weigthed image shows the absence of the parotid gland. C. T1 axial oblique plane shows the cisternal portion of the trigeminal nerve (arrows). D. The tarsal conjunctiva shows hyperemia and conjunctival concretions.

led bilateral atrophy of the LG and the parotid gland (Figure 3). Moreover, a biopsy of the labial SG showed tissue hypotrophy and diffuse lymphocytic infiltration, but not the typical signs of SS, which are foci of lymphocytic infiltration (Figure 3C).

DISCUSSION

The observations revealed DES is associated with exposure to RA, AAS, and PRL or, in case 3, with PRL chronic inhibition. RA is used to treat acne vulgaris and as an anti-aging cosmetic, of which DES is a reversible side effect[7]. The atrophic LG outcome reported may represent an underdiagnosed event in persistent DES cases. Moreover, the potential association with MGD or other OS changes and discomfort caused by evaporative DES should be considered.

The use of AAS, which causes side effects as DES, can be more difficult to correlate in this setting because many patients omit this information. Many side effects are being reported, some severe, but this drug's popularity and its abuse are rampant among teenagers and adults[8]. The causes of its side effects are associated with disturbance of the hypothalamus-hypophysis axis, the impact on the brain's neuropeptides, and calcium imbalance; moreover, its effects on several organs have been described, including the liver, pancreas, and testis, but the association with LG atrophy was not reported previously, to the best of our knowledge[11].

The association between PRL and DES and SS is attributed to its bimodal trophic effect on the exocrine glands and the proinflammatory actions of this hormone[1,4,6]. In the case reported here, the long period of existence of a prolactinoma, treatment with a pharmacological inhibitor, and lowering the sex hormones could have induced inflammation in the LG and SG at the very beginning of the PRL rise. Further, it treatment may have caused atrophy and PRL inhibition over the subsequent decades, and a combined negative effect of sex hormone senescence and PRL inhibition in older age. The exact natural history of this case is unclear.

In summary, prospective cohort studies are required to support the atrophic collateral effects of excessive exposure to RA, AAS, and PRL on the LG, mimicking SS.

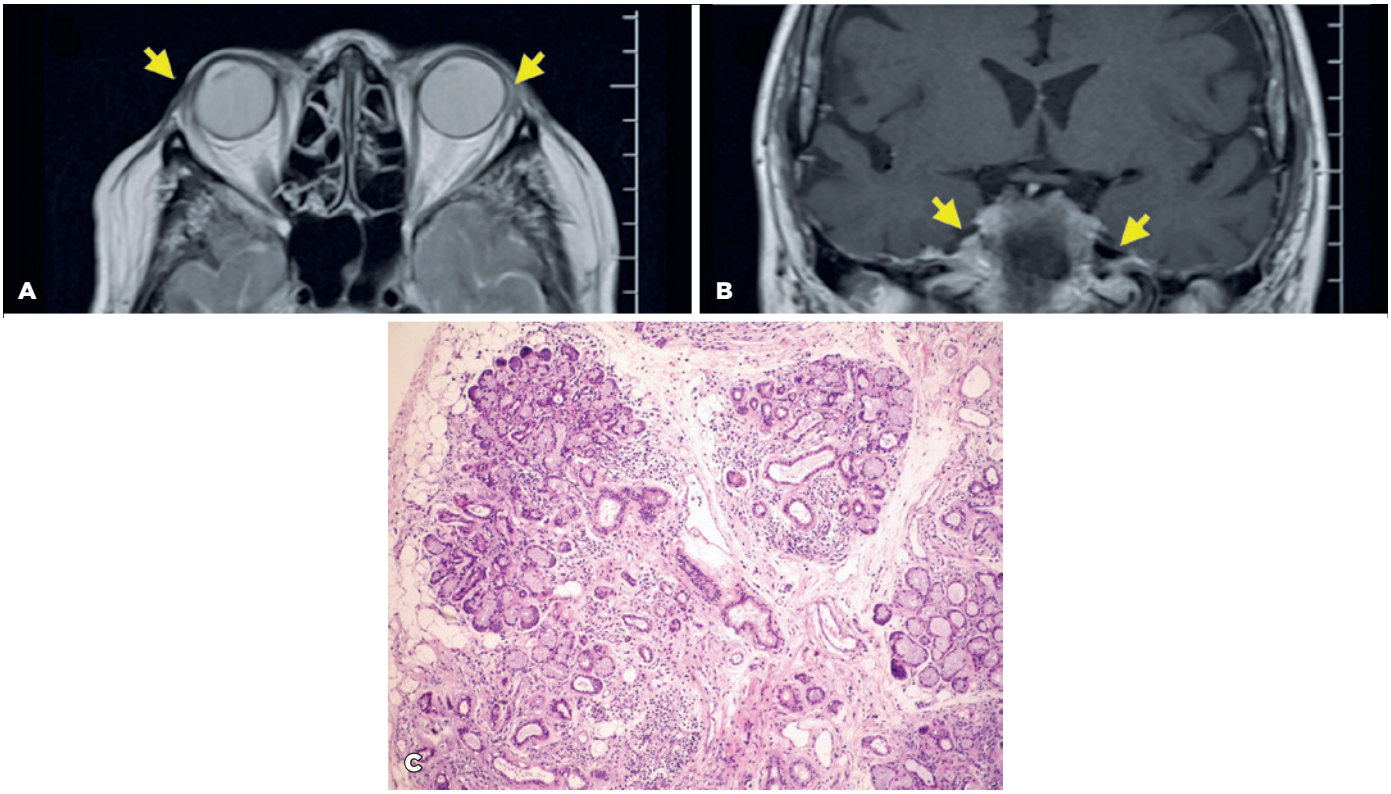

Figure 3. Case 3. A. Axial T1-weigthed magnetic resonance (MR) image at the upper level of the orbits shows the absence of the lacrimal glands (arrows) and the absence of the parotid glands. B. T1 Axial oblique plane shows the cisternal portion of the normal trigeminal nerve (arrows). C. Labial salivary gland biopsy, stained with hematoxylin and eosin, shows acinar hypotrophy, lymphocytic diffuse infiltration, and ductal enlargement.

Based on the frequency of those conditions, they must be included in differential diagnoses of DES and SS.

ACKNOWLEDMENTS

This study was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (nº 2014/23211-0 and 2014/22451-7) (São Paulo, SP, Brazil), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (nº: 474450/2012-0) (Brasilia, DF, Brazil), Research Core of Ocular Physiopathology and Therapeutics from Universidade de São Paulo (NAP-FTO) (nº 12.1.25431.01.7) (Ribeirão Preto, SP. Brazil), *FAEPA*.

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Arquivos Brasileiros de
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Bilateral cavernous sinus and left dural sigmoid sinus thrombosis associated with extreme exertion: a case report

Trombose bilateral do seio cavernoso e do seio sigmoide esquerdo associada a exercício extremo: relato de caso

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ABSTRACT | Septic cavernous sinus thrombosis is a rare but often debilitating and potentially fatal disease. We describe a case of bilateral orbital cellulitis with rapidly progressing cavernous sinus thrombosis and left sigmoidal sinus thrombosis in an immunocompetent 20-year-old military man who had undergone intensive physical training. The patient presented with rapid painful swollen left eye for 2 days. The examination results were gross proptosis with total ophthalmoplegia. He was treated with intravenous antibiotics and corticosteroid. At 1 week, visual acuity improved to 20/20 OU, with a normal intraocular pressure. There was a significant improvement in proptosis. The ocular motility of the right eye was fully restored, with slight residual ophthalmoplegia in the left eye. There was no residual illness or recurrence of illness at 3 months' follow-up.

Keywords: Cavernous sinus thrombosis; Exercise; Physical training; Orbital cellulitis, Immunocompetence

RESUMO | A trombose séptica do seio cavernoso é uma condição rara, mas frequentemente debilitante e potencialmente fatal. Descrevemos um caso de celulite orbital bilateral com progressão rápida para trombose do seio cavernoso e trombose do seio sigmoide esquerdo, em um militar imunocompetente de 20 anos de idade que havia sido submetido a treinamento físico intenso. O paciente apresentou um inchaço rápido e doloroso no olho esquerdo por 2 dias. Os resultados do exame foram proptose macroscópica com oftalmoplegia total. Ele foi tratado com antibióticos intravenosos e costicosteróide. Em 1 semana, a acuidade visual melhorou para 20/20, com pressão intraocular normal. Houve uma melhora significativa na proptose. A motilidade ocular do olho direito foi totalmente restaurada, com leve oftalmoplegia residual no olho esquerdo. Não houve doença residual ou recorrência da doença após três meses de acompanhamento.

Descritores: Trombose do corpo cavernoso; Exercício físico; Celulite orbitária; Imunocompetência

INTRODUCTION

Cavernous sinus thrombosis (CST) has become an uncommon condition with the availability of antibiotics. The most common causes of CST are sinusitis, otitis, and odontogenic and facial skin infections[1]. In contrast to common belief, athletes and sportsmen are at increased risk of infections, especially during periods of heavy training[2-3]. We describe a case of rapidly progressing CST with left sigmoidal sinus involvement in an immunocompetent young man who had undergone intensive physical training.

CASE REPORT

A 20-year-old healthy military man complained of a sudden, rapidly progressing painful and swollen left eye of 2 days' duration. It was associated with blurring of vision, diplopia, and swelling of the left cheek. The patient had undergone intensive training in a military camp for 5 days, consisting of a total of 8 hours of running, marching, and physical strength training.

The patient was restless and febrile. The left maxillary area was swollen, tender, and warm. The neurological examination was normal except for a positive Kernig's sign. Examinations of other systems were not suggestive of infection.

Submitted for publication: September 24, 2019
Accepted for publication: April 2, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Informed consent was obtained from all patients included in this study.

Visual acuity was 20/30 OD and 20/60 OS. There was gross proptosis bilaterally (23 mm OD and 24 mm OS). There was total ophthalmoplegia with swollen and chemotic conjunctiva (Figure 1). The intraocular pressure was elevated (24 mmHg OD and 30 mmHg OS). No relative afferent pupillary defect was observed. The anterior and posterior segment examinations were normal.

The total white cell count was elevated to 23,000/μl, with predominantly neutrophils (86%). Blood culture was repeated twice and grew methicillin-sensitive *Staphylococcus aureus*. Lumbar puncture showed normal glucose and protein levels with negative culture results. Screening for thrombophilia, which included protein C, protein S, anti-thrombin III, activated protein C resistance, and lupus anticoagulant screening, was negative.

Contrast-enhanced computed tomography (CECT) showed bilateral prominent superior ophthalmic veins, proptosis, and frontal soft tissue swelling with an absence of loculation. However, no sign of distended cavernous sinus with a non-fat density-filling defect was observed.

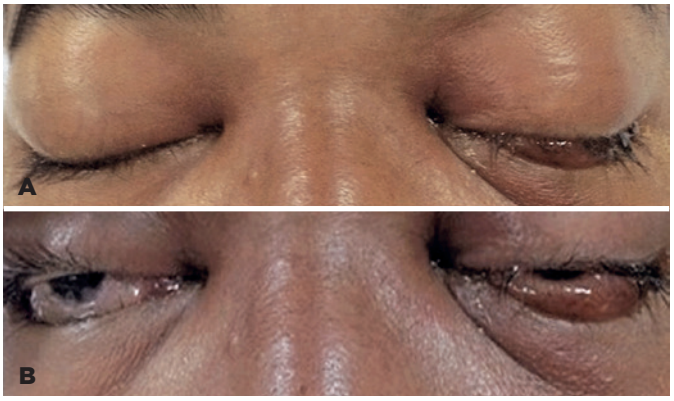

Figure 1. (A, B). Photographs on presentation showing bilateral gross proptosis and chemosis with left periorbital swelling.

Magnetic resonance imaging (MRI) revealed proptosis of both eyes with diffuse, symmetrical soft tissue thickening and areas of enhancement with engorgement of orbital vessels and inflammatory fat stranding involving the preseptal, postseptal, intraconal, and extraconal spaces. Magnetic resonance venography (MRV) did not show flow-related enhancement at the left sigmoid sinus. T2-weighted MRI showed a persistent filling defect within the cavernous sinus on both sides and the left sigmoid sinus. The sphenoid, left maxillary, and left ethmoidal sinuses showed mucosal thickening with an air-fluid level (Figure 2).

A diagnosis of bilateral orbital cellulitis and CST with evidence of left sigmoid sinus thrombosis complicated by sphenoid, left ethmoidal, and maxillary sinusitis was made. The patient was started on IV ceftriaxone 2 g twice daily, IV cloxacillin 1 g 6 hourly, IV hydrocortisone 50 mg 8 hourly, and IV heparin 6000 IU 6 hourly. Gutta moxifloxacin 4 hourly, gutta timolol 12 hourly, and gutta hydroxypropylmethylcellulose 6 hourly were prescribed for both eyes.

At 1-week, visual acuity improved to 20/20 OU, with a normal level of intraocular pressure. There was a significant improvement in proptosis. Ocular motility of the right eye was fully restored, with slight residual ophthalmoplegia in the left eye (Figure 3). There was no residual illness or recurrence of illness at 3 months' follow-up.

DISCUSSION

CST is the rarest form of dural venous sinus thrombosis, with a mortality rate of up to 30% and a morbidity rate as high as 22%[2]. The most common causes are sinusitis, otitis, and odontogenic and facial skin infections[1] due to the close proximity of the structures[3]. Our case

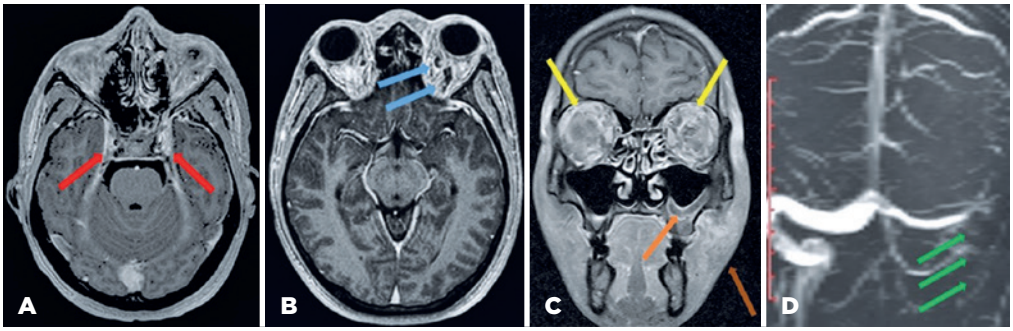

Figure 2. (A) Magnetic resonance imaging (MRI) showed features suggestive of bilateral cavernous sinus thrombosis (red arrow), (B) distended superior ophthalmic vein (blue arrow), (C) bilateral orbital cellulitis (yellow arrow), left maxillary sinusitis (orange arrow), and left cheek soft tissue swelling (brown arrow), (D) left sigmoid dural sinus thrombosis (green arrow).

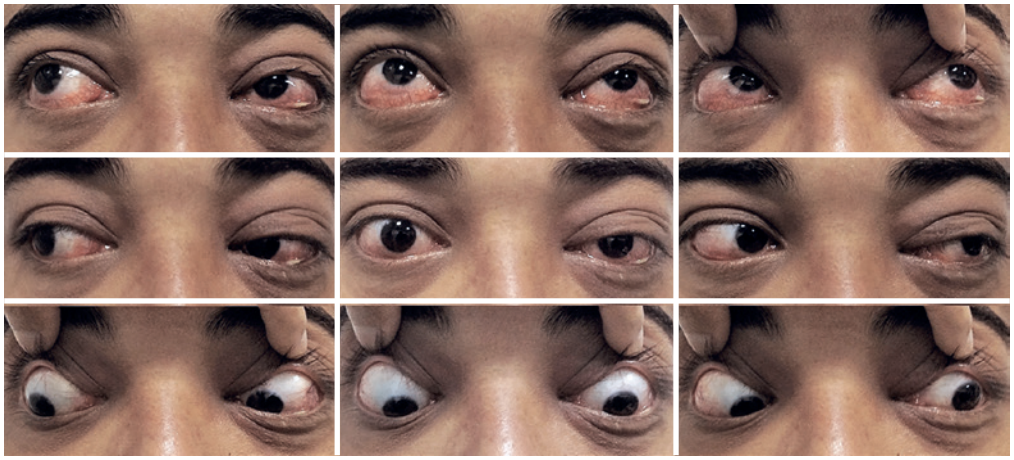

Figure 3. Photographs after completion of treatment. Nine-gaze photographs showed resolution of proptosis and ophthalmoplegia.

report showed an increased risk of infection in a healthy individual due to extreme physical exertion.

It has been reported that intensive training and overtraining are associated with immunodepression and susceptibility to infection[2,3]. The "inverted J hypothesis" in exercise immunology suggested that disease susceptibility increased in sedentary and over-trained subjects in comparison with subjects who underwent regulated, moderate training. Depression of natural killer cell function, reduction in expression of toll-like receptors, and increased release of cortisol and proinflammatory cytokines, such as tumor necrosis factor, interleukin-1b, and interleukin-6, are well-documented mechanisms that may have contributed to the immunocompromised state of our patient[4].

Another possible mechanism of the rapid progression of CST to intracranial thrombosis is the rebalanced hemostatic state, simultaneously causing hypercoagulability and enhanced fibrinolysis induced by extreme physical exertion. Hypercoagulability appears to persist longer, from a few hours to a day, than fibrinolytic activities after strenuous training[5]. Hence, we presumed that our patient was likely in a prothrombic state, which favored intracranial thrombus formation.

Staphylococcus aureus is the most common organism isolated in CST. Other organisms, including *Streptococcus*, fungi, Enterobacteriaceae, and anaerobes, have also been reported[6]. Predisposed to an increased risk of infection associated with extreme physical exertion[4], our patient developed methicillin-sensitive *S. aureus* septicemia from uncomplicated sinusitis and progressed to bilateral CST with left sigmoid sinus involvement. Our case is similar to the cases described by van der Poel et al., who reported that most of their patients recovered without any permanent deficits[7].

High-resolution CECT provides superb bone-air soft tissue details of the orbit and sinuses. CST may present as multiple irregular filling defects in the cavernous sinus on CECT. Our patient had normal CECT scan findings, similar to the report of Komatsu et al.[8]. Thus, the managing clinician should have a high index of suspicion towards the diagnosis of CST based on clinical presentation, even if the CECT scan is normal.

High-resolution MRI visualizes the enlargement of the CST as filling defects over time. Thin-slice gradient recalled echo sequences with gadolinium contrast have been shown to be more sensitive than routine MRI pulse sequences for detection of filling defects in the cavernous sinus[9]. MRV is helpful when the clinician suspects that dural sinuses are involved. In our case, MRI and MRV mapped out the complete extension of the CST in detail.

CST remains a life-threatening condition. Our case is an example of intensive physical training as a possible cause of thrombosis in a young patient with a rapid onset of intracranial thrombosis.

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Acute corneal melting one week after an uncomplicated cataract surgery in a patient who previously underwent eyelid radiation and with undiagnosed rheumatoid arthritis: a case report

Ceratomalácia aguda uma semana após cirurgia de catarata sem complicações em uma paciente com irradiação prévia de uma pálpebra e artrite reumatoide não diagnosticada: relato de caso

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ABSTRACT | This is a rare case report of acute, paracentral corneal melting and perforation occurring 1 week after an uneventful cataract surgery, with discussions on possible pathogenetic mechanisms. Relevant literature was also reviewed. Herein, a case of an 86-year-old woman with acute, paracentral, and sterile corneal melting and perforation in her left eye at 1 week after an uncomplicated cataract extraction is described. This occurs at the base of ocular surface disorders due to previous radiation of her lower eyelid and cheeks for the treatment of cancer and previously undiagnosed rheumatoid arthritis. She underwent surgical treatment using Gundersen's conjunctival flap for the existing perforation due to low visual expectancies and reluctance to undergo corneal keratoplasty due to the risk of corneal graft rejection. The risk of coming across an acute corneal melting after an uncomplicated cataract surgery in the eyes with ocular surface disorders should always be considered.

Keywords: Corneal perforation; Radiation; Rheumatoid arthritis; Cataract extraction

RESUMO | É apresentado um caso raro de ceratomalácia paracentral aguda estéril e perfuração da córnea em uma paciente de 86 anos, uma semana após cirurgia para catarata sem intercorrências. Também são discutidos possíveis mecanismos de patogênese e a literatura relevante é revisada. Esses distúrbios da superfície ocular ocorreram devido à irradiação da pálpebra inferior e da bochecha em um tratamento de câncer e a uma artrite reumatoide não diagnosticada anteriormente. A paciente submeteu-se a um tratamento cirúrgico com um *flap* conjuntival de Gundersen sobre a perfuração existente, devido às suas baixas expectativas visuais e à relutância em submeter-se a uma ceratoplastia da córnea, considerando o risco de rejeição do enxerto corneano. Deve-se sempre considerar o risco de ocorrência de ceratomalácia aguda após cirurgias de catarata sem complicações em olhos apresentando distúrbios da superfície ocular.

Descritores: Perfuração da córnea; Radiação; Artrite reumatoide; Extracão de catarata

INTRODUCTION

Cataract is a major health problem in people aged >50 worldwide, and thus, cataract surgery is the most frequent surgical procedure performed nowadays. Advances in surgical techniques and instrumentation have greatly limited the occurrence of postoperative complications[(1)].

Corneal melting is an unusual complication of phacoemulsification. Several predisposing risk factors have

Submitted for publication: December 9, 2019
Accepted for publication: March 27, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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Informed consent was obtained from all patients included in this study.

been associated with this complication, such as dry eye disease, rheumatoid arthritis, topical nonsteroidal anti-inflammatory drugs (NSAIDs), and corneal infections[2-5].

Orbital and periocular radiation has been reported to have a major effect on tear film stability and ocular surface, inducing decreased corneal sensitivity, dry eye problems, and neurotrophic keratopathy[6,7].

Rheumatoid arthritis and other collagen vascular diseases have been known to affect the cornea. Although peripheral corneal ulceration is the most common corneal manifestation of rheumatoid arthritis, central and paracentral corneal ulceration and perforation may also occur[8]. These ulcers often appear with quiescent systemic arthritis[9].

Lastly, corneal melting is the most serious side effect of topical NSAIDs. Although several controversial studies have been reported through the years, NSAIDs-induced corneal melting has been reported by several researchers[4].

To our best knowledge, this is the first case report describing an acute corneal melting after phacoemulsification as a first symptom of an otherwise quiescent, undiagnosed rheumatoid arthritis in a patient with eyelid radiation history.

CASE REPORT

An 86-year-old woman was referred to our clinic due to a progressively blurring vision in her left eye. She had a history of two courses of External Beam Radiotherapy (EBRT) in her left eyelid and cheek for the treatment of basal cell carcinoma. The first treatment was performed 13 years ago and the second one was performed 3 years before the cataract surgery. Besides that, her past medical history was unremarkable.

The anterior segment examination revealed lid margin irregularity, vascular engorgement, few plugged meibomian gland orifices, and mucotaneous junction displacement in her left lower eyelid. Otherwise, it was unremarkable, showing the presence of moderate nuclear sclerosis in her left eye and no signs of dry eyes. Her best-corrected visual acuity (BCVA) was 6/15. The remaining clinical examination, including dilated fundoscopy and IOP (Intraocular Pressure) measuring, revealed no other pathologies in her both eyes.

After obtaining an informed consent, she underwent uncomplicated cataract extraction with posterior chamber IOL (Intraocular Lens) implantation in her left eye. Postoperatively, the treatment regimen included administration of 0.5% chloramphenicol/0.1% dexamethasone eye drops four times daily and 0.9 mg/ml Bromfenac twice daily. The postoperative use of NSAIDs is a common clinical practice in our clinic due to its confirmed ability to reduce the risk of Irvine-Gass syndrome[10].

One week later, she presented with a painless, paracentral area of sterile corneal melting of 4 mm in diameter and a central perforation area of 3 mm in diameter. (Figure 1) The melting was non-infiltrated and far from the incision site. She had a flat anterior chamber with a positive Seidel test, and her BCVA was hand movement.

She was immediately admitted and treated with levofloxacin 0.5% eye drops (q1h) and intravenous cefuroxime. Intravenous was preferred over intravitreal administration because there was no sign of acute endophthalmitis and it was crucial to prevent inoculation of microorganisms occurring from contiguous ocular structures inside the eye. In this way, superimposed bacterial infection and possible underlying systemic infection were also excluded. Microbiological examinations were not performed because signs of infection were not observed. Blood tests were requested, including erythrocyte sedimentation rate, complete blood count with differential, rheumatoid factor, antinuclear antibody, antineutrophilic cytoplasmic antibody levels, angiotensin-converting enzyme, and chest x-ray. Based on these test results, rheumatoid factor and antinuclear antibodies have been identified, and mild increase in ESR (Erythrocyte Sedimentation Rate) and mild thrombocytosis were observed. Afterward, the patient was diagnosed with rheumatoid arthritis by our rheumatologists in accordance with the 2010 American College of Rheumatology (ACR)/European League Against Rheumatism classification criteria, which she controlled with 2.5 mg of methotrexate (three tabs two times per week) and 5 mg of prednisolone (two tabs per day). They opted not to use intravenous steroids because of her quiescent arthritis.

Due to the urgency of the incidence, we decided to cover the perforation area with Gundersen's conjunctival flap due to the absence of limbal vasculitis, low visual expectancies, and her unwillingness to undergo keratoplasty. One day postoperatively, the anterior chamber was formed, Seidel test was negative, and no signs of infection or corneal melting were observed. Six months later, the integrity of her anterior chamber has been achieved and no recurrences occurred, whereas her BCVA was 6/60 (Figure 2).

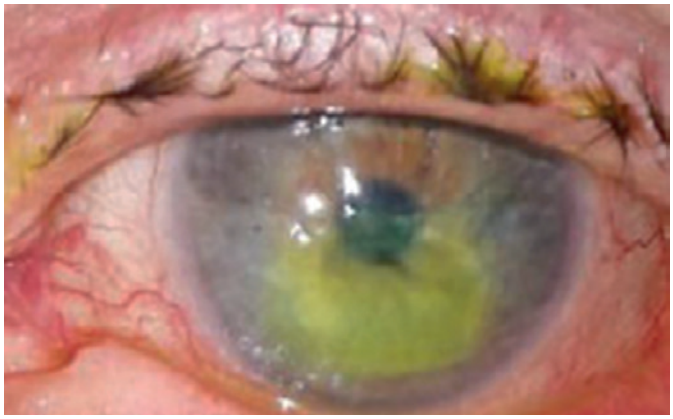

Figure 1. Acute corneal melting.

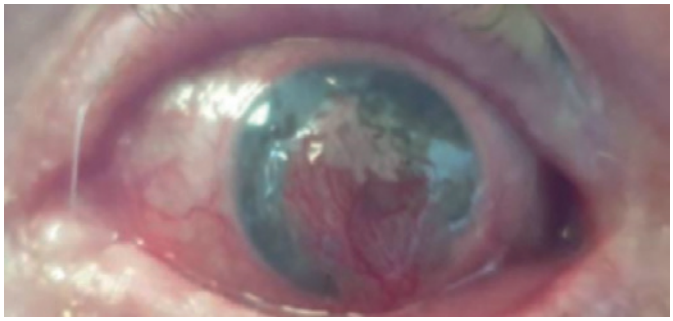

Figure 2. Six months postoperatively.

DISCUSSION

In this report, we describe the case of a patient presenting with an acute corneal melting and perforation, one week after an uneventful phacoemulsification. In our patient, we believe that the urgent progress from corneal melting to perforation was multifactorial: exacerbation of an undiagnosed post-radiation tear film dysfunction, undiagnosed rheumatoid arthritis, and NSAID treatment.

Periocular and orbital radiations have been associated with tear film instability. Radiation greatly affects the meibomian gland functionality[7] and induces morphological and functional loss of lacrimal glands[6]. Moreover, experimental studies have introduced the term radiation keratopathy as a result of corneal nerve loss and increased influx of immune cells (CD45+) in the cornea,[11] engendering tear film dysfunction due to reduced reflex tearing and corneal sensitivity. This disruption of the sensory pathway can also induce neurotrophic keratitis[12]. Lastly, studies have shown that a preexisting mild tear film instability can exacerbate postoperatively[13] and induce corneal melting[5]. In addition, studies have shown that approximately 50% of patients with tear film dysfunction are asymptomatic during preoperative clinical examination[14].

Rheumatoid arthritis can dramatically affect a human's cornea in two different ways: peripheral ulcerative keratitis (PUK) and central/paracentral keratolysis. PUK occurs due to local imbalance between the collagenase MMP-1 concentration and its inhibitor, TIMP-1[15], as a result of an immune microangiopathy and inflammatory mediator leakage that is present in the limbus. An aberrant cell-mediated response to epithelial damage, secondary to an irregular expression of HLA-II antigens in the corneal epithelium, has also been proposed[16]. The absence of limbal vasculitis distinguishes paracentral keratolysis from PUK. Apart from the irregular HLA-II antigen expression, IgG and IgM accumulation occurred in the corneal epithelium and T-cell infiltrating the stroma. The main associated molecules are CD-11c and CD3. Moreover, an antibody has been found to react against myeloperoxidase of polymorphonuclear white blood cells. The mechanism of inflammation is an epithelial barrier dysfunction that allows immune complexes entering the stroma and provoking keratolysis[8,9,16].

Finally, recent studies have shown a correlation between NSAIDs and corneal ulceration[4]. Different mechanisms have also been proposed, including metalloproteinase activation, impaired wound healing, and altered neurotrophic effect due to analgesia[17]. Although nepafenac and ketorolac have been primarily associated with sterile ulceration, other reports also demonstrated Bromfenac having the same effect[18].

Concerning the treatment of our patient, Gundersen's conjunctival flap was the golden section of ensuring globe's integrity and reluctance to undergo keratoplasty with guarded prognosis[16]. The absence of limbal and conjunctival vasculitis excluded conjunctival resection from our options, because it has been confirmed to have no therapeutic effect[8]. Finally, the perforation size made the use of cyanoacrylate glue impossible.

To our best knowledge, no other cases have been reported on sterile corneal perforation after a cataract surgery in a periocularly irradiated patient as the first symptom of a previously undiagnosed rheumatoid arthritis. Therefore, we believe that ocular surface disorders caused by a previous radiation, undiagnosed rheumatoid arthritis, and use of NSAIDs were predisposing factors associated with this complication. This case report increases the awareness on this sight-threatening com-

plication following a cataract surgery. Thorough clinical examination and systemic investigation should be performed in patients who are highly clinically suspected.

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Arquivos Brasileiros de
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REVIEW ARTICLE

Probing for congenital nasolacrimal duct obstruction: a systematic review and meta-analysis of randomized clinical trials

Sondagem no tratamento da obstrução lacrimonasal congênita: revisão sistemática de ensaios clínicos randomizados e metanálise

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ABSTRACT | Purpose: Lacrimal probing is the treatment of choice for congenital nasolacrimal duct obstruction that does not have a spontaneous resolution; however, there is no consensus about the best time for probing and if it is superior to other therapies. The present study aimed to evaluate the effectiveness of lacrimal probing compared with other treatments/no intervention to treat congenital nasolacrimal duct obstruction. **Methods:** A systematic review of literature in PubMed, EMBASE, CENTRAL, clinicaltrials.gov, and LILACS databases up to December 2019 was performed. Randomized clinical trials that enrolled children diagnosed with congenital nasolacrimal duct obstruction and undergoing lacrimal probing were considered. Data extraction and a risk of bias assessment were conducted independently and in duplicate. The overall quality of evidence for each outcome was conducted using the Grading of Recommendations, Assessment, Development, and Evaluation classification system. **Results:** Four randomized clinical trials involving 423 participants were eligible. No statistically significant differences were observed in resolution rates between early probing and observation/late probing (two studies; risk ratio 1.00 [95% confidence interval 0.76-1.33]; p=0.99; low certainty evidence). One study reported better resolution rates with bicanalicular silicone stent intubation compared with late probing in the complex congenital nasolacrimal duct obstruction cases subgroup (risk ratio 0.56 [95% confidence interval 0.34-0.92]; p=0.02; moderate certainty evidence). **Conclusions**: Low certainty evidence suggests that early probing has the same success rate as late probing. Evidence of moderate certainty suggests that late probing has a lower success rate than bicanalicular silastic intubation in patients with complex congenital nasolacrimal duct obstructione.

Keywords: Lacrimal duct obstruction/congenital; Lacrimal duct obstruction/therapy; Infant

RESUMO | Objetivo: A sondagem lacrimal tem sido o tratamento de escolha para a obstrução lacrimonasal congênita que não apresenta resolução espontânea. Contudo, não há consenso sobre qual é a melhor época para a realização da sondagem e se ela é melhor do que outras terapias. O objetivo foi avaliar a efetividade da sondagem lacrimal no tratamento da obstrução lacrimonasal congênita**. Método**: Uma revisão sistemática da literatura foi realizada usando as plataformas eletrônicas PubMed, EMBASE, CENTRAL, clinicaltrials.gov e LILACS até o período de dezembro de 2019. Foram considerados ensaios clínicos randomizados envolvendo crianças com obstrução lacrimonasal congênita submetidas a sondagem lacrimal. A extração dos dados e avaliação do risco de viés foram feitas por dois autores independentemente. A análise da qualidade da evidência para cada desfecho foi realizada por meio do sistema GRADE (*Grading of Recommendations Assessment, Development and Evaluation*). **Resultados:** Quatro ensaios clínicos randomizados foram incluídos, envolvendo 423 participantes. A metanálise mostrou que não houve diferença estatística na resolução da obstrução lacrimonasal congênita entre o grupo submetido à sondagem lacrimal precoce e o submetido à observação/sondagem tardia (2 estudos; risco médio 1.00 [intervalo de confiança de 95% 0.76, 1.33] p=0,99, I2=79%, baixa certeza de evidência). Um estudo evidenciou

Submitted for publication: September 10, 2019
Accepted for publication: February 3, 2020

Funding: This study received no specific financial support.

Disclosure of potential conflicts of interest: None of the authors have any potential conflicts of interest to disclose.

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melhores resultados da intubação bicanalicular com silicone em comparação a sondagem tardia no subgrupo das obstruções lacrimonasais congênitas complexas, (1 estudo; risco médio 0.56 [intervalo de confiança de 95% 0.34, 0.92] p=0,02, moderada certeza de evidência). **Conclusões**: Há evidências de baixa qualidade de que a sondagem precoce tem a mesma taxa de sucesso que a sondagem tardia. Evidências de moderada certeza sugerem que a sondagem tardia tem menor chance de sucesso do que a intubação bicanalicular com silicone em casos de obstruções lacrimonasais congênitas complexas.

Descritores: Obstrução dos ductos lacrimais/congênito; Obstrução dos ductos lacrimais/terapia; Lactente

INTRODUCTION

Nasolacrimal duct obstruction (NLDO) is widespread in the pediatric population, occurring in up to 20% of newborns[1]. NLDO is usually congenital in origin and occurs due to a failure of canalization in the nasolacrimal duct[2]. The main symptoms of NLDO include epiphora, lash crusting, and reflux of mucopurulent discharge upon compression of the lacrimal sac[3].

The natural history of NLDO is favorable, with resolution in most cases during the first year of life either spontaneously or after conservative treatment such as lacrimal sac massage[4-6]. When NLDO persists, lacrimal probing is the treatment of choice because it is relatively easy to perform[7,8].

However, controversy exists with respect to the best time to probe. The decision to probe early (<12 months of age) versus late (>12 months) is usually based on the surgeon's clinical judgment and experience. Some studies have reported a higher failure rate with late probing compared with early probing[9-11]. Studies have also reported a decrease in the success rate of lacrimal probing with an increase in the age of the child[9-11]. In complex cases, probing may be less effective than other more expensive therapies, such as lacrimal system intubation[12].

A previous systematic review compared the success rates and complications of various types of NLDO treatment. However, this review included randomized controlled trials (RCTs) and non-randomized prospective studies, and did not use the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification system to evaluate the quality and certainty of the evidence[13]. A recently published Cochrane review, which included only two RCTs, concluded that the effect and cost of immediate versus deferred probing for NLDO remain uncertain for most outcomes[14].

Therefore, we performed an updated systematic review of the literature to assess the effectiveness of probing compared with clinical observations or other treatments to treat congenital NLDO.

METHODS

The methods used to perform this review were guided by the Cochrane Handbook for Intervention Reviews[15]. This systematic review was conducted by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement[16].

Eligibility criteria

RCTs and quasi-randomized studies that enrolled children up to 10 years old with congenital NLDO, irrespective of gender and etiology, were included. Interventions included office-based probing or hospital-based probing under general anesthesia. Studies included a control group that did not undergo probing (or in whom probing was deferred) or other interventions, including observation alone, antibiotic drops alone, antibiotic drops plus massage of the lacrimal sac (Crigler massage or emptying massage), canalicular intubation, dacryocystorhinostomy, endoscopic endonasal dacryocystorhinostomy, the association of two or more therapies, or no intervention.

The outcome measures included a primary outcome to report probing success, which was defined as the absence of clinical signs and symptoms of congenital NLDO. The secondary outcomes included the best time to perform lacrimal probing (early probing if patients were <12 months of age and late probing if patients were >12 months of age); the proportion of participants with anatomic and functional injuries due to probing (creation of a false passage and injury to the nasolacrimal duct, canaliculi, and puncta); quality of life; and cost (assessed narratively) of the intervention.

Animal studies, case series, cohort studies, case reports, and review articles were excluded from this review.

Data source and searches

The following electronic databases were searched for relevant articles: the Cochrane Database of Clinical Trials (CENTRAL; 2019, issue 12); PubMed (1966 to December 2019); EMBASE (1980 to December 2019); the Latin American & Caribbean Health Sciences Literature (LILACS; 1982 to December 2019), and clinicaltrials.gov. Using Medical Subject Headings terms and free terms related to "congenital nasolacrimal duct obstruction,"

"probing," and "treatment," the search strategy was replicated for CENTRAL, PubMed, EMBASE, LILACS, and clinicaltrials.gov (Appendix 1). There were no language or publication year restrictions. The search strategy was adapted for each database.

Study selection and data extraction

The titles and abstracts were reviewed by two researchers to identify potentially relevant papers. The papers were obtained and independently read by two reviewers. If necessary, differences were resolved by consulting a third reviewer. Reasons for exclusion were identified. The data was also extracted independently by two reviewers based on a priori inclusion and exclusion criteria.

The following information was extracted: references (authors, setting, year of publication, study design, allocation generation, allocation concealment, blinding); patients (age, sex, number); intervention (type and time); follow-up period; and outcomes (measures of results and adverse effects).

Risk of bias assessment

Two reviewers independently assessed the risk of bias in the RCTs using a modified version of the Cochrane Collaboration's tool[15], which includes nine domains: adequacy of sequence generation, allocation sequence concealment, blinding of participants and caregivers, blinding of data collectors, blinding for outcome assessment, blinding of data analysts, incomplete outcome data, selective outcome reporting, and the presence of other potential sources of bias not accounted for in the previously cited domains. When information was unavailable on the risk of bias or other aspects of the methods or results, the reviewers attempted to contact study authors for additional information.

Certainty of evidence

The reviewers used the GRADE classification system for the certainty of evidence[17]. Each outcome was rated as either high, moderate, low, or very low. Detailed GRADE guidance was used to evaluate the overall risk of bias, imprecision, inconsistency, indirectness, and publication bias. The results were summarized in an evidence profile. If an outcome was subject to one or more of these factors, the reviewers downgraded the quality of the evidence from high to moderate, low, or very low depending on the number of reasons identified[18,19].

Appendix 1. Search strategy

[(nasolacrimal duct) or (nasolacrimal ducts) or (lacrimal duct Obstruction) or (lacrimal duct Obstructions) or (congenital nasolacrimal duct obstruction) or (congenital nasolacrimal ducts obstruction) and (probing) or(office probing) and (treatment) or (therapy)].

Data synthesis and statistical analysis

All outcomes were analyzed using dichotomous variables and pooled Mantel-Haenzel risk ratios (RRs) and associated 95% confidence intervals (CIs) using the random-effects models. The analyses were based on eligible patients who had reported outcomes in each study. Review Manager 5.3.5 software[20] was used for all analyses.

If the results of the principal analysis reached statistical significance, the reviewers planned to conduct sensitivity analyses to test RCTs with a low risk of bias versus a high risk of bias, and withdrawal rates for each outcome were evaluated (i.e., <20% versus ≥20%).

Variability in the results was addressed using the I^2 statistic and the p-value obtained from the chi-squared test for heterogeneity. Heterogeneity was considered when I^2 >75%[15]. We performed a subgroup analysis according to the complexity of NLDO (simple vs. complex)[12].

RESULTS

Study selection

Figure 1 presents the process of identifying eligible studies. A total of 550 citations were identified after duplicates were removed. Based on screening of the title and abstract, 98 full texts were assessed, four of which were RCTs involving 423 participants (Al-Faky 2015, Lee 2013, Young 1996 e PEDIG 2012)[12,21-23].

Study characteristics

Table 1 describes the study characteristics such as design; country; the period of study and length of follow-up; number of participants; age; gender; inclusion and exclusion criteria; intervention; and outcomes. Two studies were conducted in the USA[21,23], one in Saudi Arabia[12], and one in the United Kingdom[22]. One study was a single-center study[12] and the other three studies were multicenter studies[21-23] This review includes 510 nasolacrimal ducts from 423 participants. The sample sizes of the RCTs ranged from 22[22] to 181[12] participants. Typical participants were infants aged from six months of life to 90 months. The follow-up period of the studies ranged from six months[12] to two years[22].

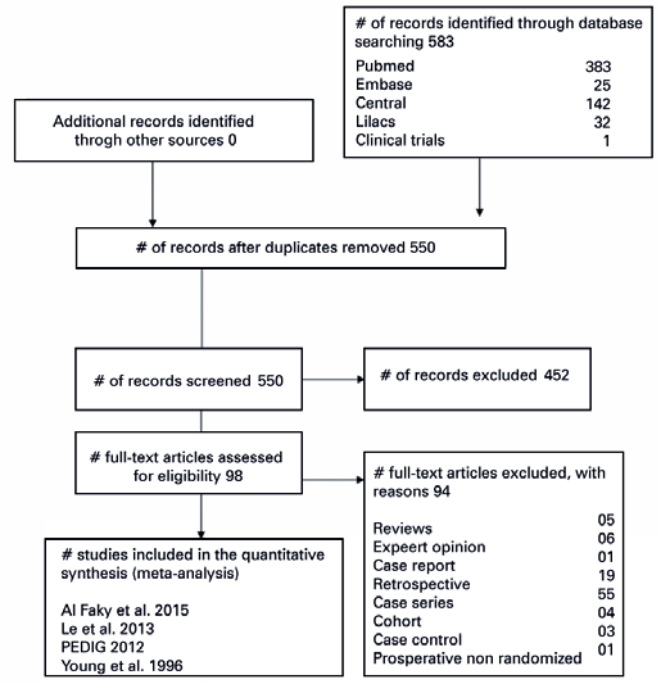

Figure 1. Review flowchart.

Risk of bias in the included studies

The risk of bias in the four individual studies included in the review and judgments is presented in figure 2. The major issue in relation to the risk of bias was due to lack of information about allocation concealment and blinding of participants and personnel[12,21-23].

Outcomes

Results from two RCTs[21,23] suggested no statistical difference between early probing compared with observation/late probing in the congenital NLDO resolution rate (RR 1.00 [CI 95% 0.76-1.33]; p=0.99; I^2=79%) (Figure 3). Concerning the resolution rate of congenital NLDO between late probing and bicanalicular silastic intubation, according to the complexity of obstruction (Figure 4), results from one RCT in the subgroup of interest suggested a statistical difference, which favored the bicanalicular silastic intubation in complex congenital NLDO.

Table 1. Characteristics of included studies.

	Al-Faky 2015[12]	Lee 2013[12]	PEDIG 2012[23]	Young 1996[22]
Methods	**Design**: RCT [a] **Country**: Saudi Arabia (1 center) **Period:** Aug 2006 to Apr 2013 **Follow-up:** 6 months	**Design**: RCT [a] **Country**: United States (22 centers) **Period:** Nov 2008 to Sep 2010 **Follow-up:** Up to 18 months old	**Design**: RCT [a] **Country**: USA (22 centers) **Period:** Nov 2008 to Sep 2010 **Follow-up:** Until age 18 months	**Design**: RCT [a] **Country**: United Kingdom (7 centers) **Follow-up:** Not reported
Participants	**Total:** 207 eyes (181 infants) **Age:** Probing group mean age: 27.4 ± 14.6 months; bicanalicular silastic intubation group mean age: 30.7 ± 15.5 months **Sex**: 49.7% girls; 50.3% boys	**Total:** 114 eyes (57 infants) **Age:** from 6 to 10 months old (mean age 7.7 months) **Sex:** 42% girls and 58% boys	**Total:** 163 eyes (163 infants) **Age:** from 6 to 10 months old (mean age 7.7 months) **Sex:** 45.4% girls and 54.6% boys	**Total:** 26 eyes (22 infants) **Age:** Not reported, but infants were all "approaching or just after their first birthday" **Sex:** Not reported
Inclusion criteria	Children aged ≥1 year with epiphora and/or discharge before 6 months of age in absence of upper respiratory infection or ocular surface irritation. Enrolment for surgical treatment for the first time to treat NLDO was mandatory.	Children from 6 to 10 months old with bilateral NLDO (presence of epiphora, increased tear lake, and/or mucous discharge in both eyes); onset of symptoms before 6 months of age.	Onset of symptoms before 6 months of age; presence of at least one clinical sign of NLDO in the absence of an upper respiratory infection or ocular surface irritation; no prior nasolacrimal duct surgery.	Presenting within the time limits with no medical contraindication; NLDO with a history of epiphora and/or discharge starting within 3 months of birth and an abnormal FDDT.
Exclusion criteria	Punctual disease; previous surgical intervention or acute dacryocystitis; eyelid malposition; Down syndrome; craniofacial anomaly; bony NLDO.	Patients with prior NLD surgery; Down syndrome; or craniofacial anomalies.	Children with Down syndrome or craniofacial anomalies.	History of previous lacrimal procedures.
Intervention	Probing after 1 year of age (88 patients) versus bicanalicular silastic intubation (93 patients).	Bilateral office-based NLD probing within two weeks of study entry (31 patients) versus 6 months of observation followed by probing for unresolved cases (26 patients).	Immediate office-based NLD probing (82 patients) versus 6 months of observation (81 patients) followed by for persistent symptoms.	Probing at 12 to 14 months of age (10 NLD) versus no treatment until 24 months (16 NLDs).
Outcomes	Resolution of all preoperative manifestations; normal FDDT; and positive Jones primary dye test.	Absence of clinical signs and symptoms of NLDO.	Absence of clinical signs and symptoms of NLDO.	Complete or near complete remission of symptoms and signs and a normal FDDT.

RCT= randomized clinical trials; NLDO= nasolacrimal duct obstruction; NLD= nasolacrimal duct; FDDT= fluorescein disappearance dye test.

Intervention effects

Tables 2 and 3 contain the results of the GRADE classification of the certainty of evidence.

DISCUSSION

Main findings

The present review was performed to address the divergence of opinion on the treatment of congenital NLDO, especially the need for early probing in children. The study indicates that the primary outcomes (treatment success; resolution rate) did not differ between early and late probing when performed before 16 months of age. Therefore, the success rate of probing does not decrease when the procedure is performed up to 16 months of age.

Many authors advocate clinical observation as the best option for congenital NLDO since 70% to 90% of obstructions may resolve spontaneously with conservative treatment using lacrimal sac massage in the first year of life[23-27]. Probing should be reserved for non-regression cases because it is a simple, safe, and effective procedure. Other studies suggest early probing to reduce symptoms and mitigate the risk of major complications of congenital NLDO, such as chronic inflammation, fibrosis, and infection, which worsen disease prognosis[28-30].

The absence of differences between interventions (early probing vs. clinical observation/late probing) demonstrated in this meta-analysis is important to guide the surgeon's decision about the best treatment logistics, improving clinical care for patients with congenital NLDO. Also, it allows the consideration of other factors related to lacrimal probing, such as the risks involved in general anesthesia (necessary for older children) and the cost of the procedure.

Regarding the cost-effectiveness of late probing to treat congenital NLDO, the PEDIG study[23] reported a 20% increase in the final cost, including the expenses of an initial office consultation and all medications prescribed and surgeries received. According to the authors of this study, although unilateral congenital NLDO often resolves without surgery, immediate office probing is an effective and potentially cost-saving treatment option[23].

Interesting evidence for clinical practice, which should be confirmed by new studies, suggests the superiority of bicanalicular silastic intubation over late probing for complex obstructions[12]. Intubation is a complex and expensive procedure, which mostly requires general anesthesia and insertion of a stent device. Conversely, probing is simple, quick, and inexpensive. However, with complex congenital NLDO, there is greater difficulty in recanalization of the lacrimal pathway, justifying the cost of intubation and anesthetic risk.

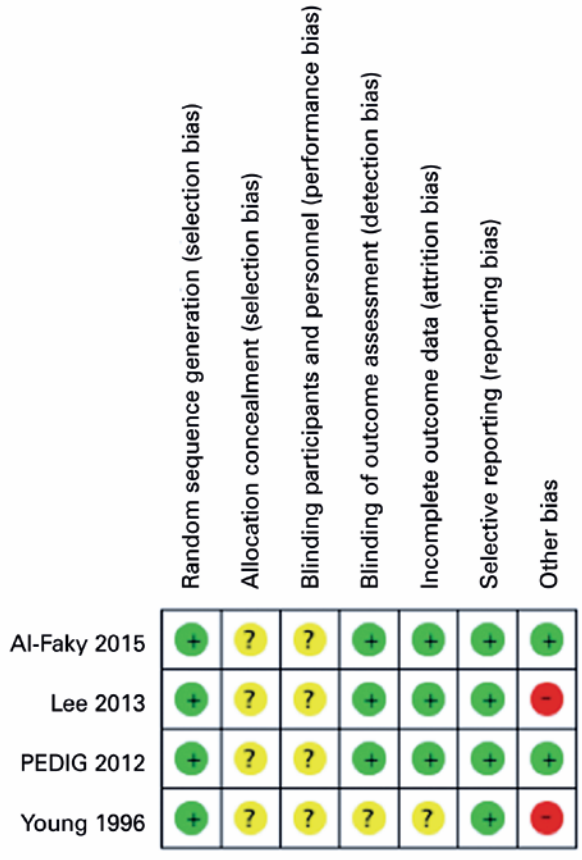

Figure 2. Risk of bias summary. Review authors' judgments about each risk of bias item for each study included in the meta-analysis.

Relation to prior work

Two systematic reviews[13,14], which are relevant to our study objectives, have been published in recent years. Lin et al.[13] included seven studies, four RCTs, and three prospective non-randomized studies. They compared the success rates and complications of various types of congenital NLDO treatment besides probing, and concluded that success rates did not differ between immediate and deferred probing; between balloon dilation and intubation; and between monocanalicular and bicanalicular intubation. However, a review by Lin et al.[13] presented limitations related to the inclusion of non-randomized prospective studies, which lower the quality and relevance of the results. It is well known that non-randomized studies are prone to confusion because

interventions are often prescribed to patients based on the perceived risk of the outcomes rather than being randomly assigned, as in RCTs[31,32]. Also, Lin et al.[13] did not use the GRADE system to assess the quality and strength of evidence.

Another review published by the Cochrane Collaboration[14] included two RCTs but used the GRADE system to qualitatively evaluate one study and did not perform a meta-analysis. It concluded that there is no clear difference between immediate probing and obser-

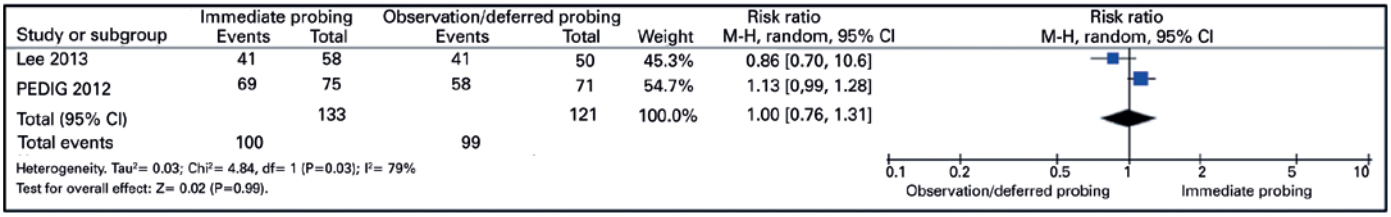

Figure 3. Meta-analysis. Resolution rate of congenital nasolacrimal duct obstruction: early probing vs. observation/ late probing according to the number of nasolacrimal ducts. CI, confidence interval; p< 0.05 was considered statistically significant.

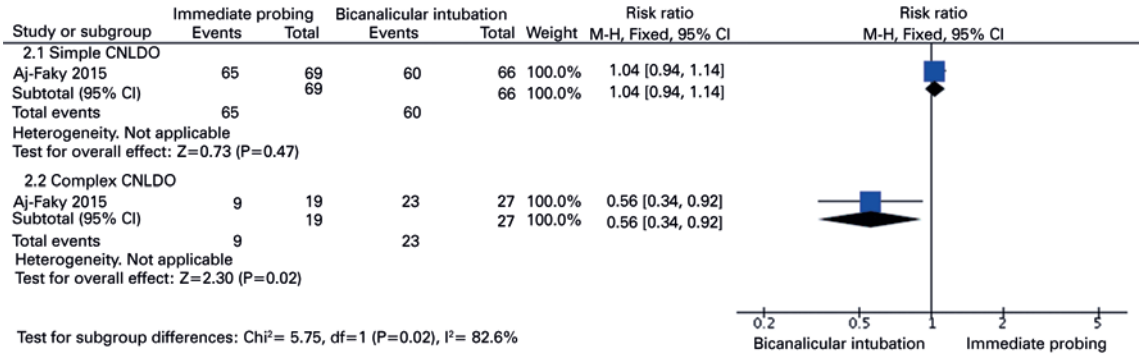

Figure 4. Resolution rate of congenital nasolacrimal duct obstruction. Late probing vs. bicanalicular silastic intubation according to the complexity of nasolacrimal duct obstruction.

Table 2. Summary of findings for the comparison of early probing vs. observation/late probing for congenital nasolacrimal duct obstruction.

Early probing compared with observation/late probing for congenital nasolacrimal duct obstruction

Patient or population: children with congenital nasolacrimal duct obstruction (CNLDO)
Context: community-based population in the USA
Intervention: early probing
Comparison: observation/late probing if needed

Outcomes	Anticipated absolute effects (95% CI)		Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with observation/ late probing	Risk with early probing				
Resolution of CNLDO according to NLDs (follow-up: 9 to 12 months)	**818 per 1,000**	**818 per 1,000** (622 to 1000)	**RR 1.00** (0.76 to 1.31)	254 (2 RCTs)	⊕⊕⊖⊖ **Low** [+,++]	Risk estimates based on PEDIG, 2012[23] study (largest trial).

*The basis for the assumed risk is the mean control group risk. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI= confidence interval; RR= risk ratio; CNLDO= congenital nasolacrimal duct obstruction; OR= Odds ratio; NLD= nasolacrimal duct; RCT= randomized clinical trial.

GRADE working group grades of evidence.
High certainty: Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[+] Downgrade for imprecision because CI 95% for absolute effects inclsuded clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.
[++] Downgrade of inconsistency because I^2 = 79%.

vation alone for the resolution of congenital NLDO, and that immediate probing may be more beneficial than late probing for unilateral obstruction.

Thus, the results of this review overlap with those of the previous two reviews; however, our findings provide a higher level of evidence, as they are based on a meta-analysis of RCTs.

Strengths and limitations

The present review has numerous strengths, including an extensive and sensitive search of the literature with no restrictions on language or publication status. The analysis of risk factors for bias in the included studies, which followed strict Cochrane Collaboration assessment standards, indicated a low risk of bias and good methodological quality. The only exception was in the study by Young et al.[22], which presented an uncertain risk of bias.

In addition to the methodological evaluation, the present review utilized the GRADE system, which has been used by several international institutions to classify the strength of the recommendation of health evidence. Among these institutions are the World Health Organization, the National Institute for Health and Care Excellence (NICE), the Centers for Disease Control and Prevention (CDC), and the Cochrane Collaboration.

A limitation of this review was the small number of studies included and the high heterogeneity observed in the meta-analysis (79%). The small sample size, surgeons' different levels of experience, and individual patient characteristics may have contributed to heterogeneity. However, as studies by Lee et al.[21] and PEDIG[23] were based on the same protocol and were therefore methodologically similar, heterogeneity can be considered inexplicable. These findings reinforce the need for additional homogeneous studies.

The certainty of evidence of the primary outcome, resolution rate of congenital NLDO, was low; therefore, future research will likely have a significant impact on confidence when estimating the effect of the intervention. The outcomes of the research are likely to alter the estimate[18]. This rate was due to serious imprecision (small sample size and wide CIs) and inconsistency (unexplained heterogeneity). In the secondary outcomes (resolution rate of congenital NLDO in complex obstructions), the certainty of evidence was classified as moderate due to imprecision (restricted sample size and wide CIs).

The evaluation of GRADE in this review revealed that the strength of recommendation of the evidence on the effectiveness of probing in congenital NLDO must improve, and new studies with greater standardization and larger sample sizes are required to draw definitive conclusions.

In the treatment of congenital NLDO, early probing performed from six months of age until ten months of age results in an equivalent chance of therapeutic success when compared with late probing performed between 12

Table 3. Summary of findings for the comparison late probing vs. bicanalicular silastic intubation for congenital nasolacrimal duct obstruction

Late probing compared with bicanalicular silastic intubation for CNLDO.

Patient or population: children with congenital nasolacrimal duct obstruction (CNLDO)
Context: community-based population in the Saudi Arabia
Intervention: late probing
Comparison: bicanalicular silastic intubation

	Anticipated absolute effects (95% CI)					
Outcome	Risk with bicanalicular silastic intubation	Risk with late probing	Relative effect (95% CI)	Nº of participants (studies)	Certainty of the evidence (GRADE)	Comments
Resolution of CNLDO according to complexity						
1) Simple CNLDO	**909 per 1,000**	**945 per 1000** (855 to 1000)	**RR 1.0** (0.94 to 1.14)	135 (1 RCT)	⊕⊕⊕⊖ **Moderate**[+]	Risk estimates based on Al-Faky et al. 2015.[12]
2) Complex CNLDO (follow-up: 6 months)	**852 per 1,000**	**477 per 1000** (290 to 784)	**RR 0.56** (0.34 to 0.92)	46 (1 RCT)		

*The basis for the **assumed risk** is the mean control group risk. The **corresponding risk** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI= confidence interval; RR= risk ratio; CNLDO= congenital nasolacrimal duct obstruction; OR= Odds ratio; NLD= nasolacrimal duct; RCT= randomized clinical trial

GRADE working group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of the effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[+] Downgrade for imprecision because CI 95% for absolute effects included clinically important benefit and no benefit. In addition, the sample size was small and did not reach CI 95%.

months and 16 months of age (low certainty of evidence). There is evidence that late probing has a lower chance of success compared with bicanalicular silastic intubation for complex congenital NLDO (moderate certainty of evidence).

Implications for clinical practice

Due to the evidence found in this review, specialists can wait for a spontaneous resolution of congenital NLDO or proceed to probing without risk of worsening the prognosis due to therapeutic choice. This decision will depend on the experience of each ophthalmologist and should be discussed with parents/guardians to ensure optimal treatment in each case. Additionally, it is important to consider the risks inherent in the procedures and the costs involved.

Implications for the research

Further RCTs with methodological quality, standardized endpoints, and larger sample sizes are needed to confirm the effectiveness of probing in congenital NLDO and to reinforce the strength of the evidence in the literature to provide robust outcome estimates. Further research is needed to provide a better understanding of the role of probing in the treatment of congenital NLDO.

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INSTRUCTIONS TO AUTHORS

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The sections should be presented according to the following sequence: Title page (as a separate document); Abstract and Keywords; Introduction; Methods; Results; Discussion; Acknowledgements (if any); References; Tables (optional) and Figures (optional) including legends.

1. Title Page. It should contain: a) title (no more than 135 characters with spaces); b) running title to be used as a page heading (no more than 60 characters with spaces); c) authors' names as they should appear in print; d)each author's affiliation* (city, state, country and, if applicable, department, school, university); e) corresponding author's name, address, phone number, and email; f) sources of financial support (if any); g) project number and institution responsible for the approval of the Research Ethics Committee; h) statement of conflicts of interests of all authors; I) clinical trial registration number on a public trials registry.

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Approval of the Institutional Review Board (IRB). All retrospective, cross-sectional, or prospective studies involving primary data collection or clinical and surgical reports should include the project number and name of the institution that provided the approval of the IRB on the title page. Studies involving humans should be compliant with the Declaration of Helsinki, whereas studies involving animals should be in accordance with the principles suggested by the Association for Research in Vision and Ophthalmology (ARVO).

As a supplementary document, the corresponding author should send the IRB approval or its report stating that the evaluation of the project by the Committee is not necessary. The author cannot decide on the need for evaluation by the Research Ethics Committee.

Letter of approval by the Human or Animal Research Ethics Committee of the organization where the study was carried out. Studies done in Brazil must inform the number of the CAAE - Certificate of Presentation for Ethical Consideration (www.plataformabrasil.saude.gov.br/login.jsf)

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ANZCTR (Australian New Zealand Clinical Trials Registry)
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ARVO (The Association for Research in Vision and Ophthalmology). Ethics and regulations in human research committee
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ReBEC (Registro Brasileiro de Ensaios Clínicos)
http://www.ensaiosclinicos.gov.br/

STARD (STAndards for the Reporting of Diagnostic Accuracy Studies)
http://www.stard-statement.org/

STROBE (Strengthening the Reporting of Observational studies in Epidemiology)
http://www.strobe-statement.org/

U.S. National Institutes of Health. Clinical Trials
http://www.clinicaltrials.gov

UMIN CTR (University Hospital Medical Information Network . Clinical Trials Registry)
https://www.umin.ac.jp/ctr/

World Association of Medical Editors.
Conflict of interest in peer-reviewed medical journals
http://wame.org/wame-editorial-on-conflict-of-interest

World Association of Medical Editors.
Declaration of Helsinki; medical research involving human subjects.
https://www.wma.net/what-we-do/medical-ethics/declaration-of-helsinki/

24 HORAS PELO DIABETES

CONSELHO BRASILEIRO DE OFTALMOLOGIA

UMA AÇÃO

QUE MARCOU A HISTÓRIA DO COMBATE AO DIABETES NO BRASIL

O 24h pelo Diabetes mobilizou profissionais de diversas áreas, entidades de saúde e um **time fantástico de voluntários médicos.**

A campanha se consolidou no dia 21 de novembro com uma grande transmissão ao vivo nas mídias digitais, envolvendo entrevistas com especialistas, depoimentos de pacientes, reportagens especiais e grandes debates.

Tudo isso com um único enfoque:
a conscientização sobre como combater o diabetes.

E todo esse conteúdo continua disponível para você ver, rever e compartilhar:

CBO

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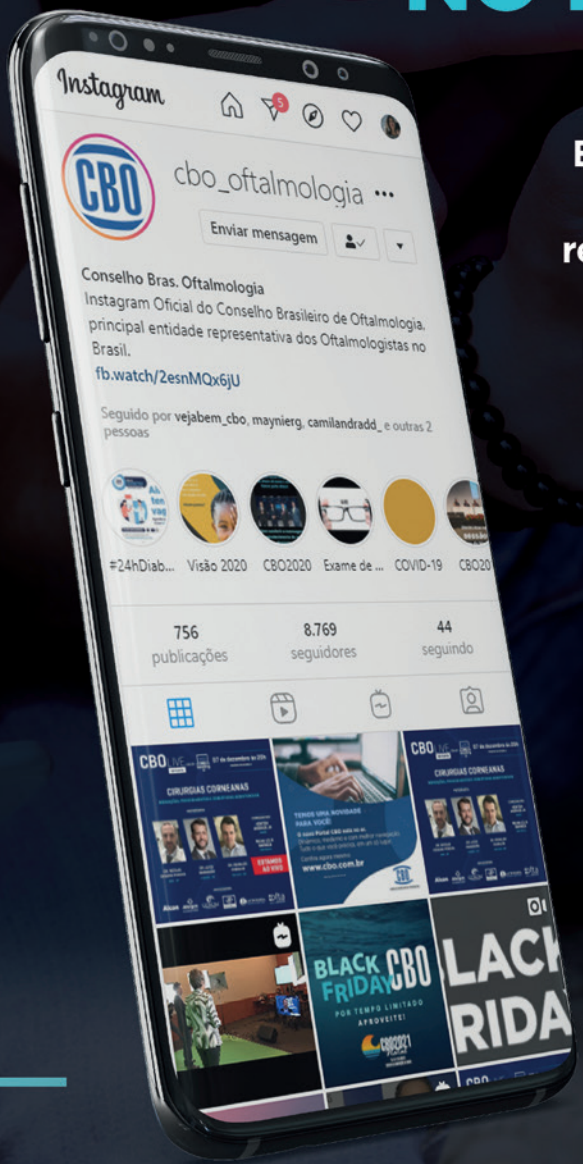
JÁ SOMOS MAIS DE 8 mil NO INSTAGRAM!



Este ano, a **Oftalmologia cresceu e se fortaleceu** ainda mais nas redes sociais. Isso é fundamental para a efetividade de nossas ações na Defesa da Especialidade e para a promoção da saúde ocular.

Afinal, é **somando forças** que nós difundimos informações relevantes para todos.

Aproveite e nos acompanhe, curta e compartilhe!

@cbo_Oftalmologia

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ANUIDADE CBO 2021

APROVEITE O DESCONTO

PAGANDO COM ANTECEDÊNCIA!

Ser associado CBO significa estar amparado pela maior entidade representativa dos oftalmologistas brasileiros.

É uma **oportunidade incrível** para se manter em dia com as novidades cientificas, engajado nas questões de defesa profissional e na promoção da saúde ocular para todos os brasileiros.

Você pode usufruir de tudo isso e ainda quitar a sua anuidade com desconto até o dia **30/03/2021.**

Não perca essa oportunidade!

Acesse!

Leia antes, leia online no moderno site dos

Arquivos Brasileiros de Oftalmologia

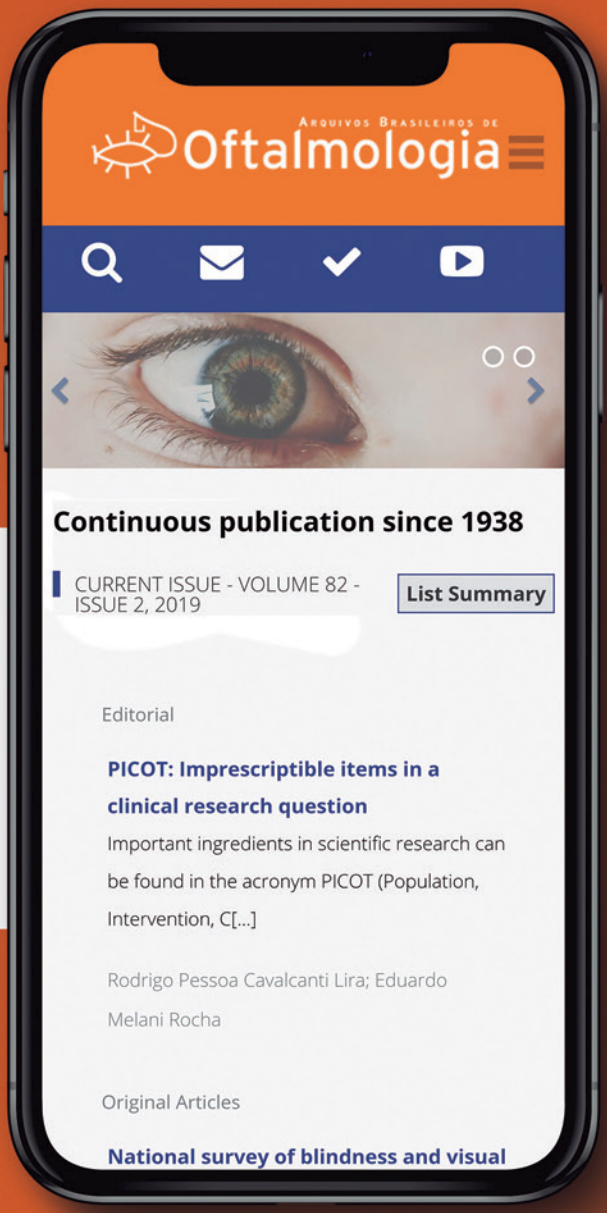
Navegação amigável ao seu dispositivo móvel.

Acesse sempre: quando puder e onde quiser!

E mais!

Visite a seção “Issues” para conhecer cada artigo **publicado nos últimos 80 anos.**

Se preferir, utilize o *Google Tradutor* para facilitar sua leitura.



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