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ORIGINAL RESEARCH

Lens capsule-related problems in patients undergoing phacoemulsification surgery

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Purpose: This study aimed to compare lens capsule-related problems in mature versus non-mature senile cataracts in patients undergoing phacoemulsification surgery.

Methods: A total of 295 patients with senile cataract were divided into two groups according to lens maturation: 105 patients with mature senile cataract comprised Group 1 (study group) and the remaining 190 with non-mature senile cataract comprised Group 2 (control group). Prior to surgery, ophthalmological examination was undertaken. Patients' best-corrected visual acuity and intraocular pressure were measured and a slit-lamp examination and funduscopy performed. All examination data were recorded and any capsule-related problems during surgery were also recorded. Patient files were reviewed retrospectively and compared between groups. Fisher's exact test was used in the statistical analysis.

Results: In Group 1, the capsule-related problems found were: inability to complete capsulorhexis (seven eyes [6.6%]), posterior capsular perforation (three eyes [2.8%]), and conversion to extracapsular surgery (one eye [0.9%]). A posterior capsular perforation was seen in one eye (1%) in the control group. An intraocular lens was inserted into the sulcus in six eyes (5.7%) and one anterior chamber (0.9%) in Group 1 and into the sulcus in one eye (0.5%) of Group 2. The lens was inserted into the capsular bag in all other patients.

Conclusion: Delaying surgery in patients with cataracts creates a high risk for capsule-related surgical complications. Although capsule dyes make capsulorhexis easier, capsulorhexis is the most problematic phase of phacoemulsification in mature cataracts.

Keywords: mature senile cataract, non-mature senile cataract, capsulorhexis

Introduction

Cataract is one of the most common causes of treatable blindness, especially in developing countries.[1] The prevalence of cataract in the world varies according to age and geographic area.[1] In recent years, cataract surgery has become safer and more effective due to surgical innovations;[2] however, phacoemulsification (PE), the currently preferred surgical technique, is indicated more for early stage cataract than previous techniques.[3] Although PE is safe and effective, there are difficulties in implementing this procedure in patients with advanced cataract, which is a serious problem in patients of poor socioeconomic status in developing countries who have delayed having surgery.[4,5] Changes can occur in the lens capsule and the lens contents of a mature cataract over time. These changes make it difficult to perform surgical procedures.[5–7] One of the most significant problems is changes in the lens capsule.[8]

The lens capsule is a transparent basal membrane that contains structural elements of the lens and epithelial cells and fibers that surround and protect the lens.[1] It differs

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from other basal membranes in the body in that it continuously thickens. The anterior capsule, measuring 8 µm thick at birth, may thicken with increasing age to 14 µm.[1,9] Patients with advanced cataract frequently have capsular fibrosis, adhesions, calcification, and weakness of the zonules.[3,9] In addition, advanced lens density prevents the red fundus reflex produced by the coaxial light of the microscope, making it difficult to differentiate the edge of the anterior capsule from the underlying white lens matter. In these cases, applying pressure on the lens capsule during capsulorhexis can cause irregular capsule rupture because of the increased and liquefied lens material. When the capsule is first pierced, milky liquefied cortical matter can leak into and thus obscure the view of the anterior chamber.[10,11] Previous surgical techniques that did not require capsulorhexis to be completed generated fewer complications than PE. However, proper capsulorhexis is necessary for seamless PE surgery.[9,11]

In the study reported here, we aimed to compare surgical problems caused by the lens capsule in patients with mature versus non-mature senile cataracts.

Materials and methods

A total of 295 eyes of 295 patients who underwent cataract surgery in our clinic were included in this retrospective study. The study was approved by the ethics committee of our university and conducted according to the tenets of the Declaration of Helsinki. Informed consent was obtained from all of patients for the surgical procedure and data collection. Exclusion criteria were traumatic cataract, infection, glaucoma, and uveitis.

Full ocular examination – including determination of best-corrected visual acuity, intraocular pressure measurement, slit-lamp examination, funduscopy, ultrasound, and biometry – was undertaken prior to surgery. Patients were divided into two groups according to maturation of the lens. The first group (study group) had white mature cataract, determined according to the Lens Opacities Classification System III criteria. The second group (control group) had non-mature senile cataract.

All cataract surgeries were performed by one surgeon (LA). Cyclopentolate 1% and phenylephrine 10% eye drops were instilled to dilate the pupils before surgery. The eyes and surrounding adnexa were cleansed using 5% and 10% povidone-iodine solution, respectively. A clear corneal incision was made and continuous, curvilinear capsulorhexis was performed. Trypan blue was used as capsule dye to allow the anterior capsule to be seen in the mature cataract group but not in the control group. PE equipment (AMO WhiteStar Signature® Phaco System, Abbott Medical Optics, Santa Ana, CA, USA) was used in the surgery. The nucleus was acquired with quick chop and PE. Irrigation and aspiration were performed for cortical material. An acrylic foldable intraocular lens (Ocuva A625, VSY Biotechnology, Istanbul, Turkey) was inserted into the capsular bag, under the side port irrigation. An intracameral antibiotic (1 mg/0.1 mL, Cefuroxime axetil) was applied into the anterior chamber at the end of the surgery. Topical corticosteroid eye drops (dexamethasone 0.1%) and antibiotic eye drops (ciprofloxacin 0.3%) were used postoperatively by patients six times per day for the following 2 weeks.

Any capsulorhexis problems and surgical complications occurring during surgery were recorded. All the data obtained for the two groups were compared. Fisher's exact test was used for the statistical analysis.

Results

Patient characteristics

In Group 1 (n = 105), 105 eyes of 59 female and 46 male patients with mature cataract stage 4 were operated on. The mean age of patients in this group was 69.93 ± SD 8.60 (range 40–88) years old. In Group 2 (n = 190), 91 eyes of 96 females and 94 males with senile cataract were operated on. The mean age of patients in this group was 67.42 ± 8.4 (range 47–84) years old (Table 1). In Group 1, visual acuity was light perception to counting fingers. The mean intraocular pressure in this group was 14.22 ± 3.14 (range 10–26) mmHg. In Group 2, mean visual acuity was 0.34 ± 0.25 Snellen units (range 0.05–0.50) and mean intraocular pressure was 14.06 ± 2.90 (10–24) mmHg.

The capsule-related problems found during cataract surgery (PE) were: inability to complete capsulorhexis in seven eyes (6.6%) of seven patients (four female and three male, mean age 72.71 ± 5.20 years old), posterior capsular perforation in three eyes (2.8%), (two female and one male, mean age 77.33 ± 6.11 years) and conversion to extracapsular cataract extraction in one eye (0.9%) (female, 84 years old) in the mature cataract group (Group 1). Posterior capsular perforation was encountered as a complication in

Table 1 The distribution of the demographic structure of patients

	First group	Second group
Male, n (%)	46 (44)	94 (49)
Female, n (%)	59 (56)	96 (51)
Total, n (%)	105 (100)	190 (100)
Age, years	69.93 ± 8.6*	67.42 ± 8.4

Note: *±: SD.

one eye (0.5%) (female, 72 years old) in the control group. Of the patients in whom capsule problems were detected, one had a Morgagnian cataract, four had white mature cataract, and two had corticonuclear cataract.

An intraocular lens was inserted into the sulcus in six eyes (5.7%) and one anterior chamber (0.9%) in Group 1 and into the sulcus in one eye (0.5%) in Group 2. Lenses were inserted into the capsular bag in all other patients (Table 2).

Compared with the control group, surgical problems occurred more often in the mature cataract group, and the difference between the two groups in this regard was statistically significant ($P < 0.05$) for the capsulorhexis stage. In terms of posterior capsular perforation, the difference between the two groups was not statistically significant ($P = 0.347$). For intraocular lens placement in mature cataract, anterior chamber and sulcus placement occurred at a high rate, and was statistically significant for sulcus placement ($P < 0.05$).

Discussion

The current cataract surgery technique of choice, which has developed over time, is PE. Unlike with previous methods, its widespread use and the increasing surgical experience of its practitioners have reduced the indication time for cataract surgery. Previously used surgical procedures were invasive and the healing process was long,[12–15] so they were more suitable for advanced-stage cataract. However, even though these techniques did not require capsulorhexis to be completed, thus resulted in fewer problems, PE requires capsulorhexis to be completed, meaning there is more risk of surgical complication. Capsulorhexis failure has been shown to have a negative impact on surgical success in mature cataract because of lens capsule changes.[14,15]

Thickening and calcification of the lens capsule and high pressure applied by the lens material to the capsule make it difficult to undertake capsulorhexis. The capsule is friable and tends to escape to the periphery during capsulorhexis.

Table 2 Capsule-related problems and intraocular lens placement results in Group 1, patients with mature cataract (n = 105), and Group 2, patients with non-mature cataract (n = 190)

	Group 1, n (%)	Group 2, n (%)	*P**
Capsulorhexis not completed	7 (6.6)	0 (0)	<0.05
Posterior capsule perforation	3 (2.8)	1 (0.5)	0.552
Intraocular lens insertion			
Sulcus	6 (5.7)	1 (0.5)	<0.05
Anterior chamber	1 (0.9)	0 (0)	0.644
Capsular bag	98 (93)	189 (99.4)	

Note: *Determined using Fisher's exact test.

In such cases, rhexis can progress to the posterior capsule easily. Sometimes, PE must be converted to extracapsular cataract extraction with extended corneal incision.[15–21] In mature cataract cases, the anterior chamber can be created with a dense viscoelastic device to overcome the tension on the capsule. To do this, the anterior capsule is perforated with a sharp cystotome then capsulorhexis is performed. Further, in mature cataracts, sometimes fundus reflexes cannot be seen because the anterior capsule obscures them. To resolve this difficulty, capsule dyes have been developed.[22–24] In our study, we used trypan blue as the capsule dye in the mature cataract surgeries performed. Trypan blue, allowing us to see the capsule, made the process capsulorhexis easier. We were unable to complete capsulorhexis in seven mature cataract patients and, in one case, extracapsular surgery was performed. Three patients had rupture of the posterior capsule at the same time. The appropriate capsulorhexis was performed in all patients in the control group. The capsule dye was not needed in these patients as their anterior capsule was easily seen.

With mature cataracts, lens changes play an important role during capsulorhexis. The increased lens volume applies pressure on the anterior capsule, making capsulorhexis difficult.[25–31] When the capsule is pierced, milky cortex material can spill over into the anterior chamber and hamper visibility of the anterior capsule. In addition, discharge of the milky cortex material diminishes on pressure to the lens capsule, so capsulorhexis becomes more difficult. In such cases, pressure balance can be achieved by adding a viscoelastic substance to the capsular bag and anterior chamber before proceeding with capsulorhexis. In the control group, the pressure exerted on the capsule was stable after viscoelastic was inserted into the anterior chamber, allowing capsulorhexis to be performed easily.

Conclusion

In mature cataract cases, changes to the lens and capsule make it difficult to perform capsulorhexis and increase the risk of surgical complications when the PE technique is used. To reduce complications and increase surgical success in future, the obstacles preventing patients from having cataract surgery early must be determined and resolved.

Disclosure

The authors declare no conflicts of interest in this work.

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CASE REPORT

Iris rubeosis and hyphema caused by chemical injury due to household detergent

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Abstract: We report an unusual case of iris rubeosis and hyphema caused by chemical injury due to household detergent. A 74-year-old man with a 15-year history of diabetes mellitus was refilling a container with household detergent at home. He splashed the detergent in his eyes. Slit-lamp examination revealed extensive epithelial damage to the left eye, leading to a persistent corneal epithelial defect. We used a bandage soft contact lens with levofloxacin eye drops as concomitant therapy in order to promote healing. However, a strain of fluoroquinolone-resistant *Corynebacterium* colonized the eye, so that the corneal ulcer eventually became severe. Use of the bandage soft contact lens was discontinued. His antimicrobial agent was changed to cefmenoxime, a drug to which fluoroquinolone-resistant *Corynebacterium* is sensitive, and topical instillation of autologous serum subsequently promoted improvement of the ulcer. On day 38 after injury, iris rubeosis led to hyphema and ghost cell glaucoma. With improvement of his corneal epithelial defect, the iris rubeosis and hyphema regressed and his visual acuity improved to 20/25 on the left eye. To the best of our knowledge, this is the first report of a case resulting in severe complications due to chemical injury by a neutral detergent. Ophthalmologists should be aware that corneal epithelial damage may become prolonged in elderly patients with diabetes, and unexpectedly severe when wearing bandage soft contact lens, with infection of *Corynebacterium* resistant to fluoroquinolones, even if the chemical agent is a neutral detergent.

Keywords: chemical injury, household detergent, persistent corneal epithelial defect, iris rubeosis, fluoroquinolone-resistant *Corynebacterium*, bandage soft contact lens

Introduction

Splashing chemicals into the eyes may not only occur as an occupational accident but also while using detergents or other products at home. Most kitchen detergents are neutral (pH 6–8) and are mainly composed of a surfactant, a stabilizing agent, and a sequestering agent. Even if a chemical injury occurs, the resulting keratoconjunctival damage is milder in most cases involving a neutral detergent than when an alkaline or acidic agent is the cause. To the best of our knowledge, no severe cases of eye injury caused by a neutral detergent have been reported.

On the other hand, a bandage soft contact lens (SCL) is used for treating a persistent corneal epithelial defect to prevent exfoliation of corneal epithelial cells, to protect from mechanical damage, and to maintain the wettability of the ocular surface.[1–6] Bacterial contamination using bandage disposable SCL is also reported,[7,8] and causes bacterial keratitis and infectious endophthalmitis in severe cases.[9,10]

We report a rare case of corneal injury due to a neutral detergent that resulted in a persistent corneal epithelial defect, exhibiting obvious symptoms of intracameral

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inflammation with iris rubeosis and hyphema after wearing a bandage SCL.

Case report

The patient was a 74-year-old Japanese man who splashed household detergent in his eyes at home in July 2009. He presented with bilateral eye pain and difficulty in opening his eyelids. Because the patient had suffered from diabetes mellitus for 15 years, he had undergone regular examinations for cataract and diabetic retinopathy at our hospital. Before the present injury, there was no diabetic retinopathy and the corrected visual acuity was 20/16 on both sides. At the time of injury, glycosylated hemoglobin was 8.9% and his antidiabetic drug therapy was limited to glimepiride (Amaryl®, Sanofi KK, Paris, France) at 1 mg in the morning. He was not taking an anticoagulant. The substance that entered his eyes was a neutral (pH 6.8) detergent (Charmy Awa no Chikara [Power of Suds], Lion Corporation, Tokyo, Japan), the major ingredient of which was a surfactant.

The right eye showed diffuse superficial keratitis, probably because little detergent had splashed into this eye. Hyperemia of the conjunctiva was the main finding and the ocular condition was grade G1 according to the Kinoshita classification.[11] On the other hand, there was extensive corneal epithelial damage, conjunctival edema, and marked conjunctival hyperemia of the left eye, which was classified as grade G2 according to Kinoshita (Figure 1).

The eyes were irrigated with 2 L of physiological saline solution for about 20 minutes. Treatment was then started with oral prednisolone, ofloxacin eye ointment, and betamethasone eye ointment. Six days later, the right eye showed almost complete epithelialization and visual acuity had returned to 20/20. However, although the size of the corneal epithelial defect in the left eye was smaller compared with that seen at the initial visit, edema and Descemet's fold were unchanged. At 10 days after injury, reduction of the corneal epithelial defect area was noted in the left eye, but visual acuity was still only hand movement. Because the epithelial defect was still present at 12 days after injury, the patient was given a therapeutic bandage SCL (Breath-O®, Toray Industries Inc, Tokyo, Japan), and treatment was started using an antimicrobial agent (0.5% levofloxacin eye drops, Santen Pharmaceutical Co, Ltd, Osaka, Japan), a corticosteroid (0.1% betamethasone eye drops, Shionogi & Co, Ltd, Osaka, Japan), and sodium hyaluronate eye drops (0.1% Hyalein, Santen Pharmaceutical Co, Ltd, Osaka, Japan), four times daily. After 7 days of wearing the bandage SCL, hyperemia was exacerbated and bacterial corneal infiltrates were suspected (Figure 2). Therefore, use of the bandage SCL and topical steroid instillation was discontinued. A *Corynebacterium* species resistant to fluoroquinolones was detected by culture on rubbing the inferior palpebral conjunctival sac with a sterile cotton swab, so his antimicrobial agent was changed to cefmenoxime, a drug to which fluoroquinolone-resistant *Corynebacterium* is sensitive. About one month after injury (10 days after starting use of the bandage SCL), the epithelial defect was almost completely resolved, except in a central area with opacity. In addition, corneal epithelial swelling was observed and the endothelial cell density was calculated to be 2237/mm^2. Because re-epithelialization did not progress, 50% autologous serum was instilled topically into the eyes. At 38 days after injury, the corneal epithelial defect was healed completely. However, hyphema occurred suddenly, with near-circumferential rubeosis of the iris (Figure 3). The intraocular pressure was around 35 mmHg, and ghost cell glaucoma developed. Treatment was started with acetazolamide at a dose of 750 mg/day and a topical long-acting beta-blocker (carteolol hydrochloride, Otsuka Pharmaceutical Co, Ltd, Tokyo, Japan) once a day. About 2 weeks later, the hemorrhage improved and secretions were absorbed, along with a decrease in intraocular pressure and spontaneous regression of rubeosis. Visual acuity was 20/100 in the left eye. After the eye was confirmed to be free from infection, a topical steroid (0.02% fluorometholone eye

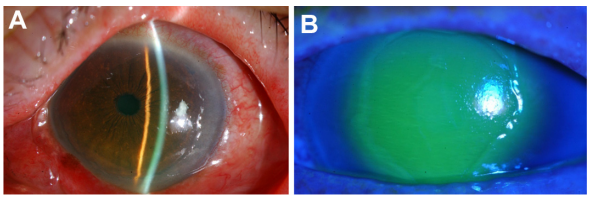

Figure 1 (**A**) Slit-lamp photograph showing marked conjunctival hyperemia and conjunctival edema in the left eye. (**B**) There is an extensive corneal epithelial defect covering almost the entire cornea in the left eye.

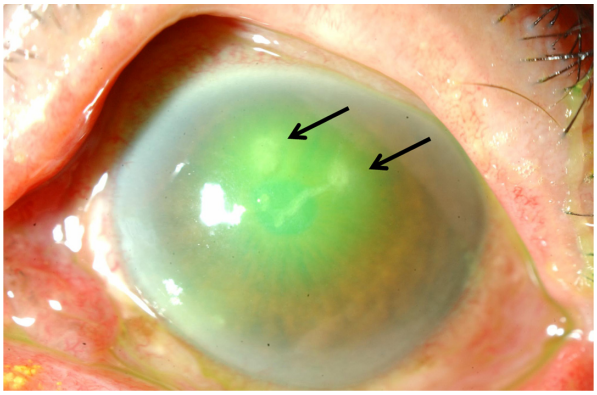

Figure 2 The corneal epithelial defect has become smaller, but it is complicated by infection (arrows) in the left eye.

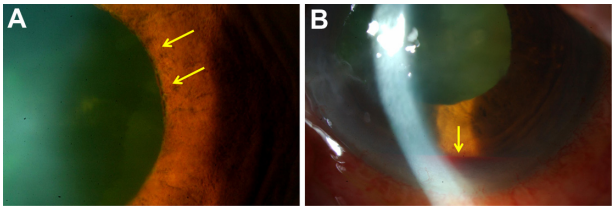

Figure 3 (**A**) Slit-lamp photograph showing iris rubeosis (arrows) at circumferential pupil margin. (**B**) There is an obvious hyphema (arrow) in the left eye.

drops, Santen Pharmaceutical Co, Ltd) was administered to clear the opacity in the center of the cornea. At 5 months after injury, his visual acuity improved to 20/20 on the right and 20/25 on the left. Fundus examination of the left eye revealed no diabetic retinopathy, no neovascularization, and normal cupping of the optic disc.

Discussion

This is a case of hyphema and iris rubeosis following secondary infection of a persistent corneal epithelial defect by *Corynebacterium*. The condition followed chemical injury by a neutral detergent.

When considering the cause of the onset of iris rubeosis in the present case, it seems highly improbable that rubeosis due to diabetic retinopathy or other ischemic disease would undergo spontaneous remission after such a short time as 2 weeks. We could exclude exacerbation of diabetic retinopathy, internal carotid stenosis, uveitis, retinal ischemia, ophthalmic arteriovenous anomalies, and neoplastic disease.

However, with respect to inflammatory rubeosis like that seen in the present patient, spontaneous regression would be expected to occur with improvement of inflammation. Due to progress with antimicrobial agents, there are no recent reports concerning bacterial corneal ulcers complicated by hyphema and rubeosis. However, there are several reports of microbial keratitis infected by *Corynebacterium*, especially following use of a bandage SCL[8] and after photorefractive keratectomy and laser in situ leratomileusis.[12,13] *Corynebacterium* is a genus of Gram-positive, rod-shaped bacteria, which are widely distributed in nature, are mostly innocuous, and constitute one kind of the normal bacterial flora found on the ocular surface.[14–16] The corneal epithelium is always in contact with the external environment and is likely to come into contact with foreign bodies and pathogens. If there is a corneal epithelial defect, the risk of microbial keratitis will be increased.

Continuous wearing of an SCL is a known risk factor for microbial keratitis.[17,18] Corneal epithelial damage is present and barrier function is impaired especially in patients who are prescribed a bandage SCL. Because continuous wearing of an SCL results in hypoxia and decreased metabolism in the cornea, this worsens the infectious keratitis already present. In addition, administration of a corticosteroid might have caused the infection to flare. In order to promote healing of the persistent corneal epithelial defect, a bandage SCL was used, with levofloxacin eye drops as concomitant therapy. However, some recent reports from Japan demonstrate a high rate of fluoroquinolone resistance in cases of *Corynebacterium*.[15,16] In our case, a strain of fluoroquinolone-resistant *Corynebacterium* colonized the eye, so that the corneal ulcer eventually became severe and intracameral inflammation also became more severe.

On the other hand, topical instillation of autologous serum subsequently promoted improvement of the ulcer in our case. Jeng et al[19] have reported the benefit of topical instillation of autologous serum in patients with persistent corneal epithelial defect, because it has a lower risk of infection and is more useful than a bandage SCL. There is only a remote possibility that topical instillation of autologous serum will cause progression of rubeosis.

What is the mechanism by which rubeosis and hyphema developed in this patient? It would be reasonable to consider that inflammatory cytokines produced in response to chemical injury were responsible for the changes in our patient. Animal studies of alkaline injury have shown a significant increase in interleukin-1α and interleukin-6 levels in the cornea[20] and that bevacizumab (an anti-vascular endothelial growth factor agent) is effective for preventing corneal neovascularization.[21] It is assumed that, after the initial chemical injury in our patient, persistent corneal ulceration caused by bacterial infection led to severe inflammation and release of the above-mentioned inflammatory cytokines from the corneal stroma into the anterior chamber, thereby increasing the concentration of cytokines in the aqueous humor. Moreover, increased interleukin-1β and interleukin-6 levels in the retina have been reported following alkaline injury.[22] In the present case, there is also a possibility that inflammatory cytokines were released from the retina into the vitreous fluid and then transferred to the anterior chamber, thereby causing rubeosis.

Furthermore, irrigation of the eye at home by this patient after the accident was only done for about 5 minutes, which is insufficient. In the future, ophthalmologists as well as emergency physicians and detergent manufacturers must inform the public that at least 15 minutes of irrigation is recommended as initial treatment at the time of injury.

In conclusion, the message conveyed by this case is that even when chemical injury is due to a neutral detergent, corneal ulceration may be persistent in elderly patients with diabetes who become infected with fluoroquinolone-resistant *Corynebacterium*, and unexpectedly severe in those wearing a bandage SCL.

Disclosure

The authors report no conflicts of interest in this work.

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This contribution is greatly appreciated.

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ORIGINAL PAPER

Outcome of pediatric retinal detachment using high-density silicone oil

Sanjay Mishra · Meenakshi Wadhwani · Ashok Kumar · Ravi Chauhan

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Abstract
Background The high-density silicone oil (Densiron), a mixture of F6H8 with silicone oil, has been used in the management of retinal detachment (RD) complicated by the presence of proliferative vitreoretinopathy (PVR) with varying rate of anatomical success and visual outcomes.
Methods We conducted a prospective interventional case series of 22 eyes in 22 children less than 18 years diagnosed with complicated retinal detachment complicated by the presence of PVR in inferior quadrant.
Results The mean age of the patients was 8.45 ± 3.36 years. There were 14 male and 8 female children. Five patients presented with total RD, 5 had subtotal RD and remaining 10 with inferior retinal detachment. There were 8 children with PVR C1, 13 with PVR C2, 3 with PVR C3. All patient's had macula off RD at presentation. The anatomical success in the form of attached retina was achieved in 21 (95.45%) eyes. Standard three-port pars plana vitrectomy without scleral buckling under general anesthesia was surgical technique employed in all cases.
Conclusion Densiron can be an important tamponade agent in pediatric retinal detachment complicated by PVR with increased success rate of retinal reattachment.

Keywords High-density silicone oil · Densiron · Retinal detachment

Introduction

The treatment of inferior retinal detachment (RD) with proliferative vitreoretinopathy (PVR) in the lower retinal periphery and especially in children represents a challenge for vitreoretinal surgeons. The incidence of pediatric retinal detachment in children is quiet low as compared to adults and reported to be 3.2 to 6.6% [1]. The multi-factorial etiology of RD in children has an effect on its management. The most common cause of RD in children is myopia, trauma, congenital retinal anomalies, previous intraocular surgery. The major problem, associated with prognosis and management in pediatric RD, is its delayed presentation, late diagnosis, and its association with factors like inferior dialysis, giant retinal tear making out makes the management further difficult. The most important

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intraoperative factor affecting the prognosis of vitreoretinal surgery is the presence of proliferative vitreoretinopathy (PVR) [2, 3]. Additionally, the childhood RD is more likely to recur due to the presence of adherent posterior hyaloid and contraction of vitreous near breaks. In order to overcome these factors, heavy oil tamponade has gained popularity among vitreoretinal surgeons over the recent years specially in cases of complicated RD with PVR in children [1–4]. To the best of our knowledge, there is no published study on efficacy and safety of Densiron as tamponade agent for complex RDs in Indian pediatric population. In the present interventional case series, we investigated the efficacy and safety of Densiron as a primary endotamponade in the treatment of these complex retinal detachments in children of Indian origin.

Materials and methods

This prospective interventional case series involved 22 eyes of 22 children with newly diagnosed pediatric RD. The study was approved by the institutional ethical committee and confirmed to the ethical standards stated in the 1964 Declaration of Helsinki. Informed consent was obtained from parents of all the subjects prior to enrollment in study.

The inclusion criteria of the study were all the patients presenting with retinal detachment complicated by the presence of PVR in inferior quadrant. The intervention was in the form of vitreoretinal surgery with the use of Densiron—a high-density silicone oil as tamponading agent. The exclusion criteria were children treated with previous retinal surgeries. The initial evaluation included complete ophthalmological examination which included determination of the best corrected visual acuity under cycloplegia, intraocular pressure tonometry, detailed slit lamp, and fundus examination. Preoperatively, the new characteristics of silicone oil were explained to all patients. Informed consent was obtained from parents of all the subjects. The patients were evaluated on day 1, 7, 2 weeks, 6 weeks, and 3 months. The details of type of RD and grades of PVR, lens status (phakic or pseudophakic or aphakic) were also noted. The surgical procedure consisted of a standard three-port pars plana vitrectomy without scleral buckling procedures under general anesthesia. Vitreous was removed up to anterior vitreous base along with release of anterior and posterior tractions. In eyes with significant retinal shortening due to long-standing retinal detachment, circumscribed relaxing retinectomies were performed to allow reattachment with perfluorocarbon liquid intraoperatively. Retinal breaks were treated by cryocotherapy and/or endolaser photocoagulation. Perfluorocarbon was replaced by balanced salt solution followed by a slow injection of Densiron. Densiron was aspirated with a 17G cannula under direct illumination at the time of removal. The primary end point was the anatomical re-attachment of retina following removal of Densiron oil, and the functional end point was improvement in preoperative visual acuity following oil removal. The statistical analysis was done using SPSS 14.0, and results were analyzed using standard statistical tests.

Results

The mean age of the patients was 8.45 $\pm$ 3.36 years. There were 14 male and 8 female children. Of these 22 children's, 5 had total and subtotal RD each and 10 presented with inferior retinal detachment. There were 8 children with PVR C1, 13 with PVR C2, 3 with PVR C3, but all patients had macula off RD. Of these 22 patients presenting with RD, only 3 were aphakic. The duration of RD was 1.5 $\pm$ 0.90 months (Fig. 1, Table 1). The mean preoperative BCVA was 0.014 $\pm$ 0.019, and mean post-operative BCVA was 0.077 $\pm$ 0.063 with average post-operative IOP spike 21.3 $\pm$ 7.28 mm Hg. The mean post-operative duration for silicone oil removal was 3.95 $\pm$ 1.25 months. Of the 26 eyes, 9 (40.91%) eyes did not undergo Densiron removal at 6 months but subsequently underwent oil removal over next 03 months. The anatomical success in the form of attached retina was there in 21 (95.45%) eyes. Five eyes had a post-operative IOP spike of more than 30 mmHg and were started on topical betoxolol 0.5%, and none of these five patients required trabeculectomy or other glaucoma surgery (Table 2). There was a significant association between duration of attachment of retina and PVR grade severity ($p < 0.05$).

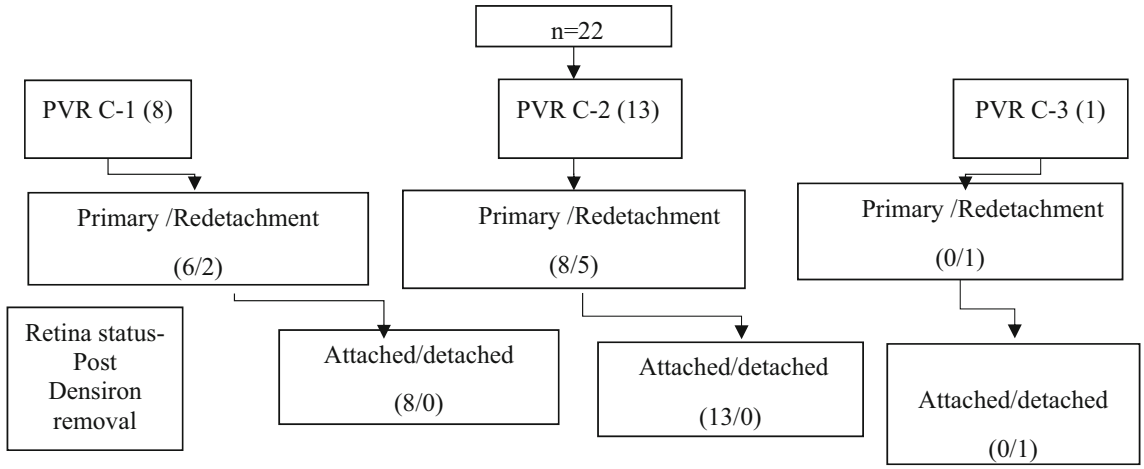

Fig. 1 Details of post-Densiron removal retina status after vitrectomy in relation to various grades of PVR

Table 1 Demographic distribution of children undergoing vitrectomy

Parameters	
Age	8.5 ± 3.4 yrs
Gender(M/F)	(14/8)
Duration of RD	1.5 ± 0.90 months
Lens status (PHAKIC/APHAKIC)	18/3
BCVA (pre-op)	0.014 ± 0.019
PVR grade (1/2/3)	8/13/1
Location of retinal detachment	Inferior
BCVA (post-op)	0.077 ± 0.063
IOP spike	21.4 ± 7.3 mmHg
SOR duration	4.0 ± 1.3 months
Post-Densiron retina status (attached/detached)	21/1

Discussion

Treating a complex RD is a very interesting and difficult challenge. However in severe PVR, especially in patients with previous multiple vitreous surgery and persistent RD of the inferior quadrants, the outcome can be discouraging even with silicone oil. Silicone oil limits, but does not exclude, the diffusion of proliferative cells and inflammatory mediators through the vitreous cavity. If the silicone does not completely fill the eye, it may lead to an incomplete tamponade in the inferior retina, exposed breaks and an accumulation of fluid containing proliferative cells. Therefore, in patients with complex inferior RD a tamponade with heavier than water density could be useful [5].

In the present study, we used Densiron 68 as a primary endotamponade agent in children presenting with complex inferior retinal detachment instead of standard procedures. The standard vitreoretinal surgical procedure with ordinary silicone oil tamponade in these patients was unlikely to achieve good anatomical success in these complex pediatric RDs. In our case series retinal reattachment was successfully achieved in 95.45% patients using Densiron 68 tamponade which is comparable to reattachment rates in adult retinal detachment surgeries.

The higher success rate with Densiron as compared to conventional heavy silicone oil was achieved since it significantly reduces the fibroblast cells and its mediators responsible for onset of PVR in inferior retina [6–8]. In few studies, it has been noted that Densiron tends to shift the PVR milieu to superior side; hence, they advocated prophylactic laser photocoagulation or cryocoagulation in their patients. In a

Table 2 Details of pre- and post-Densiron removal in children undergoing vitrectomy

Patient	Age	RD type	Indications	RD duration	PVR grade	Pre-op BCVA	Post-op BCVA	Post-op IOP spike	Densiron removal done	Post-Densiron RETINA STATUS	Post-SOR duration (months)	Remarks	Primary/ ReVR surgery
1	12	2	1 2	3	2	0.01	0.25	22	Y	A	3		P
2	10	1	3 2	3	3	0.02	0.1	16	Y	D	2		R
3	11	1	3 2	2	1	0.01	0.1	37	Y	A	3	On Brimonidine with Timolol Eye drop IOP settled after SOR	P
4	10	1	4 2	2.5	2	0.01	0.1	18	Y	A	4		P
5	11	5	5 2	1	2	0.1	0.16	23	Y	A	2		P
6	12	2	5 2	1	1	0.01	0.1	16	Y	A	4		P
7	9	1	5 2	0.5	2	0.01	0.16	18	N	A	4		P
8	12	1	1 2	2	2	0.01	0.1	21	N	A	5		R
9	6	3	1 2	1	2	0.01	0.01	19	Y	A	6		R
10	8	5	5 2	0.5	1	0.02	0.1	23	Y	A	5		P
11	5	4	5 2	3	2	0.01	0.02	32	Y	A	6	On Brimonidine with Timolol. Eye drop IOP settled after SOR	P
12	12	2	3 2	m	1	0.01	0.1	16	Y	A	4		R
13	5	3	5 2	2	1	0.01	0.02	36	Y	A	4	On Brimonidine with Timolol. Eye drop IOP settled after SOR	R
14	8	6	3 2	3	2	0.01	0.02	17	N	A	3		P

Table 2 continued

Patient	Age	RD type	Indications	RD duration	PVR grade	Pre-op BCVA	Post-op BCVA	Post-op IOP spike	Densiron removal done	Post-Densiron RETINA STATUS	Post-SOR duration (months)	Remarks	Primary/ ReVR surgery
15	11	1	5 2	1	2	0.01	0.02	16	N	A	2		R
16	1	4	1 2	1	2	0	0.01	18	Y	A	5		R
17	4	2	1 2	2	1	0.01	0.01	19	Y	A	6		P
18	12	2	5 2	1	1	0.02	0.1	16	N	A	3		P
19	10	5	3 2	3	2	0.01	0.1	17	N	A	4		P
20	9	3	5	1	1	0.01	0.1	34	N	A	5	On Brimonidine with Timolol. And Latanoprost Eye drop. Underwent SOR Densiron Early due to IOP Rise IOP Settled after SOR	P
21	3	5	2 + 5	1	2	0.01	0.01	26	N	A	4	On Timolol. Eye drop IOP Settled after SOR	P
22	5	3	2	0.33	2	0	0.01	10	N	A	3		

* *y* yes, *N* no, *A* attached, *D* detached, *P* primary vitreoretinal surgery, *R* repeat vitreoretinal surgery

prospective study by Wolf et al. using Oxane HD, nearly 45% of the patients still required an endotamponade with conventional silicone oil to maintain retinal reattachment after repeat surgery [9]. Published literature points out that ocular hypertension is an important post-operative complications with use of Densiron but can be easily controlled with medications only as observed in our study group. Other common complications are severe inflammation, emulsification/dispersion, new retinal tears in the superior retina, retinal vascular changes, cataract, and hypotension [10, 11]. There was no incidence of anterior or posterior segment inflammation in our study as also reported by Sanders et al. [7].

Though in our study, the rate of successful anatomical reattachment was 95.45%, which was similar to reattachment observed by Tognetto et al. [12] as 92.3% but higher as compared to Sanders et al. [7], who reported the primary retinal attachment as 45.8%. The reason for low success rate in Sanders et al. could be that they used Densiron in all failed retinal detachment cases. The major reason for successful anatomical reattachment in our study was due to less incidence of emulsification of silicone oil in contrary to other studies [13–16].

Therefore, Densiron can be an important tamponade agent in pediatric retinal detachment complicated by PVR with increased success rate of retinal reattachment. However, further studies with large number of subjects and control group are required to validate the efficacy and safety of Densiron oil as tamponade agent.

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ORIGINAL PAPER

Toll-like receptors in acute post-cataract surgery endophthalmitis

Tanvi Soni · Subina Narang · Sunandan Sood · Anita Tehlan

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Abstract

Objective To evaluate the expression of toll-like receptor 2 (TLR2) and toll-like receptor 4 (TLR4) on CD14 + cells in vitreous and blood of post-cataract surgery acute endophthalmitis.

Design This prospective case–control pilot study enrolled 16 patients of post-cataract surgery endophthalmitis. All the cases were subjected to 23 G pars plana vitrectomy (PPV). Ten patients undergoing 23 G PPV for non-infectious conditions were taken as controls.

Methods 23 G PPV was performed, and three undiluted vitreous samples were collected in heparinized syringes from the cases and the controls. Simultaneous venous blood sample was taken, and flow cytometry was performed to detect the expression of TLR2 and TLR4 in vitreous and blood samples. The vitreous and blood samples were incubated with fluorescein isothicyanate (FITC) conjugated anti-TLR2 monoclonal antibody Alexafluor (AX) 647 and anti-TLR4 monoclonal antibody phycoerythrin. Data acquisition was done on a pre-calibrated flow cytometer. TLR analysis of the acquired flow cytometry data was then performed. Mean channel fluorescence intensity (MFI) derived from fluorescence histogram was used to study the level of cell surface TLR expression. MFI was calculated as a ratio and recorded as the MFI of the TLR2 or -4 antibody divided by the MFI of the isotype-matched negative control antibody. Core vitrectomy was done as per the comfort of the surgeon, and intravitreal antibiotics vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml) were injected. The cytological examination was done on vitreous and blood sample.

Statistical analysis The median TLR 2 and TLR4 values between cases and controls were compared by Mann–Whitney U test. Spearman's rank correlation test was used to assess the correlation between TLR expression and disease activity.

Results Vitreous cytology evaluation showed the presence of neutrophils (81.25%, $n = 13$), monocytes (68.75%, $n = 11$) and lymphocytes (62.50%, $n = 10$). The level of expression of TLR2 in vitreous showed a statistically significant correlation with an increase in the time interval of cataract surgery and intervention for endophthalmitis ($p < 0.05$), but the same was not observed for TLR4. A drift toward higher level of expression of TLR2 and TLR4 in vitreous was observed in patients with poor outcome.

Conclusion TLR2 levels increase with the delay in presentation; thus, TLR2 ligands in vitreous could serve as a good target for the treatment of endophthalmitis.

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Keywords Endophthalmitis · Toll-like receptors · Innate immunity · Vitreous biopsy · Post-cataract surgery endophthalmitis · TLR-4 and TLR-2 · Vitreous cytology in endophthalmitis

Introduction

Postoperative endophthalmitis is one of the most dreaded complications after cataract surgery. In view of the poor prognosis of these cases [1], there has been an increasing interest to understand the basis of pathogenesis of the disease to improve the outcome by targeting the critical areas. It is well understood that in endophthalmitis it is not only the infection but the associated inflammation that leads to visual loss due to structural damage in the eye due to inflammation. Toll-like receptors (TLRs) play a pivotal role in the innate immunity. TLR has been implicated in the recognition of the microbial agent by pathogen-associated molecular patterns (PAMP) which further signals for the host defense responses against the pathogen. This involves the cascade of events involving inflammatory cytokines. The role of toll-like receptors in endophthalmitis is well defined in the experimental mice models, and it has been proven from the biopsy samples of the retinal tissues [2]. In real-life scenario, in endophthalmitis eyes, fragile retina makes the retinal biopsy technically challenging and impractical. The present study was planned to determine the in vivo level of expression of TLR 2 and 4 in the cells present in vitreous and the serum of the post-cataract surgery endophthalmitis. The hypothesis tested in the present study was that if TLR2 and 4 can be assessed from the vitreous samples of endophthalmitis patients, then accordingly these can be targeted in the treatment of endophthalmitis.

Material and methods

Study design

This was a single-center prospective pilot case–control study and was approved by the institutional research board and ethical committee. The informed consent was taken in all cases as per the principles of International Declaration of Helsinki. The study enrolled 16 eyes of 16 patients of endophthalmitis, occurring within six weeks after surgery for senile cataract, presenting to the Retina Clinic of a tertiary eye care centre. For the purpose of this study, post-cataract surgery endophthalmitis was defined as inflammation of posterior segment as evidenced by slit-lamp biomicroscopy, ophthalmoscopy and ultrasound, with or without hypopyon. All cases presented after 24 h of surgery and had localized corneal edema, unlike the one seen in TASS. All had vision $\leq$ logMAR 2.0 and were subjected to 23 G pars plana vitrectomy (PPV) with broad-spectrum intravitreal antibiotics as initial treatment. Ten patients undergoing 23 G PPV for non-infectious conditions like retinal detachment and macular hole, during the same duration, were taken as controls.

We excluded the eyes with baseline vision of no perception of light, complicated cataract, corneal oedema or keratitis precluding vitreous surgery, patients who underwent any additional surgery in the same eye during follow-up period, patients with retinal detachment or choroidal detachment and patients with immunocompromised diseases like diabetes mellitus, a history of cancer, prolonged use of steroids or other immunosuppressive drugs.

A detailed history was taken in all cases. The history was obtained regarding the time gap between the cataract surgery and the symptoms of endophthalmitis, and also the time gap between the surgery and the withdrawal of vitreous sample. The symptoms of endophthalmitis included pain, redness and decrease in vision. History of any systemic disease like diabetes mellitus, cancer, tuberculosis and use of corticosteroids was recorded. The detailed ophthalmological examination included thorough slit lamp biomicroscopy and indirect ophthalmoscopy with + 20 D lens. Visual Acuity assessment was done on the Snellen visual acuity chart, and the observed values were converted to logMAR scale for statistical analysis. If the participant could not identify the largest letter on the chart at 6 m (m), the distance was reduced to 1 m. If he/she could not still recognize the largest optotype, Visual acuity (VA) was classified using the semi-quantitative ordinal scale of counting fingers (CF), hand motions (HM), and perception of light (PL). HM and PL were noted at a distance of 30 cm. The vision of hand motions was done moving the hands in a vertical direction and horizontal direction. Similar reply 8 out of 10 times was taken as reliable.

LogMAR 2 to 2.6 was assigned to vision counting fingers at various distances of 1 to 6 m and log MAR 2.7 for vision HM and logMAR 2.8 for vision PL [3].

The anterior chamber reaction and flare evaluated according to Standard Uveitis Nomenclature (SUN) classification. The media clarity was graded from I–V using an indirect ophthalmoscope (IDO) as in EVS study [4].

Ultrasound *B* scan was done to confirm the vitreous involvement in all cases. All the eyes underwent 23 G PPV within 24 h of presentation to our hospital. At the start of the PPV, three undiluted vitreous samples of 0.5 ml each were collected under guarded aspiration in 1 cc heparinized syringes on the aspiration tubing of the cutter with air infusion in the posterior segment. The samples were taken to the microbiology, cytology and haematology laboratories immediately in syringe plugged with sterile rubber cork so as to ensure no contamination of the samples. A venous blood sample was also taken from the arm in sterile anticoagulant ethylene diamine tetra acetic acid (EDTA)-coated tubes and sent to the haematology laboratory for evaluation of TLR2 and TLR4 [5].

Core vitrectomy was done as per the comfort of the surgeon, and intravitreal antibiotics vancomycin (1 mg/0.1 ml) and ceftazidime (2.25 mg/0.1 ml) were injected. Postoperatively, all patients received oral tablet levofloxacin 500 mg for 5 days, topical eye drops vancomycin 5%, topical ceftazidime 5% and cycloplegics. Any other intraoperative and postoperative complications, if noted, were managed according to the standard protocol.

The cytological examination was done on vitreous and blood sample. Two smears were prepared from the vitreous sample. One smear was fixed in absolute alcohol and was subjected to Hematoxylin and Eosin staining. The other smear was air-dried and subjected to May Grunwald Giemsa staining. Smears were evaluated for the presence of neutrophils, monocytes and lymphocytes. A similar procedure was done for the blood sample.

Flow cytometry was performed on a freshly isolated blood sample and vitreous sample to investigate for TLR2 and TLR4 expression on Cluster of Differentiation positive (CD14 +) monocytes. 100 µl of the blood sample was incubated with anti-TLR2 monoclonal antibody conjugated with fluorescein isothicyanate(FITC) fluorescent dye Alexafluor (AX) 647 and anti-TLR4 monoclonal antibody conjugated with FITC dye PhycoErythrin (PE) for 30 min in dark. (Fig. 1) Further, 2 ml of flow cytometry lysing solution (FACS; BD Biosciences) was added and incubated for 10–12 min. The sample was spun at 1200 to 1300 rotations per minute for 3 to 5 min. The supernatant was discarded. The test tube with the remaining pellet was used for flow cytometry. Data acquisition was done on a pre-calibrated flow cytometer. A similar procedure was done for the vitreous sample also. Isotype-matched antibody controls were used to detect nonspecific staining (Fig. 2).

TLR analysis of the acquired flow cytometry data was then performed. The cytometry results were obtained in the form of fluorescence histogram. Monocytes were identified with the help of their characteristic forward and side-scatter flow cytometry profiles and CD14 (a monocyte marker). The histogram showed two peaks, blue colored which is the level of expression of TLR2 and TLR4 in vitreous/blood depending upon the sample being analyzed (M1) and green colored which is isotype-matched antibody controls to detect nonspecific staining (M2). Mean channel fluorescence intensity (MFI) is calculated by the ratio of these two peaks [5]. MFI indirectly equals the level of receptor density on the cell surface. MFI of 1 represents no significant expression and MFI of more than 1 indicated higher expression of receptors.

The vitreous sample sent for microbiological evaluation, included smear examination with potassium hydroxide for fungus, gram staining for bacteria and culture for both bacteria and fungus. The smear

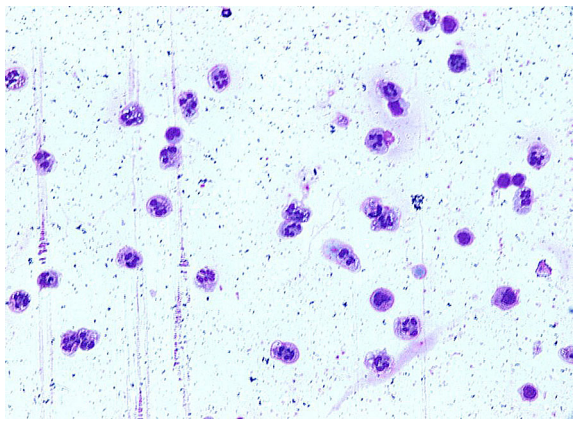

Fig. 1 Smear prepared from vitreous fluid showing neutrophils (red arrow head) and monocytes (green arrow head)Hematoxylin & Eosin, 400X maginification

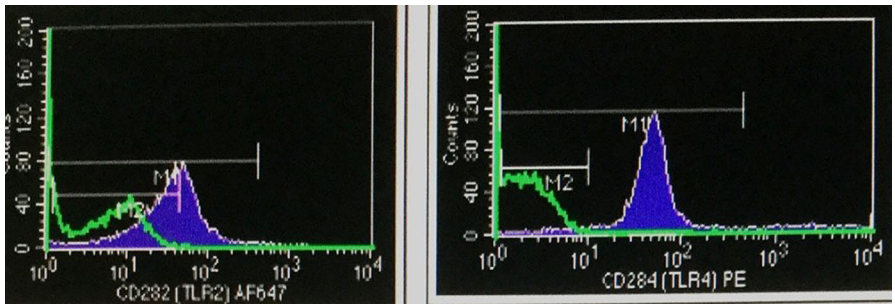

Fig. 2 Fluorescence histogram showing TLR2 (left) and TLR 4(right) expression in vitreous M1 represents level of expression in vitreous(blue peak) and M2 represents level of expression in isotype-matched antibody control (green peak). M1/M2 = MFI

and culture sensitivity reports were used to further guide the treatment. Laboratory confirmed growth was defined as at least semi-confluent growth on a solid medium, any growth on two or more media, or growth on one medium supported by positive gram stain [6].

Patients were followed-up as per the institute's protocol. At each visit to the hospital, the patient was subjected to a detailed anterior and posterior segment examination including visual acuity assessment. The eyes were examined for the visual outcome at three months, and the expression of TLR was correlated with the final outcome. A successful functional outcome was taken as pre-study defined criteria of best-corrected visual acuity (BCVA) $\geq$ 20/400 (log-MAR value $\leq$ 1.3) [7], and a successful anatomical outcome was taken as preserved anatomy of the globe and no sign of active inflammation at follow-up.

Statistical analysis

The presence or absence of endophthalmitis was considered as the primary explanatory variable. TLR2 and TLR 4 status in vitreous and blood was considered as primary and secondary outcome variables, respectively. Age, gender, hypopyon, visual acuity at 3-month follow-up period were considered as other explanatory variables. Descriptive analysis of all the parameters was done using a median and interquartile range for quantitative variables, frequency and percentage for categorical variables. As the data obtained was skewed, the medians and distributions of MFI value of TLR 2 and TLR4 values between cases and controls were compared by Mann–Whitney U test and independent-sample median test. A similar comparison was done in TLR 2 and TLR 4 values between both genders and between people with good and poor visual outcome. The association between quantitative explanatory variables like visual acuity, hypopyon and TLR values was done by Spearman's rank correlation coefficient (r-value). An r value of $r < 0.31$ was taken as modest correlation, 0.32 to 0.55 was taken as moderate correlation, and > 0.55 was interpreted as strong correlation. P-value < 0.05 was considered statistically significant. IBM SPSS version 21 was used for statistical analysis (Fig. 3).

Results

The mean age of cases was 55.50 years (range 12.75–66.50 years) and in controls, it was 54.50 years (range 35.50–60.00 years). Both groups were age and sex-matched. The time interval between cataract surgery and vitreous sample withdrawal for endophthalmitis varied between 2.00 days to 2.00 months. (Mean value = 8.94 days). All patients had poor visual acuity and the details of the initial presentation are as in Tables1 and 2.

Vitreous cytology evaluation showed the presence of neutrophils (81.25%, n = 13), monocytes (68.75%, n = 11) and lymphocytes (62.50%, n = 10). The details of the MFI of TLR2 and TLR4 in vitreous and blood of cases and controls are shown in Table 3.

In vitreous, MFI of TLR2 in CD14 + cells was > 1 in 93.75% cases (n = 15) and < 1 in 6.66% (n = 1) cases (range -0.88 to 5.04, median value -1.22). The MFI of TLR4 in CD14 + cells in vitreous was > 1 in all 100% (n = 16) patients (range -1.01 to 9.74, median value -1.85).

In blood, MFI of TLR2 in CD 14 + cells was more than 1 in 100% (n = 16) cases (range-1.02 to 6.15, median value -1.26). MFI of TLR4 in CD 14 + cells

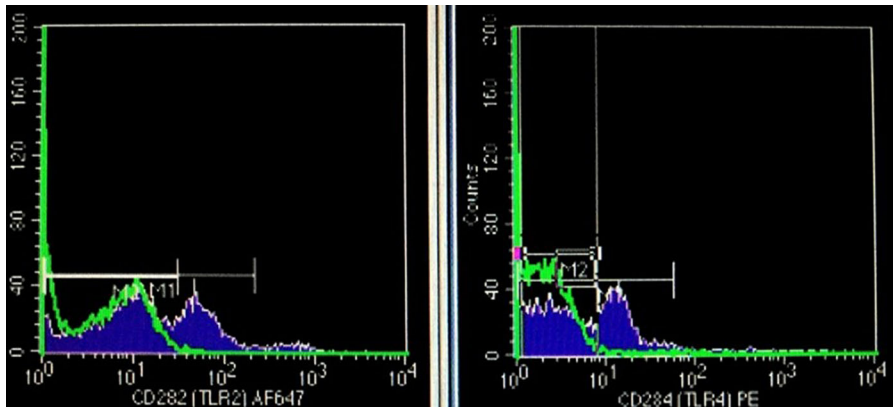

Fig. 3 Fluorescence histogram showing TLR2 (left) and TLR 4(right) expression in blood. M1 represents level of expression in blood (blue peak) and M2 represents level of expression in isotype matched antibody control (green peak). M1/M2 = MFI

Table 1 Baseline variables in study and control group

	Study group (%)	Control group
Visual acuity		
Light perception LP HMCF	2(12.5%)	0
CFCF	6(37.5%)	0
CFto20/200	8(50%)	0
> 20/200	0	1(10%)
	0	9(90%)
Anterior segment inflammation		
Cells + 4	16(100%)	0
Hypopyon	16(100%)	0
Media clarity		
≥ GradeII	0	10(100%)
GradeIII	3(18.8%)	0
GradeIV	13(81.2%)	0
Vitritis	16(100%)	0
Any systemic ailment (DM, cancer, uveitis)	0	0

in blood was > 1 in 87.5% cases (n = 14) and < 1 in 12.5% cases (n = 2) (0.65 to 17.14, median value-1.58) (Table 2). The median value of MFI of TLR2 and TLR 4 in CD 14 + cells of blood in cases and controls was comparable (Table 3, $p > 0.05$).

The level of expression of both TLR2 and TLR4 was not statistically significantly associated with the demographic profile of the patient. A weak correlation was present between the vitreous TLR2 and TLR4 with visual acuity at presentation (r = 0.190 and 0.498, respectively) which was not statistically significant (p-value = 0.498 and 0.804, respectively). The correlation between MFI of vitreous TLR2 and TLR 4 to other baseline variables was not statistically significant (0.456). There was a significant correlation between the time interval from cataract surgery to intervention for endophthalmitis with the level of expression of vitreous TLR2.(r = 0.577) (p-value = 0.024). The correlation between MFI of vitreous TLR4 with the time interval from cataract surgery to intervention for endophthalmitis was weak (r = 0.086) which was not statistically significant (p-value = 0.761). (Table 4).

The microbiological evaluation of vitreous showed growth of organisms in 3 (18.75%) endophthalmitis patients. The organisms were methicillin-sensitive *Staphylococcus aureus* (n = 1) and *Staphylococcus epidermidis* (n = 2). Successful final functional outcome was seen in 50% (n = 8) of patients. The median value of MFI TLR2 and TLR4 in vitreous of endophthalmitis patients did not correlate with the visual outcome.

Table 2 TLR 2 and TLR 4 Mean fluorescence index in vitreous study group

	Age	Sex	Time interval between surgery and PPV	Visual acuity at presentation logMAR value	Microbial culture	N	M	L	MFI TLR2	MFI TLR4	Successful visual outcome VA ≥ 20/200	Successful anatomical outcome
1	52	F	7 days	2.7	No growth	+	+	+	1.11	2.16	no	yes
2	62	F	15 days	2.7	No growth	+	+	−	2.83	1.14	no	yes
3	21	M	2 days	2.7	No growth	+	+	+	1.28	2.14	yes	yes
4	55	F	4 days	2	No growth	+	+	+	1.18	2.61	yes	yes
5	60	F	6 days	2.3	*Staphylococcus aureus*	+	+	−	2.32	5.57	yes	yes
6	70	M	60 days	2.7	*Staphylococcus epidermidis*	+	+	+	4.41	4.17	no	yes
7	55	M	7 days	2	*Staphylococcus epidermidis*	+	+	+	1.27	1.39	yes	yes
8	48	F	7 days	2	No growth	+		+	1.25	4.7	no	yes
9	45	M	7 days	2.7	No growth		+		1.03	3.65	no	yes
10	68	M	5 days	2.8	No growth	+		+	1.06	1.47	yes	yes
11	56	F	4 Days	2.8	No growth	+	+	+	2.4	1.12	no	yes
12	50	F	4 days	2.7	No growth	+	+		1.6	5.04	no	yes
13	70	M	4 days	2	No growth		+	+	1.04	1.56	yes	yes
14	72	M	4 days	2.3	No growth	+	+	−	5.04	9.74	yes	yes
15	45	M	3 days	2.3	No growth	+	−	+	0.88	1.39	yes	yes
16	62	F	4 days	2	No growth	+	−	+	1.07	1.01	no	yes

Table 3 Comparison of TLR2 and TLR4 expression in blood between cases and controls was comparable

Parameter	Cases (N = 16)	Controls (N = 10)	Mann–Whitney U test	Independent sample median test
TLR2 MFI	1.26(1.02–6.15)	1.38(1.01 to 2.84)	0.856	1.00
TLR4 MFI	1.58(0.65 to 17.14)	2.54(0.94 to 7.98)	0.897	0.688

Table 4 Correlation between delay in presentation to vitreous TLR expression

Parameter	Correlation	P value
TLR2 MFI	0.577	**0.024**
TLR4 MFI	0.086	0.7611

Bold value indicates to signify the level of significance ($P < 0.05$)

Discussion

Postoperative endophthalmitis leads to the development of an inflammatory reaction by the host. This inflammatory response generated by the host is a double-edged sword. On the one hand, it is necessary to remove the infection, on the other, it is responsible for causing irreversible damage to the retina [8]. The inflammatory reaction is directly related to the amount of innate and adaptive immune responses generated. The most important step in the initiation of this immune response is the recognition of pathogen by TLRs present on cells associated with innate immunity like neutrophils and monocytes [9]. TLR recognize microbes by highly conserved biochemical structures called pathogen-associated molecular patterns (PAMP). TLR provides considerable specificity for a different class of pathogens. TLR 1,2,4,5 and 6 are present on the surface of cell and are involved in

recognition of PAMPs derived from bacteria, fungi and protozoa while TLR3, 7, 8 and 9 are intracellular and are involved in the recognition of viruses. The TLR-mediated signaling is a complex and less understood area. The cytokines and other mediators released in the blood stream after any localized inflammation may lead to upregulation of systemic TLR expression [10].

TLR2 has been linked with the recognition of gram-positive bacteria and TLR4 is recognized as a receptor for gram-negative bacteria [11].

The current treatment protocol for endophthalmitis involves the intravitreal injection of broad-spectrum antibiotics and pars plana vitrectomy (PPV). The only available anti-inflammatory treatment option is corticosteroids. There are conflicting reports on the role of corticosteroids in the management of fungal endophthalmitis which is not so rare in tropical countries [12, 13]. Main concerns are emerging resistance to antibiotics and lack of definitive treatment for inflammation-induced damage [14].

It is a well-known fact that few cells are present in the normal vitreous gel, predominantly in the cortex. These cells consist of hyalocytes, astrocytes and glial cells. Coupland et al. studied vitreous cytology and noted that abundant neutrophils in vitreous fluid cytology suggest bacterial (suppurative) endophthalmitis [15]. Thus, the cytological evaluation of vitreous is a valuable modality in diagnosing intraocular disease in adjunct to microbiological evaluation [16]. In the present study also, cytological evaluation of vitreous in endophthalmitis cases showed the presence of neutrophils (87%%, $n = 14$), monocytes (75%, $n = 12$) and lymphocytes (68.8%, $n = 11$).

In our study, the level of expression of TLR2 and TLR4 on CD14 + cells was evaluated by calculating MFI from fluorescence histogram. In vitreous TLR2 evaluation of endophthalmitis patients, MFI of more than 1 was seen in 93.75% of cases and MFI of TLR4 was observed to be more than 1 in 100% cases ($n = 16$). This result suggests that upregulation of TLR2 and TLR4 can be detected from the vitreous samples of endophthalmitis patients. To the best of our knowledge, this is the first study on the detection of TLRs from the human vitreous of endophthalmitis patients. Since the level of detection of TLRs in endophthalmitis cases is high, it may be possible that the neutrophils and monocytes were attracted to the site of infection. The negative culture results in the majority of the cases do not rule out endophthalmitis as there was a delay in inoculation of samples due to logistic reasons. In various studies, the culture positivity results in endophthalmitis seem to vary between 30–63% [17, 18]. The possibility of other microorganisms like fungi or slow growing micro-organisms cannot be excluded. Pan bacterial and pan fungal PCR could be complementary to cultures from the vitreous biopsy in clinical endophthalmitis cases.

With the added knowledge, more weapons can be added to our armor to control the damage caused by the induced inflammatory response. Every effort needs to be done to save the precious vision of the patients. More studies with larger sample size are needed to validate the above result.

Studies conducted by Kumar et al. in experimental mice models of *Staphylococcus aureus* endophthalmitis have shown that microglial cells (macrophages of central nervous system) have surface expression of TLR and with pre-endophthalmitis injection of TLR2 ligand, Pam3cys, and there was decreased inflammation and increased phagocytic response [2]. In experimental *Bacillus cereus*, endophthalmitis that retinal function was preserved to a greater degree in TLR2 and TLR4 deficient mice proving that TLRs are an important component of intraocular inflammatory response in endophthalmitis [16, 19]. The above studies suggest that mechanism of TLR2-mediated immune response in different organisms may be different and level of expression varies with timing of sampling. The role of TLRs and polymorphonuclear neutrophil infiltrations has also been established in fungal endophthalmitis [20].

To identify the systemic influence of endophthalmitis, the blood level of TLRs in CD14 + monocytes was evaluated. In blood, MFI of TLR2 was more than 1 in 100% patients and MFI of TLR4 was more than 1 in 87.5% of patients suggesting upregulation of receptors in blood. However, the blood levels of TLR in cases and controls were comparable. Chang et al. evaluated TLR2 and TLR4 polymorphism in blood neutrophils and monocytes of 9 patients with acute anterior uveitis (AAU) by flow cytometry [5]. They found significant reduction in the level of TLR2 expression in patients of AAU when compared with healthy controls. The 5 of 9 patients with AAU were having a systemic disease, and 7 patients were positive for HLA-B27. So, the possibility of specific alteration could be due to associated systemic disease.

The level of expression of TLR2 in vitreous showed a statistically significant correlation with an increase in the time interval of cataract surgery and intervention for endophthalmitis ($p < 0.05$), but the same was not observed for TLR4. The correlation of TLR with the delay in presentation is suggestive of the increasing inflammatory load and uncontrolled multiplication of invading pathogen with late presentation. This highlights the importance of early intervention in endophthalmitis cases. Further studies are needed to understand the basis of the differential response of TLR2 and TLR4.

To compare if there is any selective perturbation in the level of expression of TLRs, ten age and gender-matched control patients were taken who were undergoing vitrectomy for causes other than an infection. TLR status in vitreous of control patients was not evaluated due to acellularity of the sample. In the blood of control patients, MFI of TLR2 was more than 1 in all patients and MFI of LTR4 was more than 1 in 90% of patients. The elevation of TLR in peripheral blood has been proposed in many non-infective diseases like neurological diseases, glial damage, diabetes mellitus and heart diseases, etc.[21, 22].The understanding of the TLR upregulation in non-infective diseases is still in its infancy. We did not specifically exclude systemic co-morbidities in our control group, and this could explain the presence of TLR in the control group.

The varying level of TLR expression in vitreous may depend upon the precise timing of vitreous sampling, and there may be a dynamic change in the level of TLR expression with the evolution of the disease. The findings of the present study implicate TLR activation in the pathogenesis of endophthalmitis. Further studies involving a greater number of patients are needed to confirm and expand the present findings.

Study limitations

1 The study was conducted on small sample size.
2 The poor culture positivity in our study can be due to non-availability of immediate inoculation of vitreous sample for microbiological evaluation.
3 The timing of vitreous sampling after acquiring the infection was variable. In the control group, the patients with any systemic disease were not excluded which can influence the level of expression of TLRs in blood.

Funding This study was not funded by any other agency.

Compliance with ethical standards

Conflict of interest None of the authors has any conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. (cleared by institutional review board, IEC Regd No. ECR/658/Inst/PB/2014/RR-2017).

Informed consent
Informed consent was obtained from all individual participants included in the study.

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THE EFFECTS OF BODY MASS INDEX AND ATHEROGENIC INDEX ON RETINAL MICROVASCULAR STRUCTURE IN OBESE PATIENTS

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Full Title:	THE EFFECTS OF BODY MASS INDEX AND ATHEROGENIC INDEX ON RETINAL MICROVASCULAR STRUCTURE IN OBESE PATIENTS
Article Type:	Original Article
Keywords:	obesity; atherogenic index; body mass index; optical coherence tomography angiography; retina
Abstract:	Purpose: This study aimed to evaluate the ocular alterations especially on retinal microvasculature of obese patients and to determine the association of these alterations with clinical features. Material and Methods: Height, body weight, blood lipid and glucose levels were recorded in all patients. BMI was calculated.In all participants, biochemical examinations were performed including cholesterol levels, fasting blood glucose, fasting insulin,CRP,Hb A1C levels.The atherogenic index of plasma was calculated as a logarithm of the ratio of the molar concentration (mmol/l) of TG to HDL-C (log [TG/HDL-C]).Patients with a BMI ≤ 25 kg/m 2 were included in the control group. Obese patients were sub-grouped into 3 according to their BMI as group 1 (BMI between 30-34.99 kg/m 2), group 2 (BMI between 35-39.99 kg/m 2), and group 3 (BMI ≥ 40 kg/m 2).The macular and peripapillary thicknesses were measured using an SD-OCT device. The foveal avascular zone (FAZ), the vessel density (VD) of the superficial capillary plexus and deep capillary plexus of the macula, and the VD of the retinal peripapillary capillary plexus (RPCP) for the optic disc were quantified by OCT-A. Results: Totally 110 patients, 27 control cases,and 83 obese patients were included in the study. There was not any significant difference between four groups regarding the gender (p= 0.192). HbA1C, fasting insulin,HOMA-IR,CRP,AI levels were significantly higher in obese patients compared with the control cases. Superficial (p= 0.003) and deep (p= 0.001) VD's of retina significantly decreased and FAZ significantly increased (p= 0.032) in obese patients. In correlation analysis performed between the clinical features and OCT-A findings, the superficial and deep vessel densities inversely correlated with age, BMI, Hb A1C, and AI. Conclusion: Retinal superficial and deep vessel densities are decreased in obese patients and there was an inverse relationship between the retinal vessel densities and age, BMI, Hb A1C, and AI.

THE EFFECTS OF BODY MASS INDEX AND ATHEROGENIC INDEX ON RETINAL MICROVASCULAR STRUCTURE IN OBESE PATIENTS

Short title: OCTA findings in obese patients

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Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Abstract

Purpose: This study aimed to evaluate the ocular alterations especially on retinal microvasculature of obese patients and to determine the association of these alterations with clinical features.

Material and Methods: Height, body weight, blood lipid and glucose levels were recorded in all patients. BMI was calculated.In all participants, biochemical examinations were performed including cholesterol levels, fasting blood glucose, fasting insulin,CRP,Hb A1C levels.The atherogenic index of plasma was calculated as a logarithm of the ratio of the molar concentration (mmol/l) of TG to HDL-C (log [TG/HDL-C]).Patients with a BMI $\leq$ 25 kg/m^2 were included in the control group. Obese patients were sub-grouped into 3 according to their BMI as group 1 (BMI between 30-34.99 kg/m^2), group 2 (BMI between 35-39.99 kg/m^2), and group 3 (BMI $\geq$ 40 kg/m^2).The macular and peripapillary thicknesses were measured using an SD-OCT device. The foveal avascular zone (FAZ), the vessel density (VD) of the superficial capillary plexus and deep capillary plexus of the macula, and the VD of the retinal peripapillary capillary plexus (RPCP) for the optic disc were quantified by OCT-A.

Results: Totally 110 patients, 27 control cases,and 83 obese patients were included in the study. There was not any significant difference between four groups regarding the gender (p= 0.192). HbA1C, fasting insulin,HOMA-IR,CRP,AI levels were significantly higher in obese patients compared with the control cases. Superficial (p= 0.003) and deep (p= 0.001) VD's of retina significantly decreased and FAZ significantly increased (p= 0.032) in obese patients. In correlation analysis performed between the clinical features and OCT-A findings, the superficial and deep vessel densities inversely correlated with age, BMI, Hb A1C, and AI.

Conclusion: Retinal superficial and deep vessel densities are decreased in obese patients and there was an inverse relationship between the retinal vessel densities and age, BMI, Hb A1C, and AI.

Key Words: obesity, atherogenic index, body mass index, optical coherence tomography angiography, retina

INTRODUCTION

Obesity is an important public health concern worldwide, which is associated with increased risk for cardiovascular morbidity and mortality (1). Obesity, diabetes, dyslipidemia, insulin resistance, smoking and, hypertension are well-known risk factors that affect the vascular endothelium and endothelial response to the oxidative stress; resulting in microvascular remodeling (2-4). Nowadays, the atherogenic index of plasma is regarded as a novel predictive biomarker for cardiovascular diseases (5).

Microvascular dysfunction is considered a crucial pathway in the development and progression of cardio-metabolic diseases. Inflammatory processes, oxidative stress, and endothelial dysfunction are the main mechanisms of microvascular dysfunction (6). Metabolic diseases are also known to have severe effects on the structure of the retinal circulation, mostly associated with endothelial dysfunction and inflammation (7). However, the data regarding the effects of obesity on ocular functions and retinal microvasculature is limited. Nowadays, retinal microvasculature is an easy-to-reach network structure where we can get the easiest and fastest information about the microvascular network all over the body by non-invasive methods (8). Retinal vessel diameters were shown to have a predictive role for long-term adult cardiovascular outcomes and atherosclerotic cardiovascular diseases (9). In daily ophthalmology practice,

optical coherence tomography (OCT) is a widely used, non-invasive imaging method that offers high-resolution cross sectional scanning of ocular tissues. Moreover, with the development of spectral domain OCT (SD-OCT), the sensitivity and speed of OCT systems are increased, enabling to visualize blood vessels through repeated scans. OCT angiography (OCT-A), provides detailed data on the microvascular structure of the retina and the choroid.

This study aimed to evaluate the ocular alterations especially on retinal microvasculature of obese patients and to determine the association of these alterations with atherogenic index and body mass index.

MATERIAL and METHOD

This retrospective study was performed in the ophthalmology department of Erzincan Binali Yıldırım University, Faculty of Medicine, Mengucek Gazi Training and Research Hospital between September 2019 and March 2020. The study was approved by the local ethics committee and performed in concordance with the principles of the 2008 Declaration of Helsinki. Informed consent was obtained from the participants.

Study population

Patients between the ages of 18 and 60 years, who were followed in our obesity center and agreed to participate in the study were included. The other inclusion criteria were as follows: refractive error $\leq \pm 1$ D or axial length between 22 and 24 mm, visual acuity $\geq$ 20/20, intraocular pressure $\leq$ 21 mmHg. Patients younger than 18 and older than 60 years of age, patients under treatment for diabetes mellitus, hyperlipidemia, or hypertension or any suspicious findings related to these diseases, patients diagnosed with any other systemic diseases such as sleep apnea syndrome, psychiatric disorders, cardiovascular diseases, kidney or renal failure, acute or chronic infection, anemia, thyroid pathologies that could affect the measurements were excluded from the study. Participants with a history of alcohol or drug use and smoking participants were excluded from the study. Extensive biochemical evaluation was performed by taking fasting venous blood samples of all participants. Patients with any pathology in their values were excluded from the study. Patients having any ocular diseases (such as ectatic corneal diseases, chorioretinal

diseases, cataract, glaucoma etc.) or ocular surgery were also excluded from the study. All patients were evaluated in endocrinology outpatient clinics, and patients with diabetes mellitus were not included in the study.

Height, body weight, and blood lipid and glucose levels were recorded in all patients. Body mass index (BMI) was calculated using the following formula: BMI = body weight (kg)/height^2 (m^2).

In all participants, for biochemical examinations, after 8h of fasting, 5 mL of venous blood was obtained from the cubital vein the following morning. Levels of total cholesterol (TC), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride (TG), fasting blood glucose (FBG), fasting insulin, and hemoglobin A1c (HbA1c) levels were determined. The Homeostasis Model Assessment of IR (HOMA-IR) was calculated for the assessment of insulin resistance (11). For the evaluation of subclinical inflammation, C-reactive protein level was studied. The atherogenic index of plasma (AI) was calculated as a logarithm of the ratio of the molar concentration (mmol/l) of TG to HDL-C (log [TG/HDL-C]) (12).

Patients with a BMI $\leq$ 25 kg/m^2 were included in the control group. All obese participants had a history of at least 5 years of obesity. Obese patients were sub-grouped into 3 according to their BMI as group 1 (BMI between 30-34.99 kg/m^2), group 2 (BMI between 35-39.99 kg/m^2), and group 3 (BMI $\geq$ 40 kg/m^2). Overweight patients having a BMI between 25.01 and 29.99 were not included in the study.

Detailed ocular examinations were performed in all patients. All participants underwent detailed ophthalmologic examinations. In this context, refraction measurement (Tonoref III, Nidec Co. Ltd, Aichi, Japan), best corrected visual acuity, slit lamp biomicroscopy, indirect ophthalmoscopy, non-contact biometry (AL-SCAN, Nidek Co. Ltd, Aichi, Japan), intraocular pressure (IOP) (Tonoref III, Nidec Co. Ltd, Aichi, Japan) measurement were carried out. Retinal nerve fiber layer thickness (RNFLT), central macular thickness (CMT), and ganglion cell layer thickness (GCLT) were measured by SD-OCT , FAZ and VD measurements examined by OCT-

A (RS-3000 Advance AngioScan (Nidek Co. Ltd, Gamagori, Japan)). Only the right eyes of the participants were examined.

Scan Protocol

The macular and peripapillary thicknesses were measured using an SD-OCT device (Nidek Co. Ltd., Aichi, Japan). The foveal avascular zone (FAZ), the vessel density (VD) of the superficial capillary plexus (SCP) and deep capillary plexus (DCP) of the macula, and the VD of the retinal peripapillary capillary plexus (RPCP) for the optic disc were quantified by OCT-A (RS-3000 Advance, Nidek Co. Ltd., Gamagori, Japan). The Nidek RS-3000 Advance OCT system and updated AngioScan software were used to evaluate SD-OCT and OCT-A images. The fovea is focused on using an OCT-A prototype internal fixation lamp, and 3x3 mm macula cubes, each consisting of 256 B-scans are generated. For RPCP, the scans included a 2.4 × 4 mm disc map centered on the optic nerve head. The macular and peripapillary vascular density as well as FAZ can be automatically calculated with this device.

The SD-OCT and OCT-A measurements were performed by an experienced ophthalmologist after pupil dilation with 1% tropicamid eye drop (Tropamid, Bilim Ilac Ltd, Istanbul, Turkey). In cases where the signal strength index quality was <7/10, scanning was repeated. The FAZ and VD measurements in the superficial capillary plexus (Figure 1) and deep capillary plexus were measured. The automated segmentation determines the en face slab for the superficial retinal layer and deep retinal layer to extend from the internal limiting membrane to 13 μm below of the inner nuclear layer, and 8 μm below of the inner nuclear layer to 13 μm below of the outer nuclear layer respectively. VD was calculated as the percentage area occupied by flowing blood vessels in the selecting region. The VD of the retinal peripapillary capillary plexus (RPCP) for the S/I and TSNIT sectors can be observed from the OCT-A scans of the peripapillary area (Figure 2).The average retinal nerve fiber layer thickness (RNFLT) and central macular thickness (CMT) were also measured through SD-OCT analysis.

Statistical Analyses

Statistical analyses were performed with the SPSS version 21.0 (SPSS Inc, Chicago Illinois) statistical program. The parametric variables were expressed with mean ± standard deviation, while categorical variables were expressed with percentage (%). In the comparison of

parametric data between 2 independent groups, an independent sample t-test was performed. For non-normally distributed data, the analysis was performed with the Mann-Whitney U test. In more than two group comparisons; One-Way Anova and Bonferroni post-hoc analysis were used for parametric data. Pearson correlation analysis was performed to determine the association of clinical parameters with the OCT-A findings. $P<0.05$ was regarded as statistically significant.

RESULTS

Totally 110 patients, 27 control cases (24 female, 3 male), and 83 obese patients (62 female, 21 male), were included in the study. There was not any significant difference between the control cases and obese patients regarding gender (p= 0.180).

The participants were grouped into four according to their BMI as follows;

Control group: BMI between 20-25 $kg/m^{2:}$ 27 patients (24 female, 3 male)

Group 1: BMI between 30-35 $kg/m^{2:}$ 27 patients (21 female, 6 male)

Group 2- BMI between 35.01-40 $kg/m^{2:}$ 27 patients (22 female, 5 male)

Group 3- BMI > 40 $kg/m^{2:}$ 29 patients (19 female, 10 male)

There was also not any significant difference between the four groups regarding gender (p= 0.192).

Demographic features and laboratory data of the study participants are summarized in Table 1. Hemoglobin A1C, fasting insulin, HOMA-IR, CRP, TG, HDL-C, and AI levels were significantly different between groups (p=0.008, p=0.001, p=0.001, p=0.001, p=0.015, p=0.001, p=0.008, respectively).

Ocular findings of study participants are summarized in Table 2. There was not any significant difference between groups regarding the RNFLT, GCLT, CMT, or RPCP values. However, superficial and deep global vessel densities were significantly decreased in obese

patients (p=0.003, p=0.001, respectively). FAZ measurements were significantly higher in obese patients (p=0.032).

In correlation analysis performed between the clinical features and OCT-A findings, there VD superficial and deep vessel densities inversely correlated with age, BMI, HbA1c, and AI; while FAZ only correlated with the BMI (Table 3).

DISCUSSION

In this study, we investigated the ocular findings in obese patients and we did not determine any significant alteration in retinal nerve fiber layer thickness, ganglion cell layer thickness, central macular thickness, or radial peripapillary capillary plexus vessel density with obesity or with an increase in BMI. However, both superficial and deep vessel densities of retina decreased with obesity. To the best of our knowledge, this is the first study evaluating the relationship of retinal vascular alterations with metabolic parameters in obese patients and we determined that with an increase in age, BMI, Hb A1C and/or, atherogenic index, superficial and deep vessel densities of the retina was decreasing significantly.

In recent years, the OCTA device has been widely used due to its short imaging time and no side effects. Nidek has recently updated the AngioScan software, but the normative data for the new version of the device are limited in the literature (10). Although it is not possible to standardize the measured values since different gravity techniques are used in different OCTA devices, the benefit of the evaluated data in the ophthalmology clinics is obvious in terms of evaluating the retinal microvascular structure.

Obesity is a well-known risk factor for microvascular alterations and remodeling. In this study, we investigated the ocular changes in retinal microvasculature in obese patients and associations of these alterations with metabolic parameters. We determined an inverse correlation between BMI and superficial and deep retinal vessel densities. Similar to our results, in a meta-analysis, Köchli et al reported that a higher BMI was associated with narrower retinal arteriolar and wider venular diameters in children (13). In another meta-analysis Boilot et al (14) also reported that higher BMI was associated with narrower retinal arteriolar and wider venular

calibers. We also determined a significant decrease in both superficial and deep vessel densities of the retina with an increase in BMI.

With an increase in BMI, there was a significant increase in AI, and a significant decrease in superficial and deep vessel densities of the retina. Moreover, there was an inverse significant correlation between AI and vessel densities. To the best of our knowledge, this is the first study in the literature evaluating the association of AI with OCT-A findings. On the same way with our findings, Krasnicki et al (15) reported that flow disturbances within the ocular blood vessels of patients with type 2 diabetes were associated with atherogenic changes of coronary arteries. In a population-based cohort study, Shankar et al (16) reported that wider retinal venules were positively associated with the risk of developing obesity, suggesting a role for microvascular dysfunction in early periods of obesity. However, in a recent population-based cohort study, it was reported that; age and FPG were inversely associated with retinal microvascular functions, but 24-h systolic blood pressure, waist circumference, and total-to-HDL cholesterol ratio were not associated with these microvascular functions (17). Xiao et al (18) also reported that adolescents with dyslipidemia had significantly narrower retinal arteriolar diameters compared with normolipidemic counterparts, but they did not determine any significant relationship between lipid subclass levels and central retinal venular equivalent. We also determined an inverse relationship between age and the retinal vasculature. Nowadays, the atherogenic index of plasma is regarded as a novel predictive biomarker for cardiovascular diseases and we believe that it may also be playing an important role in vascular alterations of the retina (5, 19).

Hb A1C has been defined to have a prognostic value for cardiovascular diseases in non-diabetic patients (20, 21). In this study on non-diabetic patients, we also determined that there was a significant increase in Hb A1C levels with an increase in BMI in obese patients and there was an inverse correlation between HbA1c and superficial and deep vessel densities of the retina.

In this study, we did not determine any association between serum CRP levels and OCT-A findings. In previous literature, the data regarding the association of CRP levels with cardiovascular risk assessment is conflicting (22, 23). Though CRP is a sign of inflammation, it may be affected by many other factors and in this study, though in obese patients, the mean CRP levels were significantly higher than that of the control cases, the CRP levels were still low. The low differences in mean CRP levels between groups may be associated with the exclusion of all

patients with any chronic diseases from the study. This low difference may be the reason, we did not determine any association between the CRP levels and OCT-A findings.

There are some limitations of this study that should be mentioned. First is that, though we excluded all patients with any systemic diseases including primary hypertension, we did not note systolic and diastolic blood pressure values, which are parameters that could affect OCTA measurements. Secondly, while there was not any significant difference between groups regarding gender, evaluating males and females in different groups may be more appropriate, since metabolic factors may have different effects on both genders. The other limitation is overweight patients having a BMI between 25.01 and 29.99 were not included in the study because there was no follow-up patient with these BMI values in the obesity center.

In conclusion, retinal superficial and deep vessel densities are decreased in obese patients and there was an inverse relationship between the retinal vessel densities and age, BMI, Hb A1C, and AI. Recently retinal vessel alterations are shown to be sensitive microvascular biomarkers for cardiovascular risk stratification. Due to the association of these retinal vasculature alterations, which can be investigated with non-invasive methods, we suggest that retinal vasculature should be evaluated in patients with metabolic risk factors, such as elevated AI, BMI and older age, to treat these vascular alterations as early as possible and predict the cardiovascular morbidity and mortality at early stages. It is obvious that the cross-sectional data can provide limited information in this study where the atherogenic index and BMI effects were investigated on the OCTA measurements. We are currently performing a follow-up study to better explain this findings.

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Legends:

Table 1. Demographic features and laboratory data of the study participants.

Table 2. Ocular findings of the study participants.

Table 3. Correlation analysis performed between the clinical features and OCT-A findings.

Figure 1. OCTA image of a 29-year-old woman with BMI = 32 kg / m^2 . The FAZ metrics were autodetected by the AngioScan software. The image also displays VD measurements in the SCP layer.

Figure 2. Peripapillary vessel density colored map and VD distribution at the level of the RPCP of the same subject at the figure 1.

colour figure

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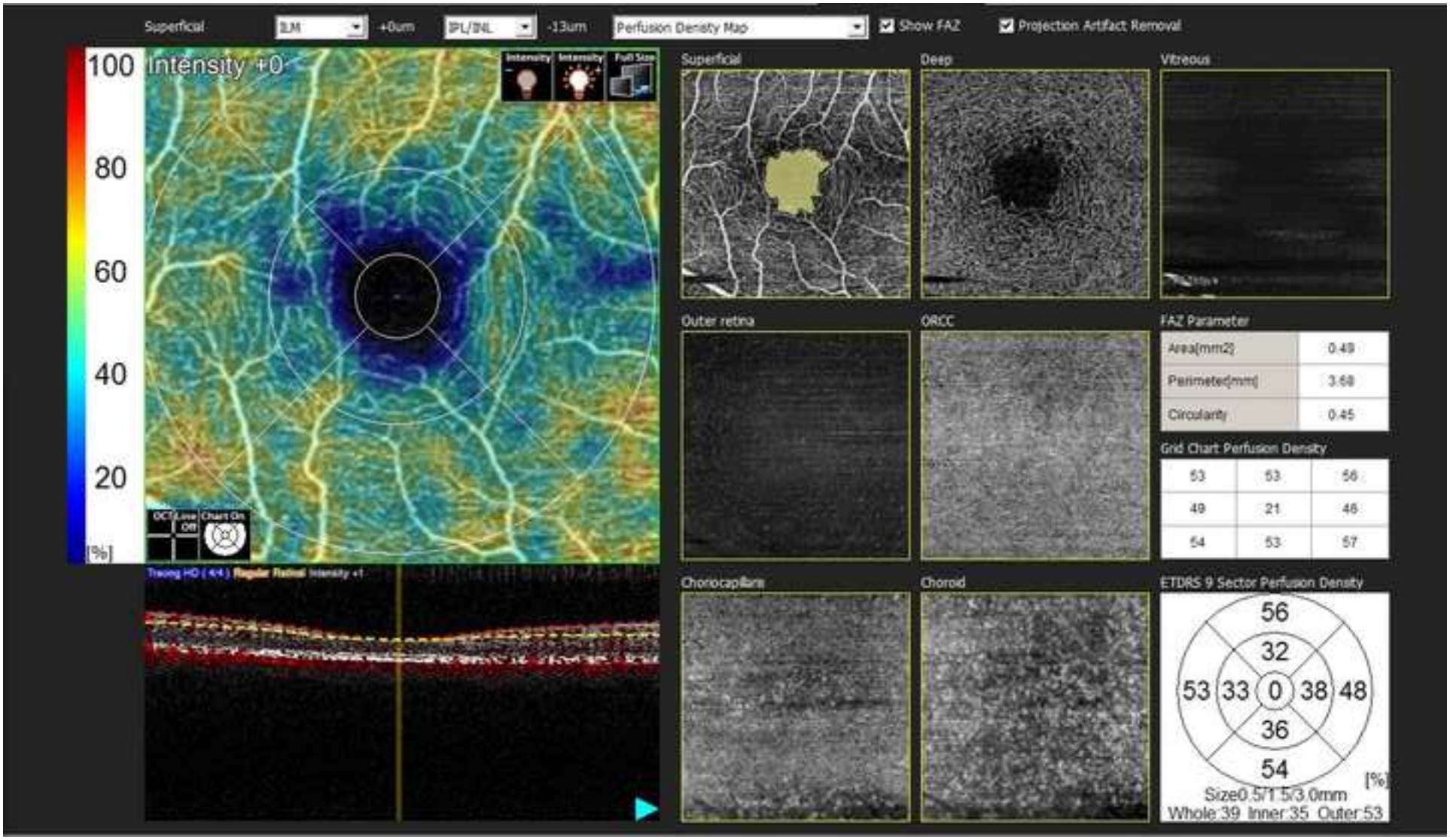

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Table 1. Demographic features and laboratory data of the study participants.

	Control group (BMI between 20-25 kg/m^2) (n:27)	**Group 1** (BMI between 30-35 kg/m^2) (n:27)	**Group 2** (BMI between 35.01-40kg/m^2) (n:27)	**Group 3** (BMI > 40 kg/m^2) (n:29)	**P-value**
Age (years)	42.03±10.44	43.12±10.87	39.55±9.97	39.41±10.32	0.122
FBG (mg/dL)	89.18±15.28	89.22±11.87	93.77±10.22	95.86±7.10	0.112
HbA1c (%)	5.28±0.25	5.40±0.30	5.51±0.24[b]	5.54±0.27[c]	**0.008**
Fasting insulin (µIU/mL)	6.48±5.26	12.26±6.17[a]	12.55±6.82[b]	14.76±10.61[c]	**0.001**
HOMA-IR	1.41±1.12	2.75±1.53[a]	2.76±1.59[b]	3.63±2.93[c]	**0.001**
CRP (mg/L)	2.71±1.63	6.99±4.31[a]	7.74±4.15[b]	7.96±4.36[c]	**0.001**
Total cholesterol (mg/dL)	178.15±36.79	193.80±46.97	186.34±39.69	179.23±41.60	0.115
TG (mg/dL)	104.18±55.69	125.31±40.28[a]	129.65±48.52[b]	134.09±53.5[c]	**0.015**
HDL-C (mg/dL)	51.20±5.61	43.35±11.17[a]	43.15±9.59[b]	42.78±8.72[c]	**0.001**
LDL-C (mg/dL)	106.11±29.40	118.74±44.26	119.25±33.15	119.46±37.00	0.082
AI	-0.08±0.015	0.022± 0.025[a]	0.066±0.019[b]	0.071±0.025[c]	**0.008**

FBG: Fasting blood glucose, HbA1c: hemoglobin A1C, CRP: C-reactive protein, HDL-C: high-density lipoprotein-cholesterol, LDL-C: low-density lipoprotein-cholesterol, AI: atherogenic index, [a]: statistically significantly different when group 1 is compared with the control group; [b]: statistically significantly different when group 2 is compared with the control group; [c]: statistically significantly different when group 3 is compared with the control group. The significant P values expressed with bold style.

Table 2. Ocular findings of the study participants

	Control group (BMI between 20-25 kg/m^2) (n:27)	**Group 1** (BMI between 30-35 kg/m^2) (n:27)	**Group 2** (BMI between 35.01-40kg/m^2) (n:27)	**Group 3** (BMI > 40 kg/m^2) (n:29)	**P-value**
RNFLT,average (µm)	115.29±5.09	111.25±9.76	108.22±14.24	110.03±9.23	0.73
GCLT, sup (µm)	101.03±3.76	100.11±7.60	97.85±8.78	99.27±7.70	0.532
GCLT, inf (µm)	103.96±5.77	101.55±7.31	100.66±9.06	103.55±8.52	0.307
CMT (µm)	260.40±14.00	260.63±20.50	259.18±24.56	265.10±21.26	0.698
RPCP VD (%)	54.01±3.23	54.37±4.02	53.44±3.82	53.51±2.97	0.834
FAZ (mm$^{2)}$	**0.32±0.083**	**0.40±0.13^a**	**0.41±0.15^b**	**0.41±0.21^c**	**0.032**
SCP VD (%)	**43.77±1.80**	**40.48±4.40**	**39.37±5.50^b**	**37.62±5.88^c**	**0.003**
DCP VD (%)	**38.03±3.56**	**32.33±7.98^a**	**32.69±7.48^b**	**29.74±7.96^c**	**0.001**

RNFLT: retinal nerve fiber layer thickness, GC: ganglion cell layer thickness, sup: superior, inf: inferior, CMT: central macular thickness, RPCP: radial peripapillary capillary plexus, FAZ: foveal avascular zone, VD: vessel density, SCP: Superficial capillary plexus, DCP: Deep capillary plexus. [a]: statistically significantly different when group 1 is compared with the control group; [b]: statistically significantly different when group 2 is compared with the control group; [c]: statistically significantly different when group 3 is compared with the control group. The significant P values expressed with bold style.

Table 3. Correlation analysis performed between the clinical features and OCT-A findings.

	FAZ		**VD superficial**		**VD deep**	
	r	p	r	p	r	p
Age (years)	0.086	0.373	-0.190	**0.045**	-0.218	**0.022**
BMI	0.275	**0.004**	-0.354	**0.001**	-0.349	**0.001**
HbA1c	0.022	0.818	-0.190	**0.046**	-0.189	**0.048**
HOMA-IR	0.022	0.817	-0.044	0.649	-0.027	0.783
CRP	0.111	0.249	-0.129	0.180	-0.145	0.131
AI	0.113	0.157	-0.254	**0.007**	-0.213	**0.026**

BMI: Body mass index, HbA1c: hemoglobin A1C, CRP: C-reactive protein, AI: atherogenic index. The significant P values expressed with bold style.

THE EFFECTS OF BODY MASS INDEX AND ATHEROGENIC INDEX ON RETINAL MICROVASCULAR STRUCTURE IN OBESE PATIENTS

Short title: OCTA findings in obese patients

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Emin Murat AKBAS[3], MD, Assoc. Prof.; Aykut ICEL[4], MD, Specialist; Yusuf Kemal ARSLAN[5]

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Conflict of interest:

Erel Icel has no conflict of interest.

Nergis Akbas has no conflict of interest.

Emin Murat Akbas has no conflict of interest.

Aykut Icel has no conflict of interest.

Yusuf Kemal Arslan has no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Dear editor,

Our manuscript entitled "The Effects of Body Mass Index on Retinal Microvascular Structure in Obese Patients" is an original study. As you know, obesity has been associated with various ocular pathologies. In this study, we investigated optical coherence tomography angiography in cases with obesity and the relation of these measurements with body mass index, atherogenic index. To the best of our knowledge, no previous studies have investigated the potential relationship. Thus this is the first study in this field. With respect to this study, the authors do not have any financial or proprietary interests.

Sincerely yours

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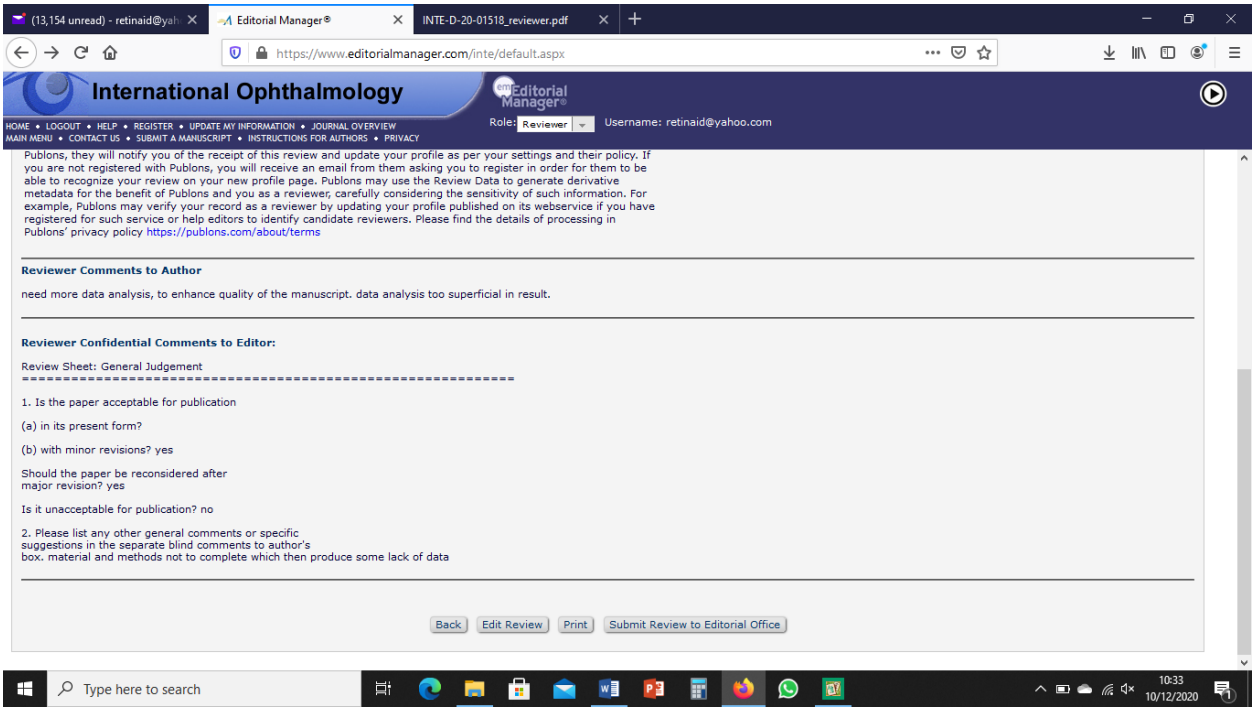
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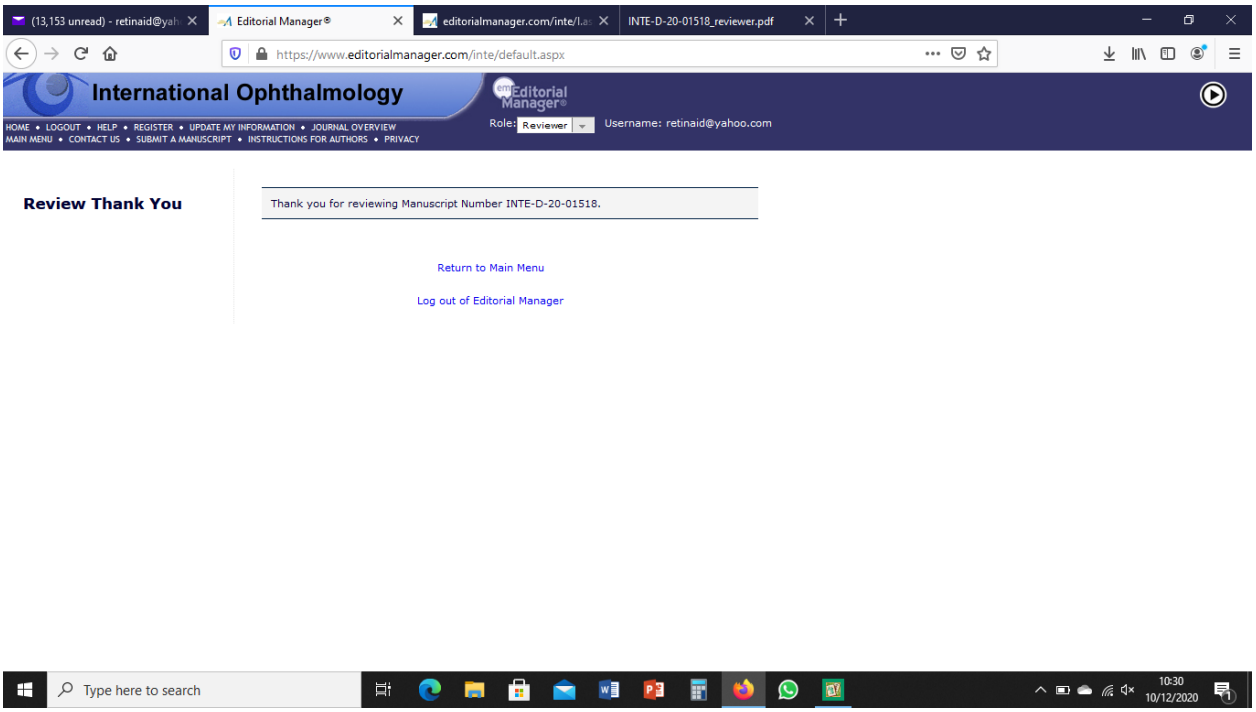
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Article type: Short Report

Author: Dr Canestraro

Journal: Eye and Brain

Abstract:
Introduction: The classic presentation of pigmentary dispersion syndrome often consists of midperipheral iris transillumination defects, Krukenberg's spindle, and dense homogeneous trabecular pigmentation. Other subtle, sometimes overlooked features include: pigment on the lens zonules, pigment on the anterior lens capsule and on the posterior lens capsule along the equator.
Case: This is a novel presentation of pigmentary dispersion syndrome with bilateral, dense, oblique and curvilinear deposition of pigment along the posterior lens capsule that changed in shape, density and extent over the span of three years.
Discussion: There have been few reports in the literature that describe a central accumulation of pigment along the posterior lens capsule associated with pigmentary dispersion syndrome. There are reported cases of pigment deposition along the central aspect of the posterior lens capsule, some changing over time, although none were bilateral and symmetric. There are suggestions that perhaps this central pigment deposition is related to a break in the ligament of Weiger, allowing communication between the posterior chamber and posterior lens capsule. Evidence of this disruption was not found in our patient. This is a case in which curvilinear, symmetric and changing pigment deposition on the posterior lens capsule is suggestive of a novel presentation of pigmentary dispersion syndrome that calls for further investigation to determine its association.

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SHORT REPORT

Curvilinear, symmetrical, and profound pigment deposition on the posterior lens capsule in a patient with bilateral pigmentary dispersion syndrome

This article was published in the following Dove Press journal:
Eye and Brain

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Jerome Sherman[2]

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Introduction: The classic presentation of pigmentary dispersion syndrome (PDS) often consists of midperipheral iris transillumination defects, Krukenberg's spindle, and dense homogeneous trabecular pigmentation. Other subtle, sometimes overlooked features include pigment on the lens zonules, pigment on the anterior lens capsule and pigment along the equator of the posterior lens capsule.

Case: This unique presentation of PDS presented with bilateral, dense, oblique, and symmetrical pigment deposition along the posterior lens capsule that changed in shape, density, and extent over the span of 3 years.

Discussion: There have been few reports in the literature that describe a central accumulation of pigment along the posterior lens capsule associated with PDS. There are reported cases of pigment deposition along the central aspect of the posterior lens capsule, some changing over time, although none were bilateral and symmetrical. There are suggestions that perhaps this central pigment deposition is related to a break in the ligament of Weiger, allowing communication between the posterior chamber and posterior lens capsule. This is a case in which curvilinear, symmetrical, and changing pigment deposition on the posterior lens capsule is suggestive of perhaps another key features of PDS.

Keywords: pigment deposition, ligament of Weiger, space of Berger, zonules, pigmentary glaucoma

Introduction

Pigmentary dispersion syndrome (PDS) has many distinct clinical features that aide in its diagnosis and management. Ritch et al[1] estimated the prevalence of PDS to be 2.45% of Caucasian patients in a glaucoma screening. Roberts et al[2] estimated the prevalence of PDS to be 0.0015% of African Americans in a primary care setting. These estimates are likely disparate because of the difference in phenotypic expression between the two ethnicities, as noted by Roberts et al.[2] Although PDS is autosomal dominant in nature[3] for both African American and Caucasian populations, it is thought to have incomplete penetrance in the African American population.[4] Myopia has been noted as a significant corollary to PDS. Scheie and Cameron[5] reported the incidence of myopia to be 65% in a group of 493 eyes with PDS, regardless of ethnicity. The classic clinical presentation of PDS includes midperipheral iris transillumination defects, Krukenberg's spindle, and dense homogeneous trabecular pigmentation.[6] Other clinical

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features that are often overlooked may include pigment on the lens zonules[7] and pigment on the anterior and posterior lens capsule.[8] It is estimated that patients with PDS have a 35%–50% chance of developing pigmentary glaucoma during their lifetime.[9] Below is a case in which the patient presented with many of the known features of PDS, along with an uncommon presentation of symmetrical pigment on both posterior lens capsules with changes in morphology and density over time.

Case

A 45-year-old Caucasian male initially presented with reduced acuities in both eyes since childhood. His medical and family history was unremarkable, with best-corrected acuities 20/60 in each eye and correction –8.00–2.00×135 OD and –8.00–1.25×020 OS. External examination was normal, but slit lamp examination revealed midperipheral iris transillumination defects (Figure 1), pigment on the corneal endothelium and dense, and symmetrical pigment on the posterior lens capsules. Gonioscopy revealed angles open to ciliary body with grade 2+ pigment in all quadrants and no evidence of angle recession. Intraocular pressures (IOPs) were 17 and 18 mmHg in each eye. Dilated fundus examination with binocular indirect ophthalmoscopy and scleral depression revealed an intact retina, with no holes or tears and no signs of pigmented cells in the vitreous. The optic nerves were small: ~1 mm ×1 mm as measured with Spectral Domain Optical Coherence Tomography (SD-OCT; © 2017; Carl Zeiss Meditec AG, Jena, Germany). We confirmed optic disc hypoplasia in both eyes as the likely cause of the patient's decreased vision. Over the course of 3 years, the IOP remained in the 15–19 mmHg range in both eyes. During this time, retinal nerve fiber layer thinning and corresponding visual field defects were evident. Given the presence of optic nerve hypoplasia in addition to PDS, it was difficult to assess the damage solely related to glaucomatous changes. For this reason, glaucoma therapy was initiated using Travatan Z ophthalmic solution once daily in both eyes. IOPs remained stable at 13 mmHg in each eye, and he continues to be monitored for any changes. Of particular interest was the unusual presentation of pigment deposition on the posterior lens capsules of each eye. The pattern of pigment was dense, oblique, and curvilinear and located along the posterior lens capsules (Figure 2). The pigment on the posterior capsule created shadows on the retina, which were best documented with Optos Daytona ultra-widefield imaging (© 2017; Optos plc, Dunfermline, UK), which provides ultra-widefield fundus imaging (Figure 3). Over time, it appeared that there was an increase in pigment deposition along the posterior lens capsule. Comparing photos 1 year apart, one can observe the apparent increase in the size of pigment deposition (Figure 4A and B). Interestingly, photos taken 2 years later showed a marked decrease in pigment deposition on the posterior lens capsules (Figure 5). There were no changes in the patient's medical history in that same time span, including a repeated denial of medication changes or incidents of trauma. A search of literature published in the last 15 years did not reveal any cases of bilateral, dense, and symmetrical pigment deposition on the posterior lens capsule with a change in morphology over time.

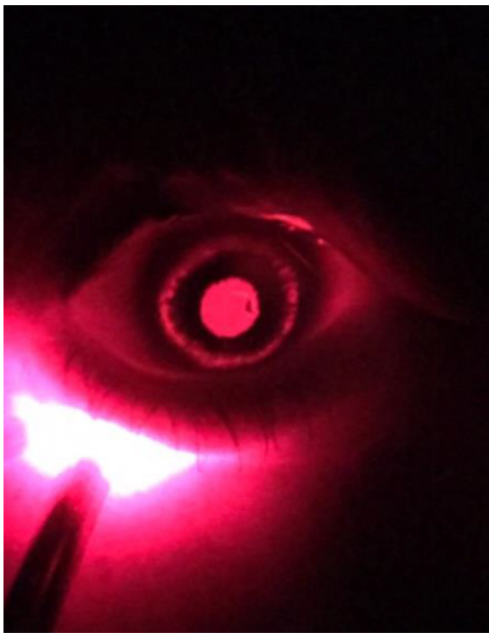

Figure 1 Midperipheral iris transillumination defects of the left eye, seen by direct illumination of the globe via transilluminator applied directly to lower lid in the dark.
Note: Transillumination of the fellow eye was almost a mirror image compared to the left.

Informed consent

The patient described in this case has given written informed consent to have the case details and accompanying images published.

Discussion

A ring-shaped deposition of pigment on the equator of the posterior lens capsule along the zonular attachments can be found in patients with PDS.[7] Proximal to the zonules is the ligament of Weiger, which is the ring-like attachment of the anterior limiting membrane of the vitreous to the posterior lens capsule. Another ring of pigment, known as Scheie's line,

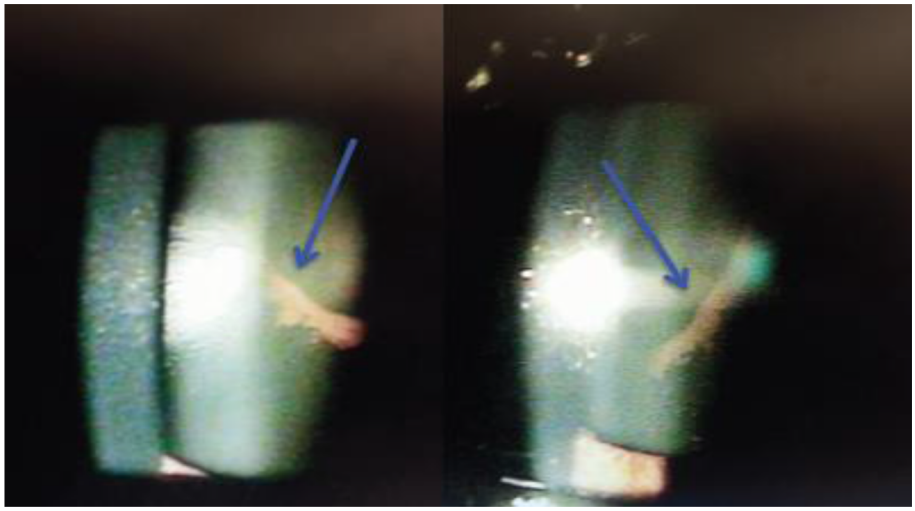

Figure 2 Circumlinear deposition of dense pigment along the posterior lens capsule of each eye.
Notes: The deposition in each eye (arrows) is virtually a mirror image of the other. The view with biomicroscopy of the posterior lens capsule matched the "shadow" seen with ultra-widefield images on each visit as seen in Figures 3–5.

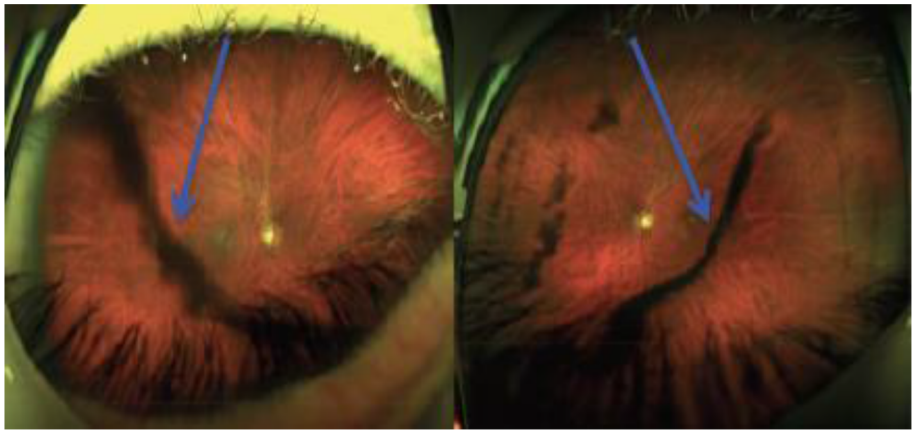

Figure 3 Optos Daytona ultra-widefield imaging of each eye reveals shadows cast on the fundus from the pigment on the posterior lens capsule.
Note: These images also highlight the symmetry of pigment deposition (arrows) in the two eyes.

can deposit at the juncture of the ligament of Weiger.[8] The ligament of Weiger encircles the space of Berger, which is located between the posterior lens capsule and the vitreous.[10] This space is located centrally through the visual axis and is typically void of debris assuming that the ligament of Weiger remains intact.[11] In our patient, we observed an unusual and dramatic deposition of pigment on the central aspect of the posterior lens capsule, which was remarkably symmetrical when comparing one eye with the other. Theoretically, if the ligament of Weiger is intact, there should not be communication between the posterior chamber and the potential space of Berger.[10] In our case, the pigment on the central aspect of the posterior lens capsule appeared to increase and then to decrease in size over time (Figures 4A and B vs Figure 5). A possible explanation for this points to a break in the ligament of Weiger. If there was a break in the ligament of Weiger and the anterior hyaloid remained intact, it would allow aqueous to traverse from the posterior chamber to the space of Berger. The constant flow of aqueous through this space could bring loose iris pigment to deposit on the central aspect of the posterior lens capsule and then over time displace this same pigment to a different location. Given there was no pigment visualized in the vitreous and there were no retinal breaks noted on fundus examination, we believe the pigment cells in our patient originated from the iris, rather than the retina. Roberts et al[11]suggested that a disruption in

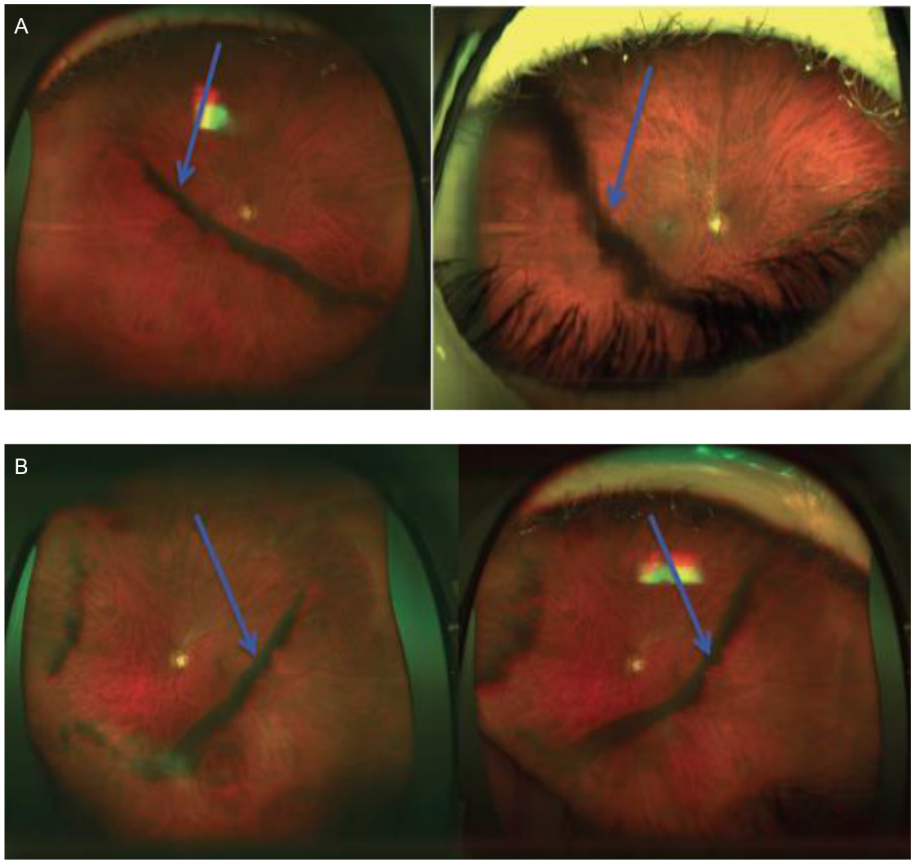

Figure 4 (**A**) Optos Daytona ultra-widefield images highlight an increase in pigment over time of the right eye from 2013 (left) to 2014 (right). (**B**) Optos Daytona ultra-widefield images highlight an increase in pigment over time of the left eye from 2013 (left) to 2014 (right).
Note: These are visualized by the shadows cast on the retina (arrows) from the pigment deposition along the posterior lens capsule.

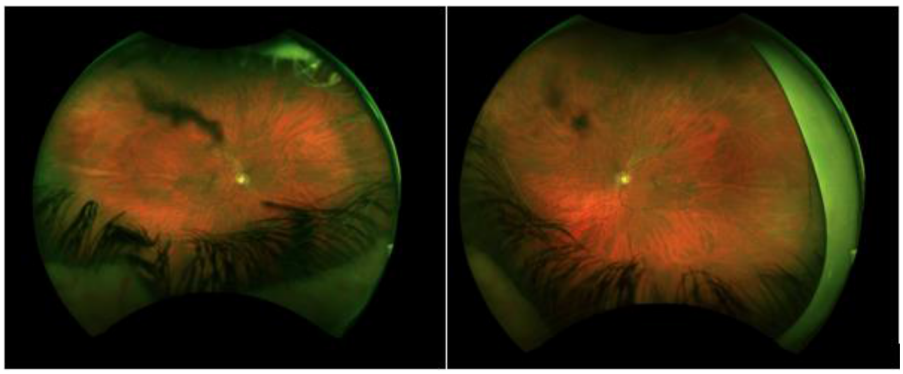

Figure 5 Optos California images from 2016 reveal a decrease in pigment over time of the right eye (left) and left eye (right) compared to 2013 and 2014 (Figure 4A and B).
Notes: These are visualized by the shadows cast on the retina from the pigment deposition along the posterior lens capsule.

this natural barrier, such as with trauma, may allow pigment to enter the potential space of Berger. However, a bilateral break in the ligament of Weiger is rare without trauma and, therefore, remains to be explained. It should be noted that the commencement of travoprost drops after the first 3 years of observation could have had an effect on the change in pigment. We do not feel that this change is significant, given that pigment deposition also decreased over time while on the same medication. Additionally, photos in Figure 4A and B were taken by the Optos Daytona and those in Figure 5 were taken by Optos California Daytona ultra-widefield imaging (© 2017; Optos plc). We do not believe that this would have

a significant impact on imaging the pigment on the posterior lens capsule.

There are few cases in the literature that describe findings of bilateral and symmetrical pigment deposition on the posterior lens capsule with changes in morphology over time. Al-Mezaine[12] reported a case of unilateral pigment deposition with a history of trauma in that same eye. Nagarajaiah and Shun-Shin,[13] Lin et al,[14] and Turgut et al[15] describe cases of unilateral pigment deposition on the posterior lens capsule without a history of trauma. Nagarajaiah's case is similar to ours in that the pigment was noted to change over time. Roberts et al[11] reported a case of bilateral pigment deposition with the history of trauma in only one eye and a second case of unilateral pigment deposition without trauma. His first case is most similar to ours in that there was bilateral pigment deposition; however, his patient did not present with symmetry between the two eyes, nor was it noted to change over time.

As hypothesized earlier, a break in the ligament of Weiger is the only way in which pigment can reach the space of Berger. Since cases of spontaneous breaks in the ligament of Weiger are rare,[16] we propose another mechanism for this break. Bernal et al[17] were able to describe and document the precise insertion of the anterior and posterior zonules to the lens capsule. Traditionally, it was thought that both the anterior and posterior zonules began at the ciliary body and inserted directly to the lens. Bernal confirmed that the anterior zonules have a straight path from the ciliary body to the lens. However, the majority of the posterior zonules first inserted into the anterior hyaloid membrane proximal to the ciliary body and then to the lens capsule. Some of these fibers inserted into areas close to Weiger's ligament before adhering to the posterior lens capsule.[17] If one could imagine the posterior bowing of the iris in a patient with PDS and its relationship to the anterior zonules, it could be perceived that such rubbing against the anterior zonules could also affect the posterior zonules, especially those which are directly adherent to the ligament of Weiger. After years of chronic contact, this would promote detachment of the ligament of Weiger, thereby allowing pigment to enter the space of Berger. Given that central posterior lens capsule pigmentation is not common in all patients with PDS, we propose that the amount of iris bowing may be related to this mechanical break in the ligament and perhaps a more concave iris would be more likely to cause a break in the ligament. The degree of iris concavity was not measured in our case but perhaps opens an area for future research.

The unusual presentation of the density, symmetry, and changing morphology of pigment has not been described previously in literature. This has clinical significance because if the known and sometimes subtle findings of PDS such as Krukenberg's spindle, iris transillumination defects, and pigmented trabecular meshwork are initially overlooked by the examiner, observation of pigment on the posterior lens capsule may promote the examiner to check for these features more closely. Additionally, future studies relating the degree of iris bowing to a break in the ligament of Weiger may confirm such a relationship and thereby identify a new subset of patients with this feature of PDS.

Disclosure

The authors report no conflicts of interest in this work.

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To whom it may concern

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This contribution is greatly appreciated.

Regards

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