Ocular ultrasonography for detection of posterior segment pathology in adult patients presenting with blurred vision

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Abstract

Background and objective: Ocular posterior segment lesions can affect individuals of both sexes at all ages. Such lesions can lead to serious manifestations such as retinal detachment and retinal hemorrhage, leading to permanent loss of eyesight. This study aimed to determine the association between age and gender and changes in ocular posterior segment based on ultrasonography findings.

Methods: This prospective cross-sectional study included 50 patients with blurry vision who had been referred from ophthalmology outpatient clinics to the radiology department of Rizgary Teaching Hospital in Erbil, Kurdistan region in Iraq. Required data were collected using a researcher-designed questionnaire, and the patients were examined using a high resolution 7.5-10 MHz linear array ultrasound transducer.

Results: The most frequent complications associated with ocular posterior segment pathologies were old vitreous hemorrhage (72%), posterior vitreous detachment (36%), and retinal detachment (34%). Diabetes and hypertension were the most frequent diseases associated with ocular posterior segment pathology. A significant association was seen between the patients' age with old vitreous hemorrhage ($P = 0.003$). A significant association was seen between the patients' medical conditions with old vitreous hemorrhage and retinal detachment. There was no significant correlation between the patients’ gender and the studied ocular posterior segment pathologies.

Conclusion: Age has a strong correlation with old vitreous hemorrhage, chronic medical conditions such as diabetes, and hypertension correlated with old vitreous hemorrhage and retinal detachment.

Keywords: Ocular ultrasonography; Posterior segment pathology; Blurred vision; Age; Gender.

Introduction

The human eye is composed of visible parts: the pupil, the iris, the sclera, and the transparent cornea. Once a light ray enters the eye, and before it focuses on the retina, it respectively passes through the cornea, the anterior chamber, the pupil, the lens, and the vitreous.\(^1\) Ultrasound can readily be utilized to detect ocular structures like sclera, choroid, retina, and vitreous. The ophthalmic artery, which associates optic nerve and is a branch of the internal carotid artery, supplies ocular structures with blood.\(^2\) As a potent non-invasive diagnostic tool, ultrasonography can be utilized to diagnose ocular conditions with accuracy, differentiate intra ocular tumors, and provide information on the acoustic characteristics, extension, location, size of the tumor.\(^2,4\) Information on diseases that are diagnosable via ophthalmoscopic examinations can be obtained through ultrasonography. Vitreous hemorrhage and cataracts have the capacity to interfere with the ophthalmoscopic examination of the posterior wall and are among numerous ocular conditions which are a principal indication for ocular ultrasound and can lead to the pacification of transparent field.\(^5\) In order to prevent the
Methods

Methods

Tragic risk of globe rupture in recent ocular trauma or surgery, ocular sonography is contraindicated. Other advantages of this diagnostic tool include inexpensiveness, ease of utilization, availability, and provision of high-resolution images. The successful use of ultrasonography depends on selecting appropriate probes and settings. It has been recommended that linear high-frequency transducers (7.5-13.0 MHz) should be used because of the superficial location of the eye. In addition, the gain setting is first adjusted for surface images (anterior chamber) and then to the deepest parts (posterior and vitreous wall). This is an ideal technique for achieving high-resolution imaging of the parts of the peripheral retina, the ciliary body, the anterior chamber, and its structures. Since the images could have been distorted at the close interface between the object being imaged and the transducer, it is recommended to use eye-cup devices to create an offset distance between the surface of what is being imaged transducer. This method should not be utilized for patients with traumatic injury or in postoperative eyes because it can lead to rupture.

Before the conduction of ocular ultrasound, patients are provided with the required information regarding its technique and protocol by giving them necessary instructions: movements of the eyes during examination with closed eyes, removal of contact lenses, and examination of the patient with closed eyelids in the supine position. Moreover, to make better probe contact, a large amount of gel needs to be used during the conduction of the examination. In order to prevent retrobulbar pressure (RBP), the placement of the probe should be carried out in a situation the upper eyelid is covered with gel with the lowest amount of pressure on the eyeball.

In addition, the examination of the eye needs to be in a dynamic method in which the eye should be moved from left to right side and from upper to lower for better visualization of the globe. Furthermore, the color Doppler examination is also carried out as part of the study. The color Doppler parameters need to be adjusted as low velocity with a small Doppler gate. Given the seriousness of ocular posterior segment for being the probable causes of chronic ocular diseases and because of the prevalence of it in the Iraqi population, this study aimed to determine the relationship of sonographic changes of ocular posterior segment with gender, age, and chronic medical conditions.

Study design

A cross-sectional study.

Sample size and sampling:

Fifty adult patients with blurry vision were selected from February 2018 to July 2018. All patients were referred by ophthalmologists to the radiology department, ultrasound unit in Rizgary Teaching Hospital in Erbil, Kurdistan region, Iraq. The exclusion criteria were having recent trauma to the eye globe and having recent ocular surgery.

Data collection

The patients were interviewed in the radiology departments, and data were collected based on a researcher-designed questionnaire. Verbal informed consent was obtained from each participant in the study. Afterward, a high resolution 7.5-10 MHz or higher linear array transducer was used for the ocular ultrasound using an ultrasound machine (GE Healthcare voluson E6) in the radiology departments. For this purpose, the patient was examined in the supine position. The closed-eyelid technique was utilized using standard water-soluble ultrasound gel. In order to create a standoff and evaluate the anterior segment, large amounts of gel were used. Also, the ocular examination was carried out in both transverse and sagittal planes in different positions of gaze. Moreover, a dynamic scanning technique was employed to assess the membranes and echoes in the posterior segment.
The patients were required to move their eyes in different directions of gaze while the probe was held fixed.

The age groups are categorized according to the classification of the World Health Organization and 2012 Fourth International Conference on Advanced Computing; adolescents are less than 18 years, adults are 19-25 years, seniors are 25-64 years, and elderlies are over 64 years.\(^\text{10}\)

**Statistical analysis**

Collected data were analyzed using the statistical package for the social sciences (SPSS software version 23). Different age and gender groups were compared based on frequencies and percentages. The Chi-square test was utilized to analyze categorical variables. Also, Fisher’s exact test was run when the expected value of more than 20% of the cells of the table was less than 5. The confidence interval was considered as 95%, and a \( P \) value of less than 0.05 was considered statistically significant.

**Ethical considerations**

This study was approved by the research ethics committee of the College of Medicine, Hawler Medical University.

| Gender | Frequency (N) | Percentage (%) |
|--------|--------------|----------------|
| Male   | 24           | (48)           |
| Female | 26           | (52)           |

| Age (years) | Frequency (N) | Percentage (%) |
|-------------|---------------|----------------|
| (< 18)      | 2             | (4)            |
| (19 – 25)   | 3             | (6)            |
| (25 – 64)   | 30            | (60)           |
| (>64)       | 15            | (30)           |
| Total       | 50            | (100)          |

| Medical conditions            | Frequency (N) | Percentage (%) |
|-------------------------------|---------------|----------------|
| Hypertension                  | 12            | (24)           |
| Diabetes                      | 13            | (26)           |
| Diabetes and hypertension     | 5             | (10)           |
| None                          | 20            | (40)           |
| Total                         | 50            | (100)          |
The study revealed the frequency of posterior segment pathologies. Old vitreous hemorrhage experienced by 36 patients (72%) was the most frequently observed complication, followed by posterior vitreous detachment in 18 patients (36%) and retinal detachment in 17 patients (34%) (Table 3).

Regarding the correlation between posterior segment pathologies in different age groups, there was a significant correlation between the patients' age and old vitreous hemorrhage ($P = 0.003$). No significant association was seen between their age and other pathologies (Table 4).

### Table 3 Study sample by posterior segment pathologies

| Pathology                              | Frequency (No.) | Percentage (%) |
|----------------------------------------|-----------------|----------------|
| Old vitreous hemorrhage                | 36 (72)         |                |
| Posterior vitreous detachment          | 18 (36)         |                |
| Retinal detachment                     | 17 (34)         |                |
| Other sonographic findings             | 13 (26)         |                |
| Total                                  | 50 (100)        |                |

### Table 4 Correlation between various posterior segment pathologies and age

| Posterior segment pathology | Adolescent <18 (n=1) | Adult 19 – 25 (n=7) | Senior 25 – 64 (n=41) | Elderly 64+ (n= 33) | Total (n= 82) | $P$ value* |
|-----------------------------|----------------------|---------------------|-----------------------|---------------------|--------------|------------|
| Retinal detachment          | 0 (0.0)              | 1 (14.3)            | 9 (21.9)              | 7 (21.2)            | 17           | 0.669*     |
| Posterior vitreous detachment | 0 (0.0)          | 1 (14.3)            | 8 (19.5)              | 9 (27.3)            | 18           | 0.103*     |
| Old vitreous hemorrhage and vascular fibrosis | 1 (100.0) | 3 (42.8)            | 17 (41.5)            | 15 (45.5)          | 36           | 0.003*     |
| Other sonographic findings   | 0 (0.0)              | 2 (28.6)            | 7 (17)                | 2 (6)               | 11           | 0.200*     |
| Total                       | 1                    | 7                   | 41                    | 33                  | 82           |            |

* Indicates Fisher Exact Test
In terms of the correlation between the ocular posterior segment sonographic findings and the patients' gender, none of the posterior segment pathologies had a significant relationship with the patients' gender. In other words, the male and female patients were not significantly different in terms of posterior segment pathologies (Table 5).

### Table 5 The correlation between the ocular posterior segment sonographic findings and patients’ gender

| Ocular posterior segment sonographic findings | Gender | Total | \( P \) value |
|---------------------------------------------|--------|-------|-------------|
|                                             | Male N = 24 | Female N = 26 | No. (%) | No. (%) | No. (%) |
| Retinal detachment                          | 8 (17.7) | 9 (23.0) | 17 (20.2) | 0.090* |
| Posterior vitreous detachment               | 9 (20) | 9 (23.0) | 18 (21.4) | 0.811* |
| Old vitreous hemorrhage                     | 19 (42.2) | 17 (43.7) | 36 (42.9) | 0.221* |
| Other sonographic findings                  | 9 (20) | 4 (10.3) | 13 (15.5) | 0.071* |
| Total                                       | 45 (100.0) | 39 (100.0) | 84 (100.0) |

* Indicate Fisher Exact Test

In terms of correlation between the patients' medical conditions and their ocular pathologies, the study demonstrated a significant correlation between their medical conditions and old vitreous hemorrhage (\( P = 0.001 \), retinal detachment (\( P < 0.001 \)), as shown in Table 6.

### Table 6 Correlation between medical conditions and ocular features

| Ocular features                                             | Medical conditions                             | Total (n= 45) | \( P \) value |
|-------------------------------------------------------------|-------------------------------------------------|---------------|-------------|
|                                                             | Diabetes (n= 23)                                | Hypertension (n=14) | Diabetes & Hypertension (n= 8) | Other medical conditions (n= 0) |                |               |
|                                                             | No. (%)                                        | No. (%)        | No. (%)    | No. (%)    | No. (%)    |               |
| Old vitreous hemorrhage and vascular fibrosis               | 12 (52.2)                                     | 11 (78.6)      | 5 (62.5)   | 0 (0.0)    | 28 (62.2)  | 0.001*       |
| Retinal detachment                                          | 11 (47.8)                                     | 1 (7.1)        | 3 (37.5)   | 0 (0.0)    | 15 (33.3)  | <0.001*      |
| Other sonographic findings                                  | 0 (0.0)                                       | 2 (14.2)       | 0 (0.0)    | 0 (0.0)    | 2 (4.4)    | 0.400*       |

* Indicates Fisher Exact Test
Given the significance and prevalence of posterior segment pathology and the subsequent severe complications, the current study was conducted to understand how age and gender are correlated with posterior segment pathologies. For this purpose, 50 blurred-vision patients with a mean age of 50.08±17.08 years who were referred to the radiology unit of Rizgary Teaching Hospital located in Erbil, Kurdistan region in Iraq were studied. The results revealed that 60% of the patients suffered from either hypertension or diabetes, or both. This finding agrees with the study done by Vasuki reported that ocular complications, especially diabetic retinopathy, are common in patients with diabetes mellitus. Mendanha et al. also reported a similar association between ocular complications and diabetes mellitus. Similar to the results of the present study, Ahn et al. reported an association between ocular retinal complications and severe hypertension. Regarding the frequency of sonographic ocular posterior segment findings, the results showed that, out of 50 patients, 36 had old vitreous hemorrhage, 18 had posterior vitreous detachment, and 17 had retinal detachment. This finding is in agreement with other studies. It was also seen that the posterior segment pathologies were more frequent in elderly patients. This finding is justified by the reports in different studies indicating that elderly patients are more likely to develop ocular segment injuries. However, this association was not significant. The study revealed that age was significantly associated only with old vitreous hemorrhage and vascular fibrosis in patients with posterior segment injury (P = 0.003), such that many senior and elderly patients had experienced vitreous hemorrhage and vascular fibrosis before. Different studies demonstrated that the clinical presentation of vitreous hemorrhage in adults is not the same as in younger patients. For example, Rejdak et al. reported that due to the disability of younger children in verbalizing their symptoms, their available symptoms or/and eliciting a detailed history of the trauma and its source could be expressed difficulty. Consequently, vitreous hemorrhage of those patients may not be noted until a comprehensive eye exam is done or until they fail a vision screening. Additionally, the lack of proper patient cooperation can render simple exploratory maneuvers such as intraocular pressure or assessing visual acuity very challenging. However, as seen above, age was not significantly correlated with other studied variables, including retinal detachment, posterior vitreous detachment, choroidal melanoma, optic DiscDrusen, asteroid hyalosis, and foreign body. Almost similar findings have been reported by other previously conducted studies. According to the data presented by Khoshnevis et al., asteroid hyalosis is usually asymptomatic among patients that could be mainly diagnosed through ophthalmic examination. In situations when asteroid bodies are at a close distance to the macula or when a complete posterior vitreous detachment might be visually symptomatic, that may require vitrectomy. In line with the data presented in the present study, there is a significant relationship between two factors of asteroid hyalosis and age. While their association with the posterior vitreous detachment is inverted. In a study carried out in Iraq, the prevalence of blindness was reported to be 2.7%. The causes of these cases of blindness were respectively cataract (76.1%), diabetic retinopathy (12.9%), glaucoma (5%), corneal scars secondary to keratitis (1.6%), ocular trauma (1.2%), uveitis (1%), age-related macular degeneration (0.6%), retinal detachment (0.6%), uncorrected high reflective errors (0.4%), optic atrophy (0.2%), corneal dystrophies (0.2%), and retinal dystrophies (0.2%). Among these causes, optic atrophy and retinal detachment, which...
account for 0.6% of cases of blindness, are associated with posterior segment; therefore, early detection of ocular posterior segment can probably prevent consequent serious damage and permanent loss of vision. The results revealed no significant association between the patients’ gender and the posterior injuries \((P > 0.05)\). Therefore, it can be stated that the male and female patients were not significantly different in terms of developing ocular posterior segment pathologies. Similar to this finding, Poulsen et al. pointed out although retinal detachment was more common among males than females; however, this difference was not significant.\(^{26}\) This finding is also in agreement with a study carried out by Shao et al., who reported no significant relationship between gender and posterior vitreous detachment.\(^{27}\) Moreover, the male and female patients were not significantly different regarding the incidence of posterior segment pathologies, including choroidal melanoma, persistent hyperplastic primary vitreous, choroid hemangioma, Optic DiscDrusen, asteroid hyalosis, and foreign body. The findings of the present study, in this regard, are in line with previous studies.\(^{28-29}\) Regarding the association between medical conditions and ocular posterior segment pathologies, the results showed a significant association between patients’ medical conditions and retinal detachment \((P = 0.001)\), old vitreous hemorrhage, and vascular fibrosis \((P = 0.004)\). This finding agrees with the results of previously conducted studies that have reported retinal detachment as one of the complications of diabetes.\(^{30-32}\) Similarly, Annan and Carvounis have reported that diabetes can be associated with ocular complications such as vitreous hemorrhage.\(^{33}\) However, the results revealed no significant correlation between medical conditions and other sonographic findings (i.e., DiscDrusen and choroidal detachment).

### Conclusion

Ocular posterior segment injuries can lead to serious complications, which might lead to permanent loss of sight. Old vitreous hemorrhage, retinal detachment, and posterior vitreous detachment were among the most frequent ocular sonographic findings in patients presented with blurred vision. Senior and elderly are most frequently complaining from ocular posterior segment injuries like old vitreous hemorrhage, retinal detachment, and posterior vitreous detachment. The gender was not related to the prevalence of ocular posterior segment pathologies. Medical conditions, particularly diabetes and hypertension, were associated with old vitreous hemorrhage and retinal detachment.

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### Competing interests

None declared.

### References

1. Abramoff MD, Garvin MK, Sonka M. Retinal imaging and image analysis. IEEE Rev Biomed Eng. 2010; 3:169–208. https://doi.org/10.1109/RBME.2010.2084567.
2. Michalinos A, Zogana S, Kotsiomitis E, Mazarakis A, Troupis T. Anatomy of the ophthalmic artery: A review concerning its modern surgical and clinical applications. Anat Res Int. 2015; 2015:591961. https://doi.org/10.1155/2015/591961.
3. Medina CA, Singh AD. Imaging of intraocular tumors. Retin Physician. 2014; 11:19–25.
4. de Graaf P, Göricke S, Rodjan F, Galluzzi P, Maeder P, Castelijns JA, et al. Guidelines for imaging retinoblastoma: imaging principles and MRI standardization. Pediatr Radiol. 2012; 42(1):2–14. https://doi.org/10.1007/s00247-011-2201-5.
5. Olson RJ, Braga-Mele R, Chen S H, Miller KM, Pineda R, Tweeten J, et al. Cataract in the adult eye preferred practice pattern. Ophthalmology. 2017; 124(2):P1–P119. https://doi.org/10.1016/J.OPTH.2016.09.027.
6. De La Hoz PM, Torramilans LA, Pozuelo SO, Anguera BA, Esmerado AC, Caminal MJM. Ocular ultrasonography focused on the posterior eye segment: What radiologists should know. Insights Imaging. 2016; 7:351–64. https://doi.org/10.1007/s13244-016-0471-z.
7. Rosen DB, Conway MD, Ingram CP, Ross RD, Montilla LG. A brief overview of ophthalmic ultrasound imaging, novel diagnostic methods in ophthalmology. Anna Nowinska: Intech Open; 2019. https://doi.org/10.5772/intechopen.83510.

8. Modrzejewska M. Guidelines for ultrasound examination in ophthalmology. Part III: Color Doppler ultrasonography. J Ultrasonar. 2019; 19(77):128–36. https://doi.org/10.15557/jou.2019.0019.

9. Dimitrova G, Kato S. Color Doppler imaging of diabetic retinopathy. Rev Bras Oftalmol. 2016; 79(3):193–214. https://doi.org/10.1016/j.survophthal.2009.06.010.

10. Nithyashri J, Kulanthaivel G. Classification of human age based on Neural Network using FG-NET Aging database and Wavelets. Fourth International Conference on Advanced Computing (ICOAC) 2012; 1:1–5. https://doi.org/10.1109/ICOAC.2012.6416855.

11. Vasuki G. Prevalence of ocular retinal disorders in patients with diabetes mellitus in a tertiary care hospital. Natl J Physiol Pharm Pharmacol. 2017; 7(7):719–23. https://doi.org/10.5455/njpp.2017.0306613032017.

12. Mendanha DB, Abrahão MM, Vilar MMC, Nassararla JJJ. Risk factors and incidence of diabetic retinopathy. Rev Bras Oftalmol. 2016; 75(6):443–6. https://doi.org/10.9795/0034-7780.201608098.

13. Ahn SJ, Woo SJ, Park KH. Retinal and choroidal changes with severe hypertension and their association with visual outcome. Invest Ophthalmol Vis Sci. 2014; 55(12):7775–85. https://doi.org/10.1167/iovs.14-14915.

14. Biancotto C, Shields CL, Guzman JM, Romanelli-Gobbi M, Mazzuca D, Green WR, et al. Assessment of anterior segment tumors with ultrasound biomicroscopy versus anterior segment optical coherence tomography in 200 cases. J Ophthalmol. 2011; 118:1297–302. https://doi.org/10.1106/ophtha.2010.11.0111.

15. Rashmi MN, Ravi N, Bhamaraa. Role of high resolution ultrasonography in the evaluation of posterior segment lesions of the eye. Int J Evid Based Healthc. 2015; 2(2): 97–112. https://doi.org/10.18410/jebmh/16.

16. Ramadhas K, Chandrasekaran S. Ultrasonographic evaluation of Eyes with Opaque Media. IOSR JDSM. 2016; 15(4):24–31. https://doi.org/10.9790/0853-1504032431.

17. Sung EK, Nadigir RN, Fujita A, Siegel C, Ghafoori RH, Traand A, et al. Injuries of the globe: what can the radiologist offer? Radiographics 2014; 34(3):764–76. https://doi.org/10.1148/rg.343135120.

18. Elshafie MA, Abouelkheir HY, Othman MM, El Hefy EM. Ultrasonic evaluation of eyes with blunt trauma. J Egypt Ophthalmol Soc. 2018; 111:20–4. https://doi.org/10.4103/ojos.ejos_6_18.

19. Rejdak R, Juenemann AG, Natarajan S. Posterior segment ocular trauma: Timing and indications for vitrectomy. J Ophthalmol. 2017; 2017: 5250924. https://doi.org/10.1155/2017/5250924.

20. Rao AA, Naheed JH, Chen JY, Robbins SL, Ramkumar H. A clinical update and radiologic review of pediatric orbital and ocular tumors. J Oncol. 2013; 2013: 975908. https://doi.org/10.1155/2013/975908.

21. Parrey MUR, Bhatti MO, Channa S, Alswailmi FK. Posterior segment eye diseases detected by B-scan ultrasonography in advanced cataract. Indo Am J P Sci. 2019; 11:261–66.

22. Bond-Taylor M, Jakobsson G, Zetterberg M. Posterior vitreous detachment - prevalence of and risk factors for retinal tears. Clin Ophthalmol. 2017; 11:1689–95. https://doi.org/10.2147/OPHT.S143898.

23. Birmbaum FA, Johnson GM, Johnson LN, Jun B, Machan JT. Increased Prevalence of Optic Disc Drusen after Papilloedema from Idiopathic Intracranial Hypertension: On the Possible Formation of Optic Disc Drusen. Neuro-ophthalmic. 2016; 40(4):171–80. https://doi.org/10.1080/01658107.2016.1198917.

24. Khoshnevis M, Rosen S, Sebag J. Asteroid hyalosis-a comprehensive review. Surv Ophthalmol. 2019; 64(4):452–62. https://doi.org/10.1016/j.survophthal.2019.01.008.

25. Al-Shakarchi FI. Blindness in Iraq: Leading causes, target patients, and barriers to treatment. Middle East Afr. J. Ophthalmol 2011; 18(3):199–203. https://doi.org/10.4103/0974-9233.84044.

26. Poulsen CD, Peto T, Grauslund J, Green A. Epidemiologic characteristics of retinal detachment surgery at a specialized unit in Denmark. Acta Ophthalmol. 2016; 94(6):548–55. https://doi.org/10.1111/aos.13113.

27. Shao L, Xu L, You QS, Wang YX, Chen CX, Yang H, et al. Prevalence and associations of incomplete posterior vitreous detachment in adult Chinese: The Beijing Eye Study. PLoS One. 2013; 8(3):e58498. https://doi.org/10.1371/journal.pone.0058498.

28. Zloto O, Pe’er J, Frenkel S. Gender differences in clinical presentation and prognosis of uveal melanoma. Invest Ophthalmol Vis Sci. 2013; 54:652–56. https://doi.org/10.1167/iovs.12-10365.

29. Nahid R, Mohiuddin A. Automatic detection of optic disc in fundus images by curve operator. 2nd International Conference on Electrical Information and Communication Technologies (EICT) 2015; P. 143–47. https://doi.org/10.1109/EICT.2015.7391936.

30. Nentwich MM, Ulbig MW. Diabetic retinopathy - ocular complications of diabetes mellitus. World J Diabetes. 2015; 6(3):489–99. https://doi.org/10.4239/wjd.v6.i3.489.

31. Sternfeld A, Axer-Siegel R, Stiebel-Kalish H, Weinberger D, Ehrlich R. Advantages of diabetic fractional retinal detachment repair.
32. Roy S, Amin S, Roy S. Retinal fibrosis in diabetic retinopathy. Exp Eye Res. 2016; 142:71–5. https://doi.org/10.1016/j.exer.2015.04.004.

33. El Annan J, Carvounis PE. Current management of vitreous hemorrhage due to proliferative diabetic retinopathy. Int Ophthalmol Clin. 2014; 54(2):141–53. https://doi.org/10.1097/IIO.0000000000000027.