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Influence of posterior vitreous detachment and type of intraocular lens on lipid peroxidation in the human vitreous

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Purpose: The aim of this study was to evaluate the relationship between oxidative stress and human vitreous degeneration, using the presence of an evident posterior vitreous detachment (PVD) as a clinical sign and thiobarbituric acid-reactive substances (TBARS) and nitrite as oxidative biomarkers.
Methods: We collected 42 vitreous samples from patients undergoing *pars plana* vitrectomy for two groups of vitreoretinal diseases (macular holes and epimacular membranes). TBARS and nitrite were assessed spectrophotometrically and compared to the presence of an evident PVD, considering other clinical features potentially related to the oxidative stress in the vitreous: diabetes, plasma fibrinogen, type of intraocular lens (IOL), and the vitreoretinal disease requiring the surgery.
Results: Vitreous TBARS levels were significantly higher in patients with artificial IOLs compared to those with natural lenses and cataracts (1.39±0.64 versus 0.75±0.45; p=0.003). Furthermore, patients with PVD had a significant increase in vitreous TBARS compared to those without PVD (1.45±0.54 versus 0.53±0.38; p=0.001). The plasma fibrinogen levels explained 17% of the TBARS variance, with a significant correlation between these two markers (p=0.011). No significant differences were observed when nitrites were used as biomarkers.
Conclusions: Current IOLs, even with ultraviolet (UV) absorber, do not ensure the same photoprotection offered by natural lenses affected by corticonuclear cataracts. Furthermore, we observed a relevant correlation between the increased presence of peroxidation products in the vitreous and an evident PVD, but the nature of this relationship requires further study.

The eye is a highly metabolically active structure, continually bathed in light. Thus, oxidative and particularly photo-oxidative processes are critical factors in ocular pathologic conditions, especially those associated with aging [1,2].

In the eye, the vitreous gel is a compact, homogeneous, and clear body at birth. With aging, the vitreous gel can undergo progressive degeneration characterized by vitreous liquefaction and weakening of the vitreoretinal adhesion between the posterior vitreous hyaloid and the inner limiting membrane (ILM). In about 25–30% of the population, this degeneration may result in posterior vitreous detachment (PVD) [3,4], increasing the risks of major diseases such as macular holes, epimacular membranes, vitreoretinal traction syndrome, and retinal detachment [5]. Since they may be sight-threatening conditions, there is growing interest in unveiling their pathogenic mechanisms [6].

Age-related vitreous degeneration starts with a phase of vitreous liquefaction (or synchysis senilis) and aggregation of collagen fibrils (vitreous syneresis), which are usually dispersed and separated within the vitreous cavity [7]. This event produces thick bundles of collagen materials, which can move within the newly formed liquid pockets and generate vitreous floaters, thus decreasing the quality of vision when they are located along the visual axis. The weakening of vitreoretinal adhesion at the posterior pole is the second and most dangerous step of vitreous degeneration, since this weakening is often concurrent with the vitreous structure collapse and produces a PVD [4,8]. In the literature, these processes have been speculated to be promoted by the same molecular mechanisms [8-10], but their underlying pathogenesis is still poorly understood: different factors are presumed to play a role and, among them, an increase in the production of free radicals [11,12].

An imbalance between free radicals production and antioxidant defenses may produce oxidative stress. As previously mentioned, oxidative stress can lead to many ocular diseases, such as macular degeneration and open-angle glaucoma [13]. In the vitreous gel, oxidative stress can damage collagen fibrils [9], altering their surface coatings (required to prevent aggregation into bundles) and consequently promoting vitreous liquefaction [5,7]. Furthermore, oxidative stress can

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engender the disruption of proteins that act as molecular glue between the vitreous and the retina, such as laminin, fibronectin, and heparan sulfate, especially through the activation of matrix metalloproteinases [14,15].

Since the eye is continuously exposed to light, incident light may be a major factor that promotes the production of free radicals [16]. In addition to the photoprotection offered by some oxidative scavenger molecules of the eye, in physiologic conditions, ocular tissues such as the cornea and the lens filter harmful radiations of the visible spectrum, ensuring additional protection for the retina [17]. However, in pathological conditions where an aged lens is replaced with an implant, one of the main photoprotective tissues of the eye is lost. For this reason, intraocular lenses (IOLs) with transmittance properties similar to the human lens have been developed. Today, two main types of IOLs, differing in terms of light transmittance, are available: colorless ultraviolet (UV)-blocking IOLs and yellow-tinted IOLs. The first type effectively blocks UV light, but the transmission properties differ from those of the aged lens, which is more comparable to tinted lenses that block blue light [18,19]. Surprisingly, little is known about the influence these different types of lenses may have on the oxidative status of the vitreous.

In addition to the exogenous factors, some pathologic conditions such as diabetes and inflammation can cause oxidative stress. Diabetes can disrupt the blood–retinal barrier, promoting the leakage of oxidative products within the vitreous chamber. Furthermore, inflammation can boost the production of free radicals through pathways such as the those involving nuclear factor-kappa B (NF-kB) and tumor necrosis factor-α (TNF-α) [16].

The correlation between oxidative stress and vitreous degeneration, however, has been shown only in animal models, including rabbit and calf eyes, where the vitreous has been exposed to light sources and the effects of different photosensitizers have been tested in vitro and in vivo. Free radicals have been shown to cause a reduction in the molecular weight of hyaluronan and the aggregation of the vitreous collagen, leading to degeneration changes in the vitreous structure [11,12,20]. Based on our literature survey, we aimed at confirming, for the first time in ex vivo conditions, the relationship between oxidative stress and human vitreous degeneration, using the presence of an evident PVD as a clinical sign and thiobarbituric acid-reactive substances (TBARS, a product of membrane lipid peroxidation) and nitrite (a stable derivative of nitric oxide) as oxidative biomarkers. Since the oxidative balance of the eye can also be affected by diabetes, systemic inflammation, the type of vitreoretinal disease, and lenses in the anterior segment, we explored whether these conditions could significantly affect the levels of oxidation products in the vitreous.

METHODS

Patients: The present study was performed in accordance with the ethical principles of the Declaration of Helsinki for medical research involving human subjects and was approved by the local Institutional Review Board. Informed consent was obtained from all patients enrolled in the study. The study group was composed of 42 patients undergoing *pars plana* vitrectomy 25 gauge for two groups of diseases: macular hole (n=19) and epimacular membranes (n=23). Both diseases are potentially related to the degenerative vitreous syndrome or anomalous posterior vitreous detachment, a unifying concept introduced by Sebag in 2004 [5]. The mean age of the patients was 74±7.8 years, and 58% were male. The same surgeon in the same operation theater performed all vitrectomy procedures. Patients presenting with one or more of the following criteria were excluded from the study: previous vitreous surgery, presence of vitreous hemorrhages or hemovitreous, proliferative diabetic retinopathy, assumption of antioxidant integrators, impossibility of classifying vitreous degeneration or any of the other relevant parameters, infections, malignant neoplasias, or renal or hepatic failure.

Vitreous samples: In each patient, an undiluted vitreous sample (500–800 µl) was collected at the beginning of the vitrectomy from the central vitreous cavity, immediately placed in Eppendorf cryotubes, and stored at –80 °C until assayed (generally 2 weeks after the intervention). Particular care was taken to avoid any type of contamination or exposure to light sources. Each test was performed once per patient (the sample quantity did not allow repetition of the experiment).

Blood samples: On the same day of the vitrectomy, a blood sample was taken from the cubital vein in each participant to assess the plasma fibrinogen concentration as a marker of inflammation. All the blood samples were immediately processed for the analysis. A coagulation analyzer was employed to measure plasma fibrinogen.

PVD assessment: The presence of posterior vitreous detachment, a clear sign of vitreous degeneration, was evaluated biomicroscopically following the classification proposed by Kakehashi et al. [21] and confirmed during the vitrectomy. Information from spectral domain optical coherence tomography (SD-OCT) was integrated when needed. Any type of biomicroscopically relevant PVD was considered positive for this parameter.

Cataract and IOL assessment: Each patient was evaluated for the presence of lens cataract, and patients with corticonuclear

opacifications were included in this study. Furthermore, patients with previous cataract surgery (mean distance from the vitrectomy was 30.6 months) were enrolled as the control group. The type of the IOL implanted was evaluated, in terms of the technical features reported by the manufacturer and by peer-reviewed papers about the transmission spectrum [18,22]. Only patients with UV-blocking IOLs with comparable light transmittance were included in the study.

Diabetes: The World Health Organization (WHO) recommendations were used to classify the patients into two groups, one composed of 15 individuals with type 2 diabetes mellitus and the other of 27 patients without it. Patients with signs of proliferative diabetic retinopathy were excluded from the study.

Measurement of TBARS production: The TBARS assay was used to detect the presence of lipid peroxidation products, and the assay was performed following the indication by Yano [23]. The samples were thawed, sonicated with a 10 s burst, and then centrifuged at 18928 ×g for 5 min. Five hundred microliters of the sample were added to the TBA solution (thiobarbituric acid 0.375% and trichloroacetic acid 30% in 0.5 N HCl). The samples were boiled for 20 min, then rapidly cooled in ice, and centrifuged for 5 min at 16099 ×g. Absorbance on 300 µl of the sample was detected at 532 nm with a Packard EL340 microplate reader (Bio-Tek Instruments, Winooski, VT). Results are expressed as nmol TBARS/ml sample. For each new experiment, a fresh TBA solution was prepared, and a new calibration curve was performed.

Measurement of NO production: The concentration of nitrite, a stable product of nitric oxide (NO) synthesis, was measured in the vitreous with the Griess method, as previously described [24]. The resulting concentration was expressed as nmol nitrite/ml sample.

Statistical analysis: Data were presented as means and standard deviation, and the significance of the differences was tested with parametric or non-parametric tests when necessary. The effect of the potentially explanatory variables on the TBARS and nitrite levels was estimated using a univariate and a multivariate analysis [25]. In the multiple linear regression, the dependent variable was TBARS in one model and nitrites in the other, while the explanatory variables were PVD, previous cataract surgery, diabetes, type of vitreoretinal disease requiring the vitrectomy, and the plasma fibrinogen concentration. $p<0.05$ was considered significant.

RESULTS

As shown in Figure 1 and in Table 1, TBARS levels are significantly higher where PVD occurs, compared with patients who exhibited no biomicroscopic signs of PVD ($p=0.001$).

We also observed that the type of lens in the anterior segment of the eye was significantly related to the amount of TBARS measured within the vitreous chamber, as

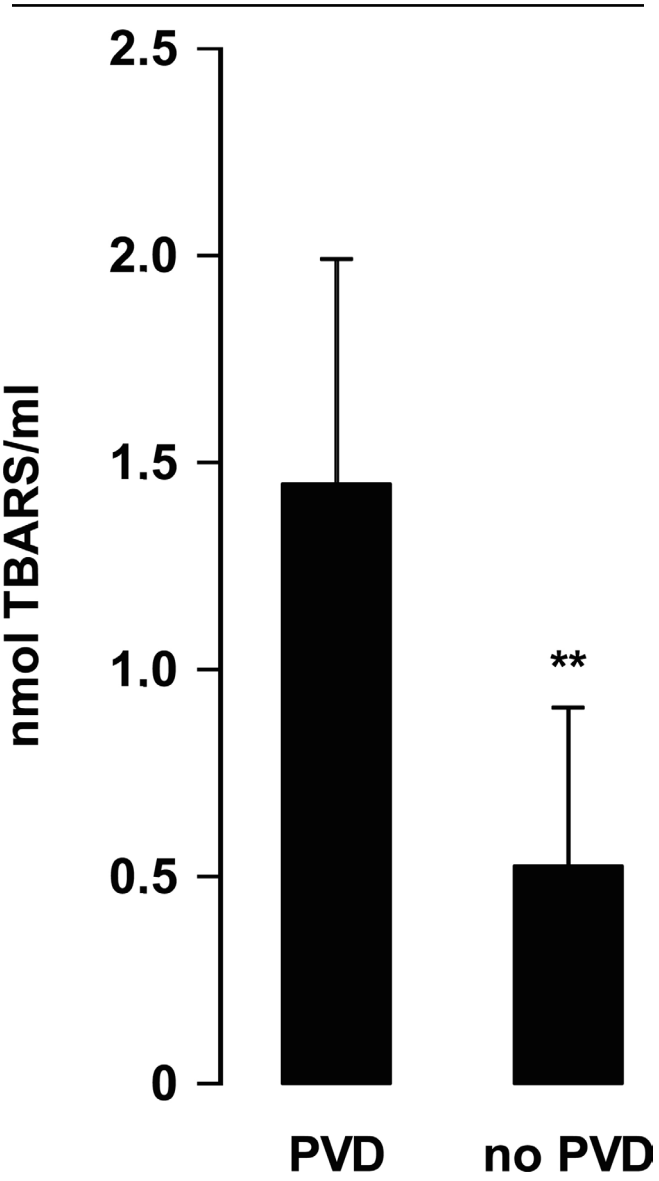

Figure 1. TBARS levels in terms of the biomicroscopic detection of a PVD. Patients with an evident posterior vitreous detachment (PVD) had significantly increased thiobarbituric acid-reactive substances (TBARS) levels compared to those without clear biomicroscopic signs of PVD (1.45±0.54 vs. 0.53±0.38 $p=0.001$). Data are shown as means ± standard deviation (SD): n=27 (PVD); n=15 (no PVD). ** $p\leq0.001$.

shown in Figure 2 and in Table 1. Subjects with a natural lens, affected by corticonuclear cataract, had lower TBARS levels compared with those with artificial IOLs implanted in place of the natural crystalline (p=0.003). We did not detect any significant correlation between the time of surgical intervention (mean distance from vitrectomy: 30.6 months) and TBARS levels in the vitreous. In this study, we did not observe any significant association between the TBARS levels and diabetes and the type of vitreoretinal disease requiring the surgery.

As shown in Figure 3, the plasma fibrinogen concentration measured on the same day (values in Table 1), before the vitrectomy, explained 17% of the variance of TBARS, with a significant association between these two markers (p=0.011). We did not observe any significant correlation between the nitrite levels and the variables included in this study (Table 1).

DISCUSSION

According to our knowledge, this study shows for the first time an ex vivo correlation between an evident PVD in human vitreous and increased oxidative stress levels, measured as the concentration of TBARS in vitreous samples collected during *pars plana* vitrectomies. If oxidative stress is considered a contributing factor in vitreous degeneration, then these results are consistent with those of Ueno [11] and Akiba [12], who found that free radicals could damage the vitreous microstructure of calf and rabbit eyes, both in vivo and in vitro, thus resulting in the formation of liquid pockets and weakening of the vitreoretinal adhesion at the posterior pole of the eye. At the molecular level, free radicals can determine the depolymerization of hyaluronic acid and the aggregation of collagen fibrils [26]. Our findings, together with those of other authors in the literature [11,12], fit with the hypothesis that oxidative stress can be considered at least part of the pathogenic mechanism promoting the degeneration of the vitreous gel.

However, where PVD occurs, the resulting mechanical stress produced by the vitreous base on the retina during eye movements may also be associated with higher TBARS levels. This hypothesis is supported by the increased TBARS levels observed in the vitreous of myopic eyes [27] where early development of PVD and precocious vitreous degeneration are commonly observed [28]. Furthermore, it was shown that lipid peroxidation might play a role in the pathogenesis of rhegmatogenous retinal detachment in myopic eyes, which often occurs in the area of firm vitreoretinal attachments [29].

In this study, we also observed that plasma fibrinogen, an inflammatory marker commonly used in the ophthalmic preoperative evaluation, is positively correlated to the TBARS levels in the vitreous. In other oxidative stress-related pathologic conditions, such as age-related macular degeneration, high plasma fibrinogen levels are recognized as a risk factor, confirming that a systemic inflammatory status can affect the oxidative balance within the vitreous chamber and the retina, as reported by the Blue Mountains Eye Study [30]. By increasing vascular permeability, fibrinogen may allow the flow of small molecules into the vitreous, thus altering the delicate homeostasis of this tissue [31]. This may contribute to explaining the mild association between TBARS and plasma fibrinogen observed in our patients. In addition, another study reported by Brzović-Šarić and coworkers [32] showed a significant association between vitreous peroxidation and levels of vascular endothelial growth factor, which is a major enhancer of endothelial permeability [33].

By far, one of the most interesting findings of the present study was the relationship between the type of intraocular lens and the TBARS levels in the vitreous. We observed that natural lenses affected by corticonuclear cataract strongly protect from the free radicals generated by incident light in

Table 1. Age, gender, type 2 diabetes, vitreous TBARS, vitreous nitrite and plasma fibrinogen with respect to the presence of cataract, IOL, PVD and no PVD.

Selected variables	AGE; mean (SD)	GENDER; number (%)	Type 2 diabetes; number (%)	TBARS; mean (SD)	NITRITE; mean (SD)	Plasma fibrinogen; mean (SD)
PVD (n=27)	72.96 (11.34)	Male: 19(67.86) Female: 8 (32.14)	10 (34.71)	1.45 (0.54)	4.40 (2.43)	353.80 (75.78)
NO PVD (n=15)	71.53 (6.03)	Male: 10 (66.67) Female: 5 (33.33)	5 (33.33)	0.53 (0.38)	3.82 (2.43)	336.55 (78.88)
Cataract (n=20)	70.63 (8.57)	Male 13 (68.42) Female 6 (31.58)	7 (36.84)	0.75 (0.45)	3.99 (2.32)	325.07 (71.03)
IOL (n=22)	73.95 (10.52)	Male 16 (69.56) Female 7 (30.44)	8 (34.78)	1.39 (0.64)	4.50 (2.78)	365.29 (76.67)

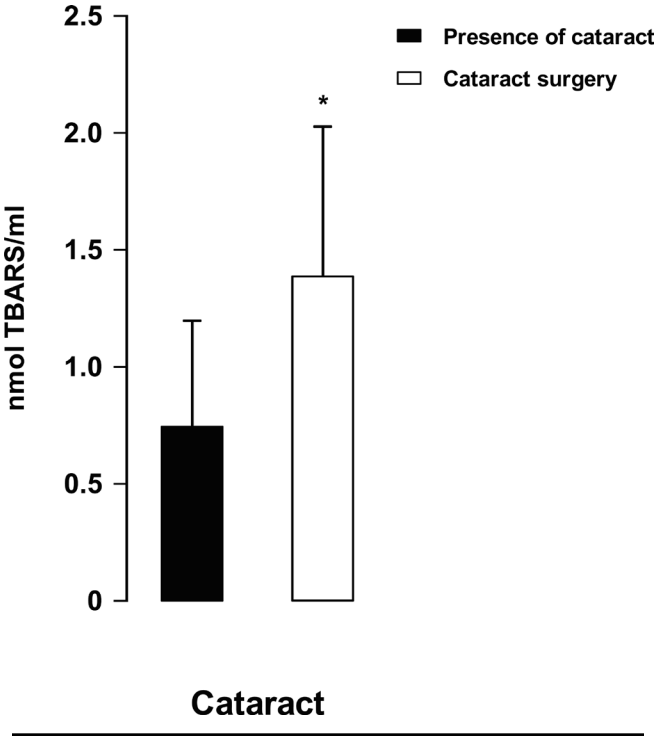

Figure 2. Relationship between the presence of either corticonuclear cataract or previous cataract surgery (phacoemulsification with IOL implantation) and the TBARS levels in the vitreous. Where an intraocular lens (IOL) is present in place of the natural lens, the thiobarbituric acid-reactive substances (TBARS) levels are significantly higher than in patients with cataract (1.39±0.64 vs. 0.75±0.45; p=0.003). Data are shown as means ± standard deviation (SD): n=20 (patients with cataract); n=22 (patients with IOL). * p≤0.003.

the vitreous and they are even more effective in photoprotection than most of the currently used IOLs. In the vitreous, the lower amount of peroxidation products generated by incident light might be explained by considering that the light transmittance decreases dramatically when a lens develops a cataract [17]. However, to determine if this effect is really due to a protective action of corticonuclear cataract, further analyses are needed. In particular, we did not observe whether blue-blocking IOLs were superior when compared to the commonly used UV-blocking IOLs regarding the free radicals generated in the vitreous by incident light. In the future, this issue should be addressed, since the main difference

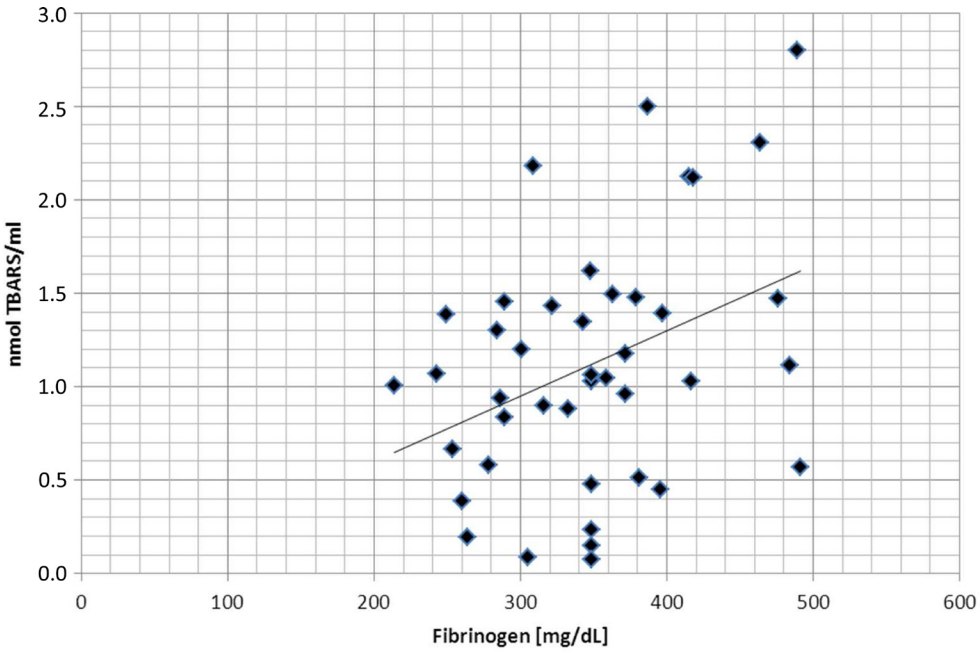

Figure 3. Relationship between plasma fibrinogen and TBARS levels in the different samples. The figure shows a positive correlation (adjusted r^2=0.17) between the plasma fibrinogen and thiobarbituric acid-reactive substances (TBARS) levels in the vitreous.

between cataract lenses and UV-absorbing IOLs lies in the transmission spectrum [34]. Although UV-absorbing IOLs do not protect the vitreous and the retina from blue light, the aging process makes the natural lens more yellow, thus reducing the transmission of this part of the visible spectrum [35]. Blue light, due to its short wavelength (approximately 400–480 nm) and its high energy, has been linked to phototoxic damage and increased oxidative stress in the retina [36]. The protective effect of blue-blocking IOLs against photo-oxidative stress has been reported by different authors [37,38]. In light of the current debate on the use of these IOLs, a further comparison parameter between them and the UV-blocking IOLs may include their influence on the oxidative balance in the vitreous.

Regarding the other relevant parameters of the present study, we did not observe any significant difference between non-diabetic and diabetic patients without signs of proliferative diabetic retinopathy, in accordance with Mancino et al.'s results [39]. Furthermore, no significant correlations among the variables were observed with nitrite as a biomarker, suggesting the need to use more specific measurement techniques to quantify the production of nitric oxide in the vitreous.

Based on these findings, we reported for the first time a significant association between PVD and TBARS levels in the vitreous, but whether this increase in peroxidation products is a causative agent in this relationship or is a consequence of the vitreous degeneration process must still be addressed. However, oxidative stress is an established risk factor for different retinal diseases, and although several interventions can be performed to prevent it, none is completely effective. Since we found lipid peroxidation was higher in the vitreous of patients with lens implants, proving whether adequate photoprotection could effectively reduce the peroxidation products in the vitreous and the retina, thus avoiding sight-threatening complications, is an important question to be addressed in future studies. These will allow us to understand whether improving light filtering could be a possible method for effectively reducing oxidative stress in the eye.

REFERENCES

1. Williams DL. Oxidative stress and the eye. Vet Clin North Am Small Anim Pract 2008; 38:179-92. [PMID: 18249249].
2. Koh H, Phil M, Henson D, Boulton M. The role of oxidative stress in the pathogenesis of age-related macular degeneration. Surv Ophthalmol 2000; 45:115-34. [PMID: 11033038].
3. Larsson L, Österlin S. Posterior vitreous detachment. A combined clinical and physiciochemical study. Graefes Arch Clin Exp Ophthalmol 1985; 223:92-5. [PMID: 4007512].
4. Foos RY, Wheeler NC. Vitreoretinal juncture: Synchysis senelis and posterior vitreous detachment. Ophthalmology 1982; 12:1502-12. .
5. Sebag J. Anomalous posterior vitreous detachment: a unifying concept in vitreo-retinal disease. Graefes Arch Clin Exp Ophthalmol 2004; 242:690-8. [PMID: 15309558].
6. Holekamp NM. The vitreous gel: more than meets the eye. Am J Ophthalmol 2010; 149:32-6. [PMID: 19875090].
7. LeGoff MM, Bishop PN. Adult vitreous structure and postnatal changes. Eye (Lond) 2008; 22:1214-22. [PMID: 18309340].
8. Bishop PN. Structural macromolecules and supramolecular organisation of the vitreous gel. Prog Retin Eye Res 2000; 19:323-44. [PMID: 10749380].
9. Jariashvili K, Madhan B, Brodsky B, Kuchava A, Namicheishvili L, Metreveli N. UV Damage of Collagen: Insights from Model Collagen Peptides. Biopolymers 2012; 97:189-98. [PMID: 22002434].
10. Kakehashi A, Ueno N, Chakrabarti B. Molecular mechanisms of photochemically induced posterior vitreous detachment. Ophthalmic Res 1994; 26:51-9. [PMID: 8134089].
11. Ueno N, Sebag J, Hirokawa H, Chakrabarti B. Effects of visible-light irradiation on vitreous structure in the presence of a photosensitizer. Exp Eye Res 1987; 44:863-70. [PMID: 3653277].
12. Akiba J, Ueno N, Chakrabarti B. Mechanisms of photo-induced vitreous liquefaction. Curr Eye Res 1994; 13:505-12. [PMID: 7924415].
13. Siegfried CJ, Shui YB, Holekamp NM, Bai F, Beebe DC. Racial differences in ocular oxidative metabolism: implications for ocular disease. Arch Ophthalmol 2011; 129:849-54. [PMID: 21746975].
14. Panickar KS, Anderson RA. Effect of Polyphenols on Oxidative Stress and Mitochondrial Dysfunction in Neuronal Death and Brain Edema in Cerebral Ischemia. Int J Mol Sci 2011; 12:8181-207. [PMID: 22174658].
15. Haorah J, Ramirez SH, Schall K, Smith D, Pandya R, Persidsky Y. Oxidative stress activates protein tyrosine kinase and matrix metalloproteinases leading to blood-brain barrier dysfunction. J Neurochem 2007; 101:566-76. [PMID: 17250680].
16. Pinazo-Durán MD, Gallego-Pinazo R, García-Medina JJ, Zanón-Moreno V, Nucci C, Dolz-Marco R, Martínez-Castillo S, Galbis-Estrada C, Marco-Ramírez C, López-Gálvez MI, Galarreta DJ, Díaz-Llópis M. Oxidative stress and its downstream signaling in aging eyes. Clin Interv Aging 2014; 9:637-52. [PMID: 24748782].
17. Boettner EA, Wolter JR. Transmission of the ocular media. Invest Ophthalmol 1962; 1:776-83. .
18. Brockmann C, Schulz M, Laube T. Transmittance characteristics of ultraviolet and blue-light-filtering intraocular lenses. J Cataract Refract Surg 2008; 34:1161-6. [PMID: 18571086].

19. Laube T, Apel H, Koch HR. Ultraviolet radiation absorption of intraocular lenses. Ophthalmology 2004; 111:880-5. [PMID: 15121363].

20. Sebag J. Is pharmacologic vitreolysis brewing? Retina 2002; 22:1-3. [PMID: 11884870].

21. Kakehashi A, Takezawa M, Akiba J. Classification of posterior vitreous detachment. Clin Ophthalmol 2014; 8:1-10. [PMID: 24376338].

22. Artigas JM, Felipe A, Navea A, Artigas C, García-Domene MC. Spectral transmittance of intraocular lenses under natural and artificial illumination: criteria analysis for choosing a suitable filter. Ophthalmology 2011; 118:3-8. [PMID: 20801517].

23. Yano E. Mineral fibre-induced malondialdehyde formation and effects of oxidant scavengers in phagocytic cells. Int. Arch. Occup. Environ. 1988; 61:19-23. .

24. Ghigo D, Aldieri E, Todde R, Costamagna C, Garbarino G, Pescarmona GP, Bosia A. Chloroquine stimulates nitric oxide synthesis in murine, porcine, and human endothelial cells. J Clin Invest 1998; 102:595-605. [PMID: 9691096].

25. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Third mid-cycles revision edition. Lippincott Williams & Wilkins, London, 2012.

26. Lapcík L Jr, Omelka L, Kuběna K, Galatík A, Kellö V. Photodegradation of hyaluronic acid and of the vitreous body. Gen Physiol Biophys 1990; 9:419-29. [PMID: 2177021].

27. Micelli-Ferrari T, Vendemiale G, Grattagliano I, Boscia F, Arnese L, Altomare E, Cardia L. Role of lipid peroxidation in the pathogenesis of myopic and senile cataract. Br J Ophthalmol 1996; 80:840-3. [PMID: 8942384].

28. Akiba J. Prevalence of posterior vitreous detachment in high myopia. Ophthalmology 1993; 100:1384-[PMID: 8371928].

29. Bosch-Morell F, Sanz A, Díaz-Llopis M, Romero FJ. Lipid peroxidation products in human subretinal.

30. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular risk factors, and age related maculopathy: the Blue Mountains Eye Study. Arch Ophthalmol 1998; 116:583-7. [PMID: 9596493].

31. Smith EB. Fibrinogen, fibrin and the arterial wall. Eur Heart J 1995; 16:11-4. [PMID: 7796823].

32. Brzović-Šarić V, Landeka I, Šarić B, Barberić M, Andrijašević L, Cerovski B, Oršolić N, Đikić D. Levels of selected oxidative stress markers in the vitreous and serum of diabetic retinopathy patients. Mol Vis 2015; 21:649-64. [PMID: 26120270].

33. Bates DO. Vascular endothelial growth factors and vascular permeability. Cardiovasc Res 2010; 87:262-71. [PMID: 20400620].

34. van Norren D, Van de Kraats J. Spectral transmission of intraocular lenses expressed as a virtual age. Br J Ophthalmol 2007; 91:1374-5. [PMID: 17895419].

35. Bron AJ, Vrensen GFJM, Koretz J, Maraini G, Harding JJ. The ageing lens. Ophthalmologica 2000; 214:86-104. [PMID: 10657747].

36. Ham WT Jr, Mueller HA, Sliney DH. Retinal sensitivity to damage from short wavelength light. Nature 1976; 260:153-5. [PMID: 815821].

37. Sparrow JR, Miller AS, Zhou J. Blue light-absorbing intraocular lens and retinal pigment epithelium protection in vitro. J Cataract Refract Surg 2004; 30:873-8. [PMID: 15093654].

38. Tanito M, Kaidzu S, Anderson RE. Protective effects of soft acrylic yellow filter against blue light-induced retinal damage in rats. Exp Eye Res 2006; 83:1493-504. [PMID: 16997296].

39. Mancino R, Di Pierro D, Varesi C, Cerulli A, Feraco A, Cedrone C, Pinazo-Duran MD, Coletta M, Nucci C. Lipid peroxidation and total antioxidant capacity in vitreous, aqueous humor, and blood samples from patients with diabetic retinopathy. Mol Vis 2011; 17:1298-304. [PMID: 21633716].

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