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REVIEW ARTICLE

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Ageing and ocular problems

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ABSTRACT

Ageing is a common problem in modern societies. Due to sophisticated new methods in medicine, the average life expectancy significantly increased in recent years. 70 is the new 50. The new principles of food intake and processing, more exercise, and less smoking contributed to a health benefits and a longer life span of human kind. Nevertheless, there are the special problems of ageing. Numerous dysfunctions of the body may arise affecting a broad range of organs and the musculoskeletal system. The eye can also be severely affected by ageing. Vision gained more importance recently especially during the COVID-19 pandemic. Elderly people who never used computers before, had to learn computer technology in order to communicate with their family and to accomplish their everyday tasks or pay their bills. Therefore, good near vision has become crucial for elderly people. In this review article the most common ageing problems of the eye, therapies and pathophysiology of ageing processes will be reviewed and discussed. There are physiological problems of ageing and there are ocular pathologies which can be treated efficiently in time to preserve near and far visual acuity.

KEYWORDS

ageing, eye, cornea, crystalline lens, retina, pathophysiology of ageing of the eye

INTRODUCTION

Ageing is a common problem of modern societies, although ocular ageing starts earlier than physiological one. Ocular ageing problems start around the age of 45 with presbyopia. As years pass by, more and more eye problems may arise, such as cataract, glaucoma, and age-related macular degeneration (AMD). At first, here are the most important examination methods in ophthalmology (Table 1) and some recommendations for elderly patients in terms of preventive eye care (Table 2).

The eye is one of the most sophisticated structures of the human body. It represents only 1% of the body surface, however, in orientation and learning its importance is about 95%. Modern life needs perfect vision for the elderly people as well.

The eye is composed of highly organised tissues, which should maintain transparency for the whole life span. The eye itself acts as a simple camera. The main task of the eye is to collect light, to focus it on the macula in order to transform the energy of light into electrical impulses which travel finally from the eye through the optic nerve to the occipital lobe of the brain. There the electrical impulse will be processed to image. Within the retina there are two different types of photoreceptors: for clear vision the cones are the most important, while for perceiving the environment in dim light the rods are needed. The processed neural pulses reach the second layer of the retina, namely the bipolar cells and the tertiary neurons, which are the ganglion cells. The nerve bundles then unify into the optic nerve (second cranial nerve).

For the perfect image a healthy tear film, transparency of the cornea, aqueous humour, the crystalline lens, the vitreous body are needed, as well as a perfect structure of the multilayer retina and the neuronal system (optic pathway) is required. Unfortunately, ageing

Table 1. Most important examination methods in ophthalmology

Most important examination methods in ophthalmology
Visual acuity testing
Eyelid and conjunctival examination
Corneal examination by slit lamp
Pupil examination (direct and indirect flashlight testing), pupil dilation
Extraocular muscles movement
Ophthalmoscopy for fundus examinations
Slit lamp examination
Visual field testing
Colour vision testing
Tonometry (Goldmann tonometry to check intraocular pressure)
Angiography (FLAG = Fluorescein Angiography)
Optical coherence tomography (OCT)
Ultrasonography
Electrophysiology: Visual Evoked Potential (VEP), Electroretinography (ERG)
CT and MRI

Table 2. What is recommended for elderly patients?

Recommendations for elderly patients
Have regular ophthalmic assessment (every year after the age of 50 yrs)
Stop smoking (increasing the incidence of cataract formation and AMD)
Exercise
Eat diet rich in green or fish
Check and control diabetes
Less fat and less carbohydrate intake
Wear protective sunglasses against ultraviolet (UV) burden outside when the sunshine is strong
Wear protective glasses during sport and during work (to avoid household and workplace accidents)

affects almost all these structures in a different way, which finally may lead to decrease in vision and thus decreased psychosocial functioning. There are some approaches to slow the ageing process of the eye, but because of the complexity of the anatomical structures, it is not an easy process.

THE MOST IMPORTANT AGE-RELATED EYE DISORDERS

Presbyopia

The inability to see close objects clearly or to read. Presbyopia starts on average at the age of 45 yrs. The cause is the stiffness of the crystalline lens and the zonules. It is part of the normal ageing process, and people need presbyopic correction to compensate for the stiffness of the crystalline lens. Those who do not want to wear reading glasses need multifocal intraocular lenses inserted during cataract/clear lens surgery.

Dry eye (keratoconjunctivitis sicca)

Cause: the quality of the tear alters with age related hormonal changes or the lacrimal gland cannot produce enough tears. It causes itching, a burning sensation, and in severe cases a decrease of visual acuity due to tear film irregularity.

Tearing

The cause is usually a blocked tear duct, when more tear is produced than drained. Normally sensitivity to pollen or dust, strong wind or intensive light may also cause excessive tearing.

Conjunctivitis

The other name is “pink eye”. The cause is local inflammation. Normally bacterial infection, mechanical injury, chemicals, and allergy may cause symptoms of conjunctivitis. Abnormal eye lid position may also cause it.

Eyelid problems

The main task of the eyelid is to protect the eye globe. Entropion means inward position of the eyelids. Ectropium means outward position of the eyelid. The cause normally is the uneven strength of the eyelid muscles which are responsible to turn inward or outward the eyelid. Most of the time the lower eyelid is affected. Abnormal eye lashes also cause problems and excessive tearing.

Corneal diseases

The human cornea represents the largest refractive power within the eye, it has on average a +43.0 Dpt of refraction and helps focusing the light. With age, the number of endothelial cells decreases. At birth the average number is cc. 5,000 mm⁻². If the number decreases below 1,000 mm⁻², endothelial cells are not able to dehydrate the cornea, and as a result oedema will appear and the transparency will be lost. Infection, toxic fluid, or injury may also endanger the transparency of the cornea.

Temporal arteritis

The inflammation of the temporal artery in the temporal region usually starts with a strong headache, pain during chewing, and tenderness at the temporal part of the head. Fever, shoulder or hip weakness may occur and the scalp becomes tender. Usually, vision will be lost soon in one eye. In untreated cases, the other eye might go blind as well. Patients need high dose steroids.

Cataract

The cause is developing cloudy areas within the crystalline lens or within the whole lens. The vision becomes blurry, the patient cannot read and cannot see well for far and near. The condition can be successfully operated with modern cataract surgery. Premium lenses may restore vision quality which the patient had only during younger ages.

Glaucoma

Glaucoma means higher intraocular pressure, which might damage the ganglion cells of the retina and the optic nerve, leading to visual field defect and in certain cases blindness. There are two main types of glaucoma: angle closure glaucoma (ACG) causes painful acute onset of very high intraocular pressure and requires quick ophthalmic intervention. The other type, primary open angle glaucoma (POAG), occurs with insidious onset. The pressure increase is gradual, there is no pain. Such patients need regular measurement of the IOP, moreover, regular check of the visual field and anti-glaucomatous topical medication is needed long term. If eye pressure cannot be controlled medically, surgery is needed.

Vitreous floaters and flashes

Floaters are tiny spots within the visual field, caused usually by vitreous collagen strands after liquefying the gel-like structure of the vitreous. If vitreous strands pull the retina, feeling of light flashes may bother the patient. The mechanical pull force causes electric signals in the retina, which the patient perceives as lightning. A dilated fundus examination is recommended in all cases.

Age-related macular degeneration (AMD)

The macular area is a tiny central part of the fundus, containing only cones and its role is crucial in sharp vision and reading. AMD causing first distorted, later blurred vision and inability to read. The cause is loss of retinal pigment epithelium (dry AMD) or growing of blood vessels (wet-AMD) under the macular area. There is no special treatment for dry AMD, anti-VEGF (Vascular Endothelial Growth Factor) intravitreal injection may offer improving visual acuity for wet-AMD.

Diabetic retinopathy

Diabetic retinopathy is always a complication of diabetes mellitus. During the early phase small retinal blood vessels leak fluid, causing blurred vision and a cystoid type macular oedema (CME) may arise within the macula. In severe cases abnormal blood vessels appear outside the retina, causing further visual deterioration (proliferative diabetic retinopathy), bleeding within the vitreous, proliferation of connective tissue around the great vessel arcade, consequent scarring and retinal detachment, and finally blindness.

Retinal detachment

It means the elevation of the retina from the choroid, causing acute visual loss if the macular area also detaches. Main symptoms: floaters, spots and flashes of light. Vision appears wavy, later dark shadow or curtain appears within the field of vision.

PHYSIOLOGICAL AND PATHOLOGICAL CHANGES WITH INCREASING AGE

Cornea together with the lacrimal gland and lids may also be affected by ageing. Less tear with altered composition may

lead to ocular surface irregularities, which decrease the visual acuity and lead to physical complaints, such as itching, pain, and foreign body sensation [1–3]. The corneal endothelial cell also diminishes with age [4]. Surgical interventions should be atraumatic, not causing more damage in the endothelium than what is unavoidable. Fuch's corneal dystrophy causing early death of endothelial cells, and consequently corneal oedema and decreasing vision, is usually associated with mutations in specific genes. Oxidative stress is an important factor causing early and accelerated endothelial cell death [5]. Environmental or man-made UV exposure may also cause oxidative stress for the cornea. Pterygium, conjunctival chalasis, benign tumour, and basal cell carcinoma occur more frequently among elderly people. Involution of the lacrimal gland and Meibomian glands may also lead to dry eye syndrome and tear deficiency [6]. Dry eye syndrome is a great socioeconomic burden and affects about 14–15% of the population above 50 years of age. The most important problem is that the disease reduces the quality of life (QoL) of the patients, decreasing productivity and generating enormous costs for patients and for the society as well [7].

During ageing the fibres within the crystalline lens and the zonular fibres stiffen, resulting in loss of accommodation. The protein concentration and types also change with the years, resulting in the discoloration of the central part of the lens [1]. Diabetes mellitus and smoking both mean oxidative stress to the body. Taking steroid medication may lead to posterior subcapsular cataract formation. Most importantly the oxidative stress contributes to developing lens opacities, which first cause change in refraction toward myopia, later non-transparent opacities which need surgical cataract operation [1].

Within the retinal tissue there is accumulation of intra- and extracellular deposits. Intracellularly this is lipofuscin, which is frequently found within the retinal pigment epithelium. If the RPE cells are exposed to oxygen and light, reactive oxygen is generated [8]. Studies also confirmed that lipofuscin deposits may drive immune dysregulation through monocytes and the choriocapillaris [9]. Drusen means an accumulation of esterified and cholesterol rich material between the RPE and basal membrane [10]. Large drusen is usually a hallmark of dry type of AMD. With progression it may develop to geographic atrophy (dry AMD) and wet-AMD. Wet-AMD is caused by choroidal neovascularisation. Both types of AMD cause vision loss. In the pathogenesis a common variant of the complement factor H (CFH) gene means an increased risk for developing AMD [11]. CFH gene reduces the alternate pathway of complement activation. Oxidative stress and inflammatory chemicals increase the progression of dry-AMD.

On the other hand, in the development of wet-AMD the role of macrophage ageing has got into focus recently. M1-like macrophages have an antiangiogenic effect. With age M1-like macrophages polarise to M2-like macrophages [12]. M2-like macrophages show an altered cytokine profile, which contributes to inflammation and loss of ability to stop angiogenesis [13, 14]. Old macrophages have higher

cholesterol content and influx, also causing pathological vascular proliferation and inflammatory processes. Drusen deposits containing lipoprotein in interaction with macrophages lead to abnormal macrophage activation. Besides the abnormal activation of the renin-angiotensin system (RAS) the development of choroidal neovascular membranes (CNV) was also affected [15]. So, the pathogenesis of AMD is multifactorial regarding dietary problems, high fat diet with apolipoprotein E genotype dominance may also cause AMD. The multifactorial development of AMD means that both genetic and environmental factors are important in the pathophysiology of AMD.

In case of dry AMD there is no specific treatment, except for special vitamin C and E with antioxidant effect [16]. On the other hand, wet-AMD can be treated with anti-VEGF (e.g., aflibercept, ranibizumab, bevacizumab, conbercept) intravitreal injection [17]. In spite of thorough medical treatment, some cases lead to legal blindness. Patients with low vision usually show depression and anxiety, which is a substantial burden for the patients, and for the families and societies as well. Earlier photodynamic therapy was also available, although today it is confined to treat myopic choroidal neovascularisation in the macular area. Further studies are needed to find more effective therapies for dry and wet AMD.

Glaucoma is a neurodegenerative disease, characterised by higher intraocular pressure and increase in cup-to-disc ratio and by the death of retinal ganglion cells (RGC). The damage of RGC can be caused by numerous problems, such as glutamate-mediated cytotoxicity, oxidative stress mechanisms, and mitochondrial dysfunction [18, 19]. Neuroprotection was a great promise, maintaining long-term ocular functioning, however, results were not as successful as expected [20]. Numerous topical treatments are available, aiming to reduce aqueous humour production or facilitating outflow mechanisms. Filtration surgery such as trabeculectomy or minimally invasive glaucoma surgery, deep sclerectomy, and glaucoma implants are available in case of POAG. Using different types of lasers was a great promise in glaucoma treatment. Today lasers may help reducing or leaving antiglaucomatous topical therapy. Lasers may treat the iris (laser iridotomy) or may act directly on the trabecular meshwork, facilitating outflow mechanisms. In case of acute angle closure glaucoma iridotomy, iridectomy, removal of the crystalline lens can be indicated besides topical therapy (pupil constriction and decreasing aqueous production).

CONCLUSIONS

In the future, gene therapy might offer better solutions for age-related ocular problems. In case of AMD, gene therapy will play an important role, glaucoma and corneal diseases are also possible targets for gene replacement or modulation. Deceleration of biological ageing are also a target for other medical professions, restriction of calorie intake, physical exercise, and activation of autophagy (especially in retinal

deposits) are promising possible solutions. As long-term solutions, the far-reaching effects on systemic ageing should be kept in mind.

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REFERENCES

- Horowitz A. The prevalence and consequences of vision impairment in later life. *Top Geriatr Rehabil* 2004;20:185–95. <https://doi.org/10.1097/00013614-200407000-00006>.
- Uchino Y, Kawakita T, Miyazawa M, et al. Oxidative stress induced inflammation initiates functional decline of tear production. *PLoS One* 2012;7:e45805. <https://doi.org/10.1371/journal.pone.0045805>.
- Moss SE, Klein R, Klein BE. Prevalence of and risk factors for dry eye syndrome. *Arch Ophthalmol* 2000;118:1264–8. <https://doi.org/10.1001/archophth.118.9.1264>.
- Joyce NC, Harris DL, Zhu CC. Age-related gene response of human corneal endothelium to oxidative stress and DNA damage. *Invest Ophthalmol Vis Sci* 2011;52:1641–9. <https://doi.org/10.1167/iiov.10-6492>.
- Jurkunas UV, Bitar MS, Funaki T, Azizi B. Evidence of oxidative stress in the pathogenesis of fuchs endothelial corneal dystrophy. *Am J Pathol* 2010;177:2278–89. <https://doi.org/10.2353/ajpath.2010.100279>.
- Prabhasawat P, Tesavibul N, Mahawong W. A randomized double-masked study of 0.05% cyclosporine ophthalmic emulsion in the treatment of meibomian gland dysfunction. *Cornea* 2012;31:1386–93. <https://doi.org/10.1097/ICO.0b013e31823cc098>.
- Kempen GI, Balleman J, Ranchor AV, van Rens GH, Zijlstra GA. The impact of low vision on activities of daily living, symptoms of depression, feelings of anxiety and social support in community-living older adults seeking vision rehabilitation services. *Qual Life Res* 2012;21:1405–11. <https://doi.org/10.1007/s11136-011-0061-y>.
- Wassell J, Davies S, Bardsley W, Boulton M. The photoreactivity of the retinal age pigment lipofuscin. *J Biol Chem* 1999;274:23828–32. <https://doi.org/10.1074/jbc.274.34.23828>.
- Ma W, Coon S, Zhao L, Fariss RN, Wong WT. A2E accumulation influences retinal microglial activation and complement regulation. *Neurobiol Aging* 2013;34:943–60. <https://doi.org/10.1016/j.neurobiolaging.2012.06.010>.
- Curcio CA, Millican CL, Bailey T, Kruth HS. Accumulation of cholesterol with age in human Bruch's membrane. *Invest Ophthalmol Vis Sci* 2001;42:265–74.
- Edwards AO, Ritter R, 3rd, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related

- macular degeneration. *Science* 2005;308:421–4. <https://doi.org/10.1126/science.1110189>.
12. Cruz-Guilloty F, Saeed AM, Echegaray JJ, et al. Infiltration of proinflammatory M1 macrophages into the outer retina precedes damage in a mouse model of age-related macular degeneration. *Int J Inflam* 2013;503725. <https://doi.org/10.1155/2013/503725>.
 13. Cruz-Guilloty F, Saeed AM, Duffort S, et al. T cells and macrophages responding to oxidative damage cooperate in pathogenesis of a mouse model of age-related macular degeneration. *PLoS One* 2014;9:e88201. <https://doi.org/10.1371/journal.pone.0088201>.
 14. Apte RS, Richter J, Herndon J, Ferguson TA. Macrophages inhibit neovascularization in a murine model of age-related macular degeneration. *PLoS Med* 2006;3:e310. <https://doi.org/10.1371/journal.pmed.0030310>.
 15. Satofuka S, Ichihara A, Nagai N, et al. (Pro)renin receptor promotes choroidal neovascularization by activating its signal transduction and tissue renin-angiotensin system. *Am J Pathol* 2008;173:1911–8. <https://doi.org/10.2353/ajpath.2008.080457>.
 16. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. *Arch Ophthalmol* 2001;119:1417–36. <https://doi.org/10.1001/archophth.119.10.1417>.
 17. Browning DJ, Kaiser PK, Rosenfeld PJ, Stewart MW. Aflibercept for age-related macular degeneration: a game-changer or quiet addition? *Am J Ophthalmol* 2012;154:222–6. <https://doi.org/10.1016/j.ajo.2012.04.020>.
 18. Feilchenfeld Z, Yücel YH, Gupta N. Oxidative injury to blood vessels and glia of the pre-laminar optic nerve head in human glaucoma. *Exp Eye Res* 2008;87:409–14. <https://doi.org/10.1016/j.exer.2008.07.011>.
 19. Abu-Amero KK, Morales J, Bosley TM. Mitochondrial abnormalities in patients with primary open-angle glaucoma. *Invest Ophthalmol Vis Sci* 2006;47:2533–41. <https://doi.org/10.1167/iovs.05-1639>.
 20. Nucci C, Martucci A, Giannini C, Morrone LA, Bagetta G, Mancino R. Neuroprotective agents in the management of glaucoma. *Eye (Lond)* 2018;32:938–45. <https://doi.org/10.1038/s41433-018-0050-2>.