Chapter 14
Aging Disorders of the Eye: Challenges and Approaches for Their Treatment

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Abstract The proportion of the global population aged 60 years and over is steadily increasing and projected to increase to almost 30 % in 2050. Among the various health problems, eye and vision problems are serious issues in the elderly. These may be manifested as basic functional disabilities or a decline in the receptive, storage, and analytical capacities of the central visual system. The major eye disorders of aging are cataract, age-related macular degeneration (AMD), glaucoma, and diabetic retinopathy. Although there are treatment methods (e.g., medications and surgical interventions) for these conditions, they are still very challenging areas due to the delicate and critical nature of the eye tissues. Compared with drug delivery to other parts of the body, drug delivery to the eye has met with significant challenges posed by various ocular barriers, which are inherent and unique to the ocular anatomy. In addition, in the case of the aging population, there are added difficulties due to multiple diseases and health problems, the several medications being taken together and the physical and psychological difficulties, including disabilities, dependence, fears, and apprehensions: opening packages, swallowing oral medication and/or reading leaflet information, fear of surgery, and device insertion and removal.

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This chapter discusses:

(a) Brief of anatomy of the eye and aging changes in the eye
(b) The major age-related eye problems, including cataract, AMD, diabetic retinopathy, and glaucoma
(c) The current treatment methods, novel drug delivery systems, and approaches being investigated for each of abovementioned eye problems

Maintaining good vision is an important part of "active aging," a concept promoted by the WHO. Active aging means continued health, security, and participation in society as people age, in order to ensure a good quality of life in later years. Nations and communities have to gear up to this challenge to ensure that good quality eye care and therapies are available to this group.

Keywords Aging disorders of the eye • Cataract • Diabetic retinopathy • Age-related macular degeneration • Glaucoma

14.1 Introduction

There is an overall change in the pattern of the world's population, mainly because of improved primary healthcare facilities and services; older people are making an ever greater proportion of the population. As this trend continues, it is projected that by 2050, 30 % of the population will be the elderly (more than 80 years). The process of aging involves a continuum of chemical, biological, functional, psychological, and social parameters which can vary depending on the genetic factors, age, vulnerability, and organ function and reserves. Among other health problems like hypertension, diabetes, arthritis, parkinsonism, and osteoporosis, eye and vision problems also emerge in the elderly; these may be due to decline in basic functions or in the receptive, storage, and analytical capacities. Various surveys and literature reports have highlighted the extent of the aging problems in vision and the challenges in this area [1–6].

14.1.1 Human Eye

The human eye is the organ that reacts to light and allows conscious light perception and vision including color differentiation and the perception of depth and can distinguish about 10 million colors. This important sense organ is highly complex and requires a great deal of care and specialized attention throughout life. Compared with drug delivery to other parts of the body, drug delivery to the eye has met with significant challenges posed by various ocular barriers. Many of these barriers are inherent and unique to ocular anatomy and physiology making

it a challenging task for drug delivery scientists. These barriers are specific depending upon the route of administration, viz., topical, systemic, and injectable. These barriers are a part of the body's normal protective mechanisms to prevent external toxicants entering the eye.

14.1.2 Structure and Functions of the Eye

Each eyeball is contained in a bony cavity known as orbit, which is a pear-shaped structure formed by several bones; along with the eyeball, it also houses associated structures, muscles, nerves, and blood vessels, as well as the lachrymal glands, and is composed of several layers.

14.1.2.1 Sclera

Sclera is the outer covering, a relatively tough, opaque, fibrous, and protective white layer (white of the eye), and is composed of collagen and elastic fiber. It is continuous with the dura mater of the brain and the cornea and maintains the shape of the globe, offering resistance to internal and external forces; besides it provides an attachment for the extraocular muscle insertions. Near the front of the eye, in the area protected by the eyelids, a thin, transparent membrane (conjunctiva) running up to the edge of the cornea covers the sclera, as well as the moist back surface of the eyelids and eyeballs. Human eyes are somewhat distinctive in the animal kingdom in that the sclera is very plainly visible whenever the eye is open, due to its white color and the relatively small size of human iris, which comprises a significantly smaller portion of the exposed eye surface compared to other animals. This adaptation evolved because of our social nature, and thus the eye is considered to be a useful communication tool [7, 8].

14.1.2.2 Choroid

Choroid is the middle layer or tunic, which is the vascular layer of the eye, containing connective tissue and lying between the retina and the sclera. The human choroid is thickest at the far extreme rear of the eye (0.2 mm), while in the outlying areas, it narrows to 0.1 mm. This layer is comprised of blood vessels, melanocytes, fibroblasts, resident immunocompetent cells, and supporting collagenous and elastic connective tissue. As one of the most highly vascularized tissues of the body, its main function has been traditionally viewed as supplying oxygen and nutrients to the outer retina, and, in species with avascular retinas, to the inner retina as well. Other likely functions include light absorption (in species with pigmented choroids), thermoregulation via heat dissipation, and modulation of intraocular pressure (IOP) via vasomotor control of blood flow. The choroid also plays an important role in the drainage of the aqueous

humor from the anterior chamber, via the uveoscleral pathway. This pathway is responsible for approximately 35 % of the drainage in humans; a higher percentage, between 40 % and 60 %, in nonhuman primates; and a much lower percentage in the cat (about 3 %) and rabbit (3–8 %) [9]. Along with the ciliary body and iris, the choroid forms the uveal tract. In addition some uveal regions have special functions of great importance, including secretion of the aqueous humor by the ciliary processes, control of accommodation (focus) by the ciliary body, and optimization of retinal illumination by the iris's control over the pupil. Many of these functions are under the control of the autonomic nervous system [10, 11].

14.1.2.3 Retina

Retina is the light-sensitive layer of tissue, lining the inner surface of the eye, and can be compared to the film of a camera. The optics of the eye creates an image of the visual world on the retina (through the cornea and lens). Light striking the retina initiates a cascade of chemical and electrical events that ultimately trigger nerve impulses, which are sent to various visual centers of the brain through the fibers of the optic nerve. The retina and the optic nerve originate as outgrowths of the developing brain; hence the retina is considered to be part of the central nervous system (CNS) and is actually a brain tissue [11]. It is the only part of the CNS that can be visualized noninvasively.

The retina contains several millions of photoreceptors, which sense light and the blood vessels that nourish them. There are basically two types of photoreceptors – rods and cones. Cones are responsible for sharp, detailed central vision and color vision and are clustered mainly in the macula, whereas the rods are responsible for night and peripheral (side) vision. Rods are more numerous than cones and much more sensitive to light and are grouped mainly in the peripheral areas of the retina. A high density of cones is present within a small area known as macula, which is the most sensitive part of the retina. This helps to create a detailed visual image. The nerve fibers linked to each photoreceptor are grouped and bundled together to form the optic nerve. The photoreceptors convert the image into electrical signals, which are carried to the brain by the optic nerve [10–12].

14.1.2.4 Process of Vision

Light enters the eye through the cornea, the clear, curved layer in front of the iris and pupil. The cornea serves as a protective covering for the front of the eye and also helps focus light on the retina at the back of the eye. After passing through the cornea, light travels through the pupil; the iris controls the amount of light that enters the eye, based on the intensity of light in surroundings. The size of the pupil is controlled by the action of the pupillary sphincter muscle and dilator muscle.

14.1.2.5 Lens of the Eye

The eye lens is situated behind the iris and is part of the anterior segment of the eye. The lens has an ellipsoid, biconvex shape. The anterior surface is less curved than the posterior. In the adult, the lens is typically circa 10 mm in diameter and has an axial length of about 4 mm, though it is important to note that the size and shape can change due to its power of accommodation and because the lens continues to grow throughout a person's lifetime. The lens is suspended in place by the suspensory ligament of the lens, a ring of fibrous tissue that attaches to the lens at its equator and connects it to the ciliary body. Posterior to the lens is the vitreous body, which, along with the aqueous humor on the anterior surface, bathes the lens. The power of accommodation of the lens is due to the action of small ciliary muscles. To focus on nearby objects, the lens becomes thicker, and to focus on faraway objects, it becomes thinner [13, 14].

14.1.2.6 Anterior and Posterior Segments of the Eye

The eyeball is divided into two sections – the anterior and posterior segments. The anterior segment extends from the inside of the cornea to the front surface of the lens and is filled with a fluid, the aqueous humor, which nourishes the internal structures. The posterior segment extends from the back surface of the lens to the retina and contains a jellylike fluid, the vitreous humor. The pressure generated by these fluids fills out the eyeball and helps maintain its shape. The anterior segment can be further divided into two chambers, the front (anterior) chamber extending from the cornea to the iris and the back (posterior) chamber, which extends from the iris to the lens. The aqueous humor is produced in the posterior chamber and flows slowly through the pupil into the anterior chamber and then drains out of the eyeball through outflow channels located where the iris meets the cornea [15, 16].

14.1.3 Aging Process in the Eye

An excellent review on aging eye is given by Salvi et al. [17]. With age, the functional abilities of the eye are affected; also the receptive, storage, and analytical capacities of the central visual system decline, resulting in the various vision problems seen in the elderly population. Two common theories to explain aging processes are the "biological clock theory" and the "wear-and-tear theory." The biological clock theory or programmed theory attributes aging to be an inherent characteristic of each individual governed by the unique genetic code in the DNA. However, lifestyle habits and other environmental factors can also contribute to the aging process. The wear-and-tear theory was first introduced in 1882, by Dr August Weismann, a German biologist. This theory explains aging to be a process wherein the body and its cells are damaged by overuse and abuse, and slowly over a period of time, all the organs, including the eye,

are worn down by dietary and environmental toxins (e.g., excessive consumption of fat, sugar, caffeine, alcohol, and nicotine; the ultraviolet rays of the sun, and also the various physical and emotional stresses). At the cellular level, the wear-and-tear process is explained as being caused by production of "free radicals," commonly referred to as reactive oxygen species (ROS). The ROS possess free electrons and are highly reactive species, which are capable of attacking the structure of cell membranes and creating metabolic waste products, like lipofuscins. In this process, key cellular processes like DNA and RNA synthesis and protein synthesis are affected; energy levels are lowered, affecting the vital body building processes and enzyme functions. In younger healthy people, the effects of ROS are less pronounced, due to the extensive repair and replacement mechanisms. With age, however the accumulated effects of free radical damage begin to show the typical aging effects. The aging effects in the eye in each of the regions of the eye are summarized in the sections below.

14.1.3.1 Eyelids and Lacrimal System

Eyelids show the typical aged look evidenced by shrinkage, folds, and wrinkles. Loss of adnexal structural support of tarsus, canthal tendons, and orbicularis muscle with thinned skin leads to orbital fat prolapse, eyelid malposition, blepharoptosis, and tearing. In the lower eyelid, horizontal lid laxity is common. Reduction in the orbital fat with aging causes the eyes to "sink in" accentuating the lid laxity. Other aging effects include ectropion or eversion of the eyelid margin from the globe and subsequent symptoms of a watery eye, inversion (entropion) instead causing eyelashes to rub against the cornea and subsequent discomfort, involutional ptosis, age-related descent of the brow (brow ptosis), and dermatochalasis or pseudoptosis, also known as "baggy eyes." In all these conditions, if they interfere with vision, oculoplastic surgery is the remedy. These operations are often carried out before a cataract operation to avoid infection. In entropion, temporary relief may be achieved by simply taping the lid to pull it outwards.

Lachrymal Glands There are two extreme conditions seen:

(a) *Watery eye* in the elderly is often caused by eyelid malposition or sometimes from true lacrimal obstruction leading to distressful watering or recurrent infections; treatment is by dacryocystorhinostomy.
(b) *Dry eye syndrome* is due to reduction in the amount of tears produced by the lacrimal gland. This condition is treated with artificial tears or punctual plugs to retain tears in the conjunctival sac [18].

14.1.3.2 Changes in the Cornea

With age, changes in corneal toricity (curvature) can cause alteration in refraction, resulting in astigmatism; and regular refraction checkups are advised to detect these changes. Besides this, there may be a decrease in corneal luster and corneal

sensitivity and increase in corneal fragility. Other observations include age-related dystrophic changes in the corneal epithelium, stroma and endothelium which involve deposition of iron, yellow white deposits of cholesterol esters and other lipids, deposition of uveal pigment, etc., and are referred to as Hudson-Stahli line, arcus senilis, Hassall-Henle bodies, Krukenberg spindle, and cornea guttata. These changes however do not interfere with vision and hence are not serious concerns [19].

Another observation is pleomorphism, which occurs as the endothelial cell density reduces with increasing age. As the cells cannot regenerate, the remaining endothelial cells enlarge to cover the gaps. Beyond a certain point, this affects corneal deturgescence, which can further cause corneal thickening, opacity, and decrease in quality of vision. If visual acuity is reduced, penetrating keratoplasty is recommended.

14.1.3.3 Changes in Trabecular Meshwork and Uvea

The trabecular meshwork is a spongy tissue in the eye located around the base of the cornea, near the ciliary body, and is responsible for draining the aqueous humor from the eye via the anterior chamber into a set of tubes called Schlemm's canal flowing into the blood system. On aging, there is often increased pigmentation of the trabecular meshwork and increase in the resistance to the outflow of aqueous humor; these changes can precipitate glaucoma. Besides this, the age-associated changes in the uvea are manifested as reduction in size of the pupil, pigment loss, and lower reactivity of the iris. Also, the shape and tone of ciliary body changes leading to decrease elasticity of the lens capsule and compactness of the lens fibers; this can affect the accommodative power of the lens, resulting in presbyopia.

14.1.3.4 Crystalline Lens Changes

On aging, the lens is known to selectively absorb more blue light (410 nm), which is a part of cataractogenic process, leading to a condition called "blue blindness." This has been attributed to the accumulation of yellow pigments in the lens. Other common and familiar sign of lens aging is the hardening (nuclear sclerosis) caused by various biochemical and photochemical changes, leading to presbyopia and further to cataract formation. Phacoemulsification and intraocular lens implantation are the methods to resolve these problems to ensure the performance of daily routine activities of the elderly [20]. Further details of cataract are given under Sect. 2.1.

14.1.3.5 Vitreous Aging

Aging processes in the vitreous humor are manifested as harmless floaters noticed by the elderly. The changes take place sequentially: condensation or liquefaction of the vitreous gel, followed by enhancement and increased mobility of the fibrillary structures of vitreous. As the liquefaction increases, there is formation of optically

empty spaces called lacunae; further accentuation of the lacunae leads to larger cavities and finally to shrinkage of vitreous body from the retina. Complications like posterior vitreous detachment (PVD) may be evident at around 50 % liquefaction; a retinal tear during acute PVD can further lead to retinal detachment, evident as a curtain-like shadow in the field of vision. In such cases, laser treatment and surgical intervention is advocated to prevent retinal detachment [21].

14.1.3.6 Retinal Aging

Retinal aging is mainly manifested as decreased visual function in various forms – acuity, field, contrast sensitivity, and increased dark adaptation threshold. A combination of changes in neuronal elements of visual system, changes in the ocular media, and pupillary miosis are responsible. Neurosensory retinal changes include decrease in ganglion cells and photoreceptors, thickening of basement membrane, and increase in corpora amylacea bodies and lipofuscin content. Several changes observed in RPE are increased pleomorphism, decrease in cells in posterior pole, decreased melanin content, decreased volume of cytoplasm, and increased lipofuscin content. Retinal macular microcirculation reduces with age and slowly results into age-related macular degeneration (AMD). Other observations evident in the optic nerve include regional swollen axons, decrease in the number of axons, increase in the thickness of the connective tissue, and increased elastic fibers. Clinical manifestations are loss of fundus reflexes, gradual fading of fundus color, greater visibility of larger choroidal vessels (senile tigroid fundus), peripapillary atrophy, and peripheral retinal degenerations. Details of some of these changes and AMD are discussed under Sect. 2.3 [22, 23].

14.2 Age-Related Disorders of the Eye

14.2.1 Cataract

A cataract is clouding of the lens of the eye, causing an obstruction in the passage of light and thereby interference with clear vision. Most cataracts are related to aging, although occasionally children may be born with the condition, or cataract may develop after an injury, inflammation, or disease. Cataract is the leading cause of blindness and responsible for 51 % of world blindness [24]. The extent of the vision loss depends on the size and location of the cataract. Cataracts may be located in the center of the lens (nuclear), in the superficial cortex (cortical), or in the posterior subcapsular area. Cataracts are also classified according to their color, which is consistent with the location and density of the cataract. Pale yellow cataracts are typically slight opacities of the cortex, subcapsular region, or both; yellow or light brown cataracts are consistent with moderate to intense opacities of the cortex, nucleus, or both; and brown cataracts are associated with dense nuclear cataracts [25].

Symptoms of cataract include near-vision image blur, abnormal color perception, monocular diplopia, glare, and impaired visual activity and may vary depending on the location of the cataract. For example, if the opacity is located in the center of the lens (nuclear cataract), myopia is often a symptom, whereas posterior subcapsular cataracts tend to be most noticeable in bright light [26].

14.2.1.1 Risk Factors for Cataract

14.2.1.1.1 Diabetes

People with diabetes have an increased risk of cortical and posterior subcapsular cataract and are also more likely to have early cataract surgery. The enzyme aldose reductase (AR) catalyzes the reduction of glucose to sorbitol through the polyol pathway, which is linked to the development of diabetic cataract. Intracellular accumulation of sorbitol leads to osmotic changes and further to degeneration of hydropic lens fibers and formation of sugar cataracts.

14.2.1.1.2 Prolonged Exposure to UVB Radiation

Increase in ultraviolet radiation resulting from depletion of ozone layer is expected to increase the incidence of cataract. Many experimental studies have shown that an increased number of UVB rays lead to a profound decrease in corneal antioxidants, which results in oxidative injury of the cornea and damage to the inner parts of the eye [27].

14.2.1.1.3 Tobacco and Alcohol Addiction

A higher prevalence of nuclear and posterior subcapsular cataracts is reported in case of people who smoked and drank heavily [28].

14.2.1.1.4 High Body Mass Index (BMI)

Study findings suggest that elevated BMI may increase the risk of age-related cataract (ARC), especially posterior subcapsular cataracts, but further trials are needed to investigate the effect of weight reduction in obese populations on the risk of ARC.

14.2.1.2 Mechanisms in Pathophysiology of Cataract Include

14.2.1.2.1 Electrolyte Disturbances

Electrolyte disturbances can result in osmotic imbalances to cause derangements in the membrane functions. These imbalances may be due to increased membrane permeability or to a depression of the [Na.sup.+]/[K.sup.+] pump or because of interference with the enzyme [Na.sup.+]/[K.sup.+] ATPase [29].

14.2.1.2.2 Oxidative Damage

Oxidative damage plays a major role in the etiology and pathogenesis of cataract, wherein the lens proteins are subjected to extensive oxidative modifications. Oxidation of lens proteins occurs due to generation of reactive oxygen species (ROS) like superoxide, hydrogen peroxide, and hydroxyl radicals. In cataractous lenses, the proteins are found in an insoluble, oxidized form. In the aging process, several posttranslational changes like racemization, glycation, -COOH terminal degradation, deamidation, and noncovalent aggregation of the proteins in the inner region of lens take place, which may markedly modify the overall conformation of the proteins. Along with this, certain key metabolically active components which protect the lens from stress appear to decrease in activity. This results in the formation of high molecular weight protein aggregates, covalently linked by disulfides. Some of these aggregates are greater than 50×10^6 Da, large enough to scatter light and contribute to the loss of transparency. Studies have shown considerable *oxidation of membrane lipids* in cataract compared to normal tissue [30]. Some studies have shown increased levels of hydrogen peroxide and significantly lower levels of glutathione (GSH) in cataractous lenses, compared to normal controls [30, 31].

14.2.1.3 Prevention and Treatment of Cataract

Cataracts are a part of aging process and not completely preventable. However, their occurrence can be delayed, by controlling the risk factors – quitting smoking, avoiding overexposure to sunlight, and avoiding excessive amounts of alcohol, which can help to a great extent. Importance of proper diet has been stressed in the elderly, especially foods rich in antioxidants. Several studies have compared the nutritional status and the occurrence of senile cataract. These investigators have reiterated the usefulness of fresh fruits and vegetables containing dietary antioxidants like ascorbic acid, carotenoids, lutein, and zeaxanthin; these are reported to lower the incidence of cataracts, severe enough to require extraction [32]. The relationship between antioxidant nutrient status and senile cataract was examined in 77 subjects with cataracts and 35 control subjects with clear lenses [33, 34].

14.2.1.3.1 Surgery

The most common option for patients with advanced cataract is surgery. The procedure involves removal of the natural opaque lens followed by insertion/implantation of an artificial intraocular lens fabricated from silicone or acrylic polymeric materials. Enormous research and surveys have been carried out in surgical techniques and the development of the lenses [35, 36]. There are two basic surgical procedures – phacoemulsification and extracapsular cataract extraction (ECCE). Lenses of various types – foldable, accommodating, and providing protections from UV light or blue light – are some examples of the features designed [35, 36]. Although safe, cataract surgeries are not without complications – posterior vitreous detachment, posterior capsular opacification or tear, retinal detachment, toxic anterior segment syndrome, endophthalmitis, glaucoma, edema of the cornea, and dislocation of implanted lens. The cost of surgery and the postoperative care are prohibitive, especially for the elderly patients. Hence, developing alternative means to control and treat cataract is an important area which is slowly gaining attention.

14.2.1.3.2 Therapeutic Drugs

Natural therapies that have been investigated and may be successful in cataract treatment are lutein and zeaxanthin carotenoids, bilberry extract, and combinations of antioxidants with vitamins, zinc, bioflavonoids, and caffeine [33]. Several drugs have been developed and investigated, aiming to treat and reverse the lens opacification in cataract. Drugs likes orbenil, aspirin, and sodium monomethyl trisilanol orthohydroxybenzoate have been studied and have shown promise in slowing down and preventing the progression of experimental sugar cataracts or partial reversal of early morphological signs [37]. A lot of research efforts have been directed on two chemically very close non-steroid anti-inflammatory drugs (NSAID), bendazac and benzydamine. These two drugs are reported to reduce the biological liquid oxidant activity and have shown some promise in clinical studies; on oral administration (500 mg, three times daily), they were able to stabilize the progression of lens opacification in cataract patients. Preliminary studies evaluating bendazac lysine 0.5% eyedrops have reported comparable results to those obtained with oral treatment. Although significant improvements in individual and mean visual acuities in treated patients have been reported by several studies, the parameters used have not been universally accepted as a reliable index of lens status; side effects observed include laxative effect and other gastrointestinal disturbances associated with oral therapy, and a transient burning sensation is the most commonly reported symptom occurring with eyedrop application [38]. The anti-cataract activity has been attributed to an active metabolite of the NSAID which has antioxidant activity. However, other possible mechanisms, such as protein and membrane stabilization and protective effect on photooxidative processes linked to free radicals, may also be responsible for effecting the reversal of cataractous opacity [39]. Further, these two drugs have also shown promise in the treatment of retinitis pigmentosa. as a drug capable of attenuating the biological effects of sun radiations on the retina [39, 40].

Based on above drugs, the potential of benzyl alcohol which is used as preservative in eyedrops has also been investigated and shown promise [41]. Pirenoxine (PRX) a pyridophenoxazine compound is another agent shown to protect the lens protein and crystallins against UVC-, selenite-, and calcium-induced lens protein turbidity; however, it was found detrimental under UVB exposure. A Japanese eye product, Catalin based on PRX, and also a Catalin-formulated vehicle are available and recommended for reducing various types of cataract development [42].

Clinical studies on Catalin eyedrops have been carried out and reports are variable. Kociecki et al. have observed that the eyedrops were well tolerated, and in patients with cortical cataract, the drug showed its effectiveness in inhibition of lens opacification and its progression, especially in group of patients with age up to 59 years [43]. Long-term studies spanning over 2 years, in 51 patients by Angra K et al., concluded that Catalin when instilled locally in the eye does not have any beneficial effect in checking the progress of senile and congenital cataract irrespective of the stage of its development. The natural course of progression of cataract was no way changed [38, 44, 45].

Another group of drugs investigated include the statins, and there are varied reports. Several groups have indicated that long-term use of statins conferred a protective effect against cataract surgery, whereas some of the reports conclude that statin therapy is associated with a modestly increased risk of cataract surgery [46].

N-Acetylcarnosine (NAC) is another important drug with potential anti-cataract efficacy. It is a derivative of carnosine, which is found in muscle tissue. These compounds have been reported to possess varying degrees of activity as free radical scavengers. NAC is particularly active against lipid peroxidation in the different parts of the lens in the eye [47]. Eyedrops containing *N*-acetylcarnosine have been studied in Russia for the treatment of cataracts and have been found to be successful. However, these drugs are not FDA approved and can be bought off the shelf as "lubricants" [48]. In China OTC products like Phacolysin, Catalin (a modified phenoxazine carboxylic acid) eyedrops, Tathion (glutathione eyedrops), and Zhangyanming tablets are used for the early and mid-stage cataracts. A Swiss product called Quinax (dihydroazapentacene or azapentacene polysulfonate) is used as a treatment for cataracts [49].

14.2.1.4 Drug Delivery Approaches for Treatment of Cataract

Topical drug application is the most widely accepted and convenient mode of ocular drug delivery to treat many eye disorders. But cornea is major barrier for drug delivery through this route for lens and retina, as large portion of drug is lost through precorneal losses. Considering the pathology of cataract, development of antioxidant formulation with optimum therapeutic efficiency and target specificity is necessary. To overcome the corneal barrier and to increase bioavailability of molecule, several novel approaches and delivery systems can be explored.

14.2.1.4.1 Liposomal Systems

Liposomal formulations are biodegradable and biocompatible in nature and have been studied and explored for ophthalmic drug delivery applications. The major focus has been to improve the corneal adhesion and permeation by incorporating various bioadhesive formulations based on hydrogels like Carbopol, polyacrylic acids, and chitosan. Another important approach involves the use of penetration enhancers, including different surfactants (Span 20, 40, and 85; Tween 20, 40, and 81; deoxycholic acid; taurocholic acid) and calcium chelators. The development of vitamin E-containing liposomes prepared with dipalmitoylphosphatidylcholine and dioleoylphosphatidylcholine indicated that instilled vitamin E-containing liposomes retard cataract progression in 12-month-old rats fed a 25 % galactose diet, mainly by the antioxidative and membrane-stabilizing actions. The development of disulfiram liposomes prevented cataract formation in rat pups with cataract induced by selenite [50]. Reports on anti-cataract effect of cationic freeze-dried liposomes containing cytochrome C were shown to be stable superior ophthalmic carriers and were able to markedly retard the onset of cataract development [51].

14.2.1.4.2 Nanoparticles (NP)

Biodegradable and biocompatible nanoparticles have been reported to enhance the pharmacokinetic and pharmacodynamic properties of encapsulated molecules. Studies on curcumin encapsulated PLGA NP for oral delivery showed better efficacy in delaying diabetic cataract in rat model [52]. NP of cerium oxide (CeO2) with antioxidant properties can also be applied in the prevention of cataract. The nano-encapsulation of quercitrin (potential anti-cataract agent) on PLA was found to enhance its antioxidant activity up to 40 % [53].

Encapsulation of biomolecules into nanoparticles may enhance protection against metabolic enzymes to decrease the dose and enhance uptake by corneal cells. This will aid in efficient treatment of cataract. Although surgery has been used for cataract treatment, it is a difficult procedure in the aged elderly population, who may also be having other disorders and complications. The aged often has difficulties in handling as well as fears and apprehensions in using devices; hence novel systems which are simple to administer should be developed as alternatives to surgery.

In a study by our group, mucoadhesive in situ gelling systems based on mucoadhesive polymers – poloxamer 407 and HPMC, incorporating catalase as active – were developed. Catalase is the endogenous enzyme responsible for eliminating the ROS. The feasibility for the prevention of cataract by these developed systems was assessed in vivo in oxidative stress-induced cataract by selenite induction, in Wistar rat pups [54]. Protective role of catalase was evident by the observation of transparency of excised lenses and also by the assessment of levels of malonaldehyde which is a marker lipid peroxidation and enzyme levels (Table 14.1 and Fig. 14.1) [55].

Table 14.1 Levels of catalase (CAT) and malonaldehyde (MDA) in the experimental selenite-induced Wistar rat pup lenses

Groups	CAT (units/mg protein)	nmol MDA/mg protein	Opacification score
(a) Normal control	1.685 ± 0.035	0.413 ± 0.015	0
(b) Cataract control	0.078 ± 0.054[a]	0.754 ± 0.172[b]	++ to ++++
(c) Cataract treated (plain enzyme solution)	1.18 ± 0.19[c]	0.474 ± 0.055[d]	0 to +
(d) Cataract treated (in situ gel)	0.93 ± 0.61[e]	0.479 ± 0.088[e]	0 to +

All values expressed as mean ± SD, (n = 6)
[a] $p < 0.01$ when compared with normal control
[b] $p < 0.05$ when compared with normal control
[c] $p < 0.001$ when compared with cataract control
[d] $p < 0.01$ when compared with cataract control
[e] $p < 0.05$
Opacification score: 0 no opacification, + slight opacification, ++ diffuse opacification involving periphery of lens, +++ diffuse opacification involving almost entire lens, ++++ extensively thick opacification involving almost entire lens

14.2.2 Diabetic Retinopathy

Diabetic retinopathy (DR) is one of the leading causes of blindness for diabetic patients due to the damaging effect on the capillaries in retina by hyperglycemia. In the count of 35 studies, 34.6% of 20,000 diabetic patients were diagnosed to have DR which means about 90 million patients are suffering from this disease [56]. DR is defined as a microvascular disease that leads to capillary occlusion and damage of light-sensitive tissues in the back of the eye as a complication of diabetes [57]. The retinal precapillary arterioles, capillaries, and venules would be all affected during its development. In the early stage, thickening of the basement membrane, loss of pericytes, and the development of microaneurysms could be detected [57, 58]. In the cellular pathology, the vascular endothelium cells have been altered by the high level of blood glucose. The abnormal endothelium will cause the platelet and leucocyte activation and thus adhesion together to cause the occlusion. At the molecular level, the occlusion leads to an ischemic retina, and the level of cytokines get elevated to promote the growth of new blood vessels through vascular endothelial growth factor (VEGF) which increase the vascular permeability in the early stage [57–60].

The development of DR can be divided into different stages: mild non-proliferative DR, moderate non-proliferative DR, severe non-proliferative DR, and proliferative DR. In the first two early stages, the vascular blockage was found but not severe enough to trigger the signal for growth of new blood vessels [61]. In the severe non-proliferative stage, the growth of new blood vessels is not as significant as the proliferative stage. Therefore, it was also known as pre-proliferative stage. In the proliferative stage, two types of new vessels will develop depending on their growth location in the eye: forward new vessels developed into vitreous cavity and flat new vessels remained on the surface of retina. There is a possibility of growing new vessels on the surface of the iris

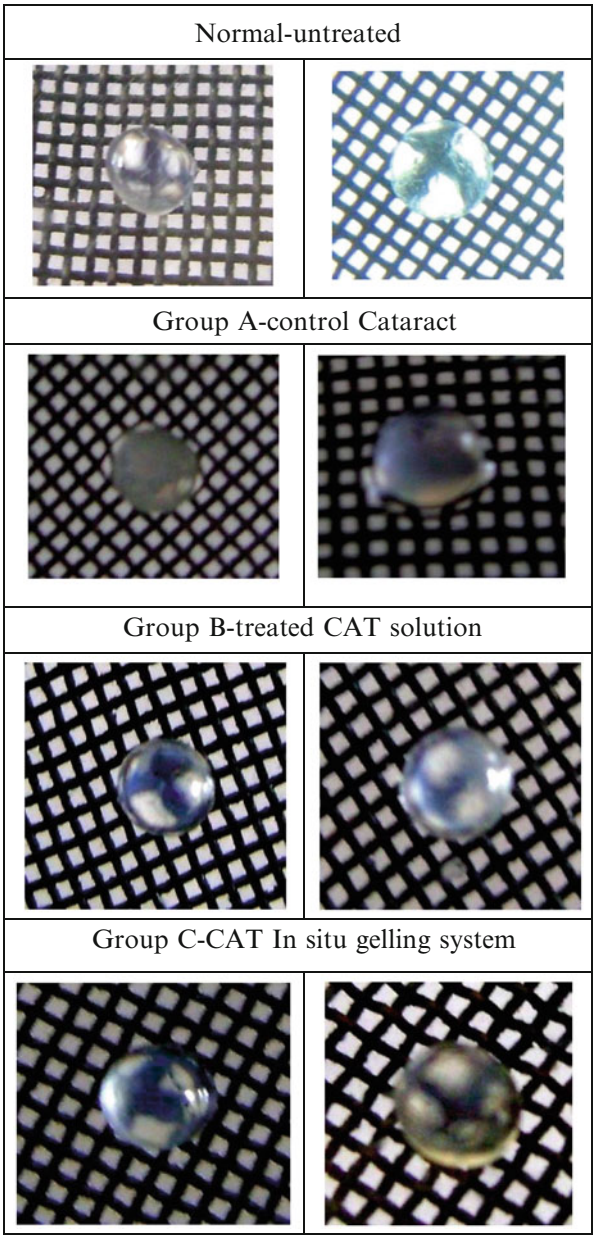

Fig. 14.1 Degree of opacification of lenses from different groups

which was known as rubeosis iridis [62]. These weak new vessels could lead to bleed, which will cause preretinal and vitreous hemorrhage. If the development of DR cannot be controlled in this stage, the fibrous tissue (gliosis) will appear around the new vessels and contracts. This will directly lead to the detachment of retina and eventually blindness for patients. The surgical treatment, such as laser treatment, is only recommended in the proliferative stage of DR. However, there are various pharmaceutical therapies to slow down the propagation of DR based on its different pathophysiology [63].

14.2.2.1 Pathophysiology and Treatment of DR

14.2.2.1.1 Polyol Pathway

The excessive glucose is the major characteristic for diabetes, and the polyol pathway is to reduce it to sorbitol by aldose reductase enzyme along with nicotinamide adenine dinucleotide phosphate (NADPH) [64, 65]. The poor permeability of sorbitol leads to its accumulation in the cells where it will be converted to fructose by sorbitol dehydrogenase (SDH) in a slow metabolism process [66]. The elevating level of sorbitol is reported to damage the retinal cells through various mechanisms, such as osmotic effect [67, 68]. The fructose, product of polyol pathway, could be phosphorylated to fructose-3-phosphate and further degraded to 3-deoxyglucosone, both of which are members of advanced glycation end products (AGEs), which are strongly related with DR conditions and retinal inflammatory diseases [68, 69]. The consumption of NADPH in polyol pathway could lead to its insufficiency in the formation of glutathione reductase which will weaken the antioxidant capacity of cells due to low level of glutathione and result in the compromise of the protection against oxidative stress [70]. Although the studies of aldose reductase inhibitors (ARIs) in animal models have shown some success, the human clinical trials have been a disappointment due to insufficient inhibition of the polyol pathway in human tissue [71]. An ARI, ARI-809, has been reported to be able to prevent retinopathy-like changes in an animal model of diabetes studies, but the clinical trials on humans are yet to be done [72]. The role of SDH in DR has attracted interest recently due to its more important role than ARIs and possibility to be a genetic factor in DR [73]. However, the targeted overexpression of SDH in retinal pericytes has shown the increase of ROS production which leads to toxicity via increased ROS production [68, 74].

14.2.2.1.2 Nonenzymatic Protein Glycation

AGEs are products from the nonenzymatic reaction of reducing sugars [64, 65]. Although the AGEs are synthesized in normal body, its accumulation rate is extremely slow in diabetic patients. AGEs and its precursors could further progress the DR by cross-linking proteins in various locations, such as cellular matrix, basement membranes, and vessel-wall components, which will eventually result into the

alteration of their structures and functions [75–77]. Moreover, AGEs could combine with various receptors (receptor for advanced glycation end products (RAGEs), galectin-3, CD36, and the macrophage scavenger receptor [77]) which would lead to cellular activation and pre-oxidant, pre-inflammatory events [78]. During the development of DR, three main mechanisms of AGEs could be concluded: (1) as adducts occurring on modified serum proteins, (2) as endogenous adducts formed as a consequence of glucose metabolism, or (3) as extracellular matrix-immobilized modifications of long-lived structural proteins [77–79]. By decreasing the accumulation of AGEs through the treatment of AGE formation inhibitor, such as aminoguanidine (pimagedine) hydrochloride and vitamin B6 derivative, pyridoxamine, the development of DR could be slowed and prevented [79]. In the latest attempt, the progression of DR might be further prevented by breaking the cross-links caused by AGE, such as ALT-711, known as alagebrium [80].

14.2.2.1.3 Protein Kinase C Activation

Protein kinase C (PKC) is a serine/threonine kinase involved in signal transduction events responding to specific hormonal, neuronal, and growth factor stimuli [64, 65]. The studies have shown the β1/2 isoform of PKC possesses a close association with the development of DR [81]. An activator of PKC, diacylglycerol (DAG), is produced under the hyperglycemic conditions through the glycolysis pathway in diabetic patients, which leads to the activation of PKC [82]. Massive changes of functions were regulated by activation of PKC, such as increasing the endothelial permeability, altering the retinal hemodynamics, and expressing the vascular endothelial growth factor (VEGF) [82]. The inhibition of activation of PKC by a PKC-β1/2 inhibitor has been studied and reported to significantly reduce the progression of DR [83, 84]. The clinical trial is undergoing at Phase III.

14.2.2.1.4 Subclinical Inflammation and Leukostasis

Inflammation is a key characteristic for diabetic patients and its role in the development of DR has been reported [85, 86]. The previous discussed pathophysiologies of DR have a synergetic relationship with inflammation through multiple pathways, including cytokines, adhesion molecules, VEGF signaling, enhanced RAGE expression, changes in nitric oxide regulation, and NF-κB signaling. Leukostasis is another major property for DR and it could lead to capillary occlusion and reactive oxygen species (ROS)-mediated cell death. Its amplifying effect on inflammation of local retinal tissue was recognized [87]. A few of conditions related to DR (VEGF overexpression, irregular vascular permeability, high levels of cell death and leukostasis, and weak visual acuity) could be addressed by anti-inflammatory drugs such as the intravitreal triamcinolone acetonide (IVTA) and nonsteroidal anti-inflammatory drugs such as nepafenac [88, 89]. However, these drugs only have a significant impact during later stages of progression of DR and their side effects mainly due to the mode of delivery, intravitreal injections [89].

14.2.2.1.5 Oxidative Stress

Oxidative stress is defined as "a disturbance in the balance between the production of RPS (free radicals) and antioxidant defenses" [64, 65]. In the diabetes, its damaging effect on tissues was widely recognized and its increase contributes to the progression of DR [90]. A study has shown an important role of the ROS-mediated activation of metalloproteinase-2 (MMP-2) in the development of DR through mitochondrial dysfunction of retinal endothelial cells [91]. The contribution of oxidative stress to the development of retinopathy and the resistance of retinopathy to reverse after good glycemic control have been demonstrated on animal model [92]. The prevention of experimental DR has been reported based on animal studies, but there is no clinical trial to reach the same conclusion yet [93].

14.2.2.1.6 Growth Factors

A list of growth factors have been reported to be associated with the development of DR: fibroblast growth factor (bFGF) [94], insulin-like growth factor-1 (IGF-1) [95], angiopoietin-1 and angiopoietin-2 [96], stromal-derived factor-1 [97], epidermal growth factor (EGF) [98], transforming growth factor-beta 2 (TGF-β2) [99], platelet-derived growth factors (PDGFs) [100], and erythropoietin [101]. VEGF was the most intensively studied due to its capability of promoting angiogenesis, breaking down the blood-retinal barrier, stimulating endothelial cell growth, and increasing vascular permeability in the ischemic retina [102–105]. The treatment of DR with some of the current anti-VEGF agents like VEGF trap has shown great promise. The success of this strategy has shown in early clinical results for the treatment of diabetic macular edema (DME) [104]. However, there is a gap in our understanding of the variation inefficacy of anti-VEGF agents in individuals and also in the unknown long-term effect for this type of treatment.

14.2.2.1.7 Other Factors

Other pathophysiologies of DR include (a) carbonic anhydrases (CAs) which could cause rapid conversion of carbon dioxide to bicarbonate and protons and (b) neurodegeneration which occurs on retinal neurons and glial cells before the development of microaneurysms [64, 65, 106]. Blood pressure is another factor to play a significant role in the progression of DR through two mechanisms [107]: mechanical stretch and shear stress of blood [108] and misbehave of endocrine system [109]. The treatment of candesartan was able to reduce the incidence of retinopathy by 18 % [110]. However, the studies have shown no significant effect on the reduction of the DR progress except the regression of early stage of type II diabetic patients [110].

14.2.2.2 Drug Delivery Approaches for Treatment of DR

Although topical, systemic, intravitreal, and periocular routes have been used in the treatment of DR, the latter two have been more ideal to reach a high dosage of drug in the back of the eyes due to the bypass of the structural barriers of the eyes. Drug delivery to the posterior segment of the eye is challenging and a few of delivery systems were developed specifically for DR.

14.2.2.2.1 Polymeric Implants

Dexamethasone Polymeric Implants

Dexamethasone is a corticosteroid which has anti-inflammatory and immunosuppressant effects. Its intravitreal implant is a sustained release drug delivery system for DME. The study has found that dexamethasone implant could improve visual acuity significantly for 90 days after insertion [111]. The platform of this delivery system is based on a biodegradable poly(lactide-co-glycolide) (PLGA) polymer which has been applied into multiple FDA-approved implants [112]. Placid trial report in American Academy of Optometry (AAO), Oct. 2010, has reported their findings on the improvement of combining laser treatment with dexamethasone implant (Ozurdex) compared with laser treatment alone, besides the visual acuity improvement [113]. It was found that the slow-release implant was able to maintain 3-month drug release and achieve improvements in visual acuity and central macular thickness for DME patients from the third day [114].

Fluocinolone Acetonide (FA) Insert

Fluocinolone acetonide [115] is another corticosteroid and its intravitreal implant has been tested and approved for DME. It is reported to be able to improve visual acuity in DME. The clinical trial on an FA insert, Iluvien, has shown benefits in reducing DME. The visual acuity improvement was observed in 16.8 %, 16.4 %, and 31.8 % of implanted eyes at 6 months, 1 year, and 3 years, respectively. The retinal macula thickening is significantly improved in 2 years [116]. The low-dosage insert has shown a lower risk-benefit ratio comparing with high-dosage group; despite this both dosages have been reported to show a significant therapeutic effect in 3 weeks [117].

14.2.2.2.2 Celecoxib Microparticles

Celecoxib is a nonsteroid anti-inflammatory drug and its efficacy for DME management has been reported [118]. The sustained release could be obtained by using biodegradable PLGA (85:15) microparticles, which has shown a 49-day release profile in vitro. Animal study has revealed that no celecoxib was detected in the contralateral eye of rats 14 days after the injection. Improvement in the oxidative

damage has been observed [119]. However, no clinical trial has been carried out with this type of treatment for DME or DR.

14.2.2.2.3 Budesonide Particles

Budesonide is a steroidal anti-inflammatory drug and an inhibitor for VEGF [120, 121]. Its PLA-based particles were studied for DME treatment. The subconjunctival administration of these particles in rats produced a sustained release profile to the posterior of the eyes, and the budesonide levels were shown to be maintained in the retina and other ocular tissues. The success of inhibition of VEGF was observed and no budesonide was detected in the contralateral eye [121]. Further preclinical and clinical studies are required for this delivery system.

14.2.2.3 Future Directions for Diabetic Retinopathy

Although multiple pathologies of DR are well recognized, the treatment of DR is still limited for their advanced stage and needs further investigations of newer therapies. The current therapies are merely targeting one or two pathways. Considering the pathogenesis of DR, there is need for therapies which will target multiple pathways. The utilization of the newer drug delivery approaches such as nano- and microparticles has a long way to clinical trial despite the effort on applying the FDA-approved material.

14.2.3 Age-Related Macular Degeneration (AMD)

AMD is an age-related, progressive degeneration of photoreceptors and their underlying retinal pigment epithelium (RPE) in the macular area of the retina, which eventually leads to vision loss. AMD is one of the leading causes of vision loss among elderly in western world, particularly in industrialized nations [122, 123]. More than 1.75 million people in the USA have AMD; also due to the rapid aging of the American population, this number is likely to increase to approximately three million by 2020 [124].

The macula, the most sensitive part of the eye, is essential for sharp, central vision and image resolution, which helps to see objects that are straight ahead. The retina consists of two layers, the inner neurosensory retina and the outer retinal pigment epithelium (RPE) cell layer. The Bruch's membrane (BM) separates RPE from the outer vascular choroid. The choroid present adjacent to BM consists of a network of fenestrated capillaries and an external large vessel layer. It plays an important role to supply oxygen and nutrients to and remove waste from the retina, especially at the macula [122].

14.2.3.1 AMD Types and Pathophysiology

AMD is mainly divided into two forms, dry and wet AMD. The dry type accounts for more than 85 % of the cases; in the dry type, the drusens, subretinal deposits start accumulating between the RPE and the underlying choroid due to aging and thinning of the macular tissue followed by atrophy of the RPE and adjacent cells in contiguous areas of the macula. The wet form of AMD, accounting for approximately 15 % of patients, is characterized by choroidal neovascularization (CNV). Although wet AMD is less prevalent than dry AMD, it is usually very destructive and can cause rapid and severe vision loss [125].

In the normal eye (Fig. 14.2a), the retinal pigment epithelial (RPE) layer sits on Bruch's membrane (BM), which is the relative diffusion barrier between RPE and the external choroid layers, and is composed of collagen and elastin. The RPE cells are large, the bipolar and ganglion cells at the macula are displaced, and there are no retinal blood vessels in this region; the fovea, forming the macular center, is concave in cross section and consists only of cone photoreceptors. Hence there is minimal interference with the incoming image. In dry AMD (Fig. 14.2b), drusen accumulate between RPE cells and BM. Reticular drusen accumulate between the RPE layer and photoreceptor cells. Pigmentary irregularities including atrophy and hypertrophy/hyperplasia of RPE cells appear, along with choriocapillaris atrophy and thickening of BM. Extensive atrophy leads to geographic atrophy, a form of late/advanced AMD. Wet AMD (Fig. 14.2c), a more severe form of AMD, is characterized by choroidal neovascularisation (CNV). In initial stages, within the choroid, new vessels break through a gap in BM to grow under/within the retina. The CNV leaks fluid and blood, disrupting the organized architecture of the retinal cells. This results in distortion of central vision, often the first symptom of CNV experienced by the patient. Wet AMD can also occur from intraretinal neovascularization (retinal angiomatous proliferation – RAP). Consequent thickening and elevation of the retina can be detected clinically. Eventually the CNV scars, with permanent disruption of the retinal architecture.

14.2.3.2 Risk Factors for AMD

14.2.3.2.1 Age

One of the major risk factors for the development of AMD is age. The prevalence of AMD is observed in subjects over the age of 50.

14.2.3.2.2 Smoking

Epidemiologic studies have shown cigarette smoke to be the single and greatest risk factor for development of both wet and dry AMD [126]. The smoker subjects aged more than 85 years possess a 6.6-fold increased risk of development of AMD than

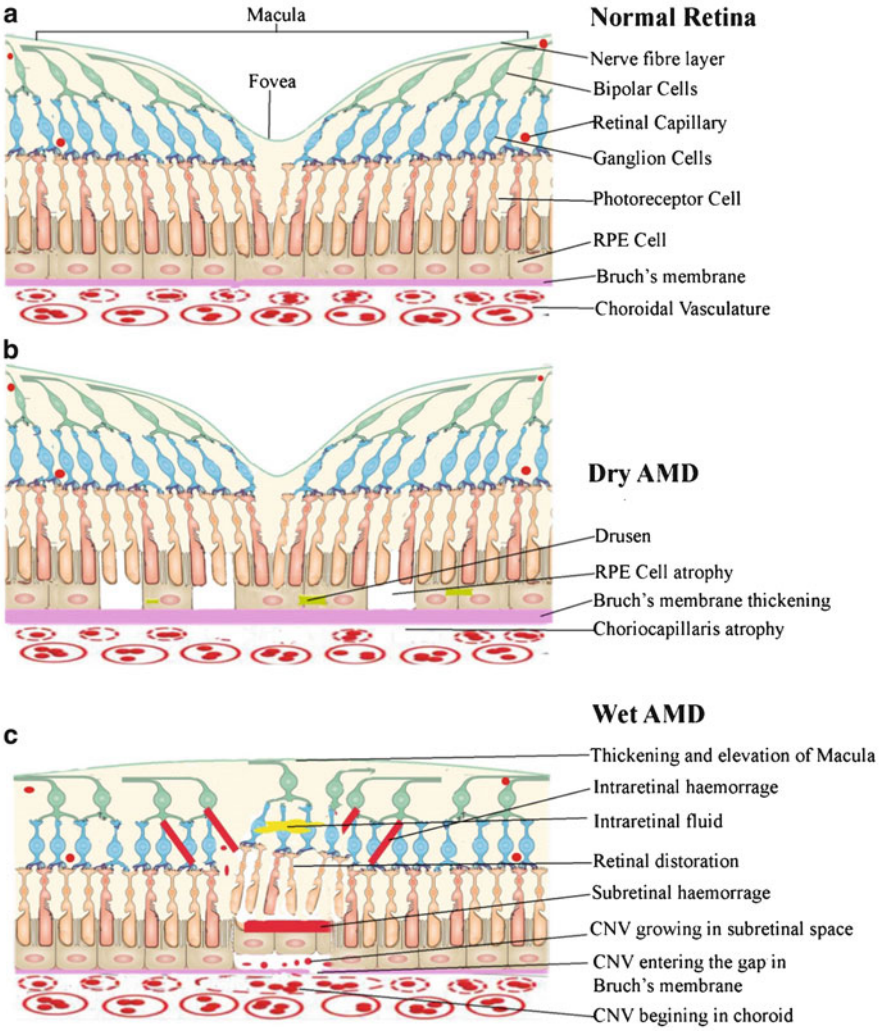

Fig. 14.2 Cross-sectional pathological changes occurring in macula in age-related macular degeneration (AMD). (**a**) Normal retina, (**b**) dry AMD, (**c**) wet AMD

nonsmokers (95 % CI, 2.8–15.9) [127, 128]. A study on the effect of smoking in male twins showed that both current and past smokers had risk of AMD development. Current smokers had about twofold, while past smokers had 1.7-fold risk of AMD development compared to nonsmokers [129, 130]. Studies have also shown a relationship between smoking and genetic polymorphisms. The risk for AMD is high in smokers bearing likely polymorphisms in the LOC387715 or CFH genes [130–132].

14.2.3.2.3 Light Exposure

Light exposure produces reactive oxygen species (ROS) that are harmful to the eye and responsible for retinal damage. Only blue light is able to reach retina as UV light is absorbed by the lens and the cornea [133]. The macular pigment protects macula against light damage by absorbing blue light [134–141]. Many studies have proven the effect of light exposure in the development of AMD [142].

14.2.3.2.4 Greater Body Mass Index (BMI)

Several studies reported the association of high BMI with AMD [143–145]. The prevalence of AMD in obese patients may be due to higher oxidative stress, changes in the lipid profile, and other physiological changes resulting in increased inflammation, leading to cellular destruction of the macular cells [145].

14.2.3.2.5 Cataract Surgery

There are several studies which have demonstrated that cataract surgery increases the incidence of AMD [145–152]. The data from the Andhra Pradesh Eye Disease Study in South India demonstrated the relationship between prior cataract surgery with increased occurrence of AMD [145].

14.2.3.2.6 Others

The other miscellaneous risk factors reported for the prevalence of AMD are systemic hypertension, genetic and family predisposition, cardiovascular (atherosclerotic) disease, and diet high in saturated fat.

14.2.3.3 Treatment of AMD

14.2.3.3.1 Dry AMD

The oxidative mechanisms play an important role in the visual system degeneration. Hence, the use of minerals, vitamins, and antioxidant supplements is recommended for treatment of AMD [153]. For dry AMD, daily dietary nutrient supplementation has been shown to reduce the risk of disease progression in individuals. The clinical trial of Age-Related Eye Disease Study (AREDS) showed reduction in AMD development with oral supplementation of a combination of vitamin E, vitamin C, beta-carotene, cupric oxide, and zinc oxide [122, 154].

14.2.3.3.2 Wet AMD

Laser Photocoagulation and Photodynamic Therapy (PDT)

The laser photocoagulation is a type of laser surgery involving the use of an intense beam of light, which is focused on the retinal region; this procedure helps to burn small areas of the retina and the abnormal blood vessels beneath the macula. The burns form scar tissue that seals the blood vessels, keeping them from leaking under the macula. Thus there is a slowing down of the buildup of fluid under the retina that distorts the shape and position of the macula and hence can arrest the progression of AMD by destroying choroidal neovascular membranes. One of the studies on laser photocoagulation demonstrated a 1.5 relative risk reduction of severe vision loss. However, recurrence of neovascularization was high [155].

Photodynamic therapy (PDT) was developed as an alternative to the laser photocoagulation. In this therapy pharmacologic photo-sensitizer (verteporfin) was administered intravenously followed by activation with a laser having drug absorption wavelength. Thus, PDT selectively damages the tissue that contains dye. When PDT was used in the treatment of wet AMD, there was an approximately 50 % reduction in vision loss, but improvement in vision was difficult [156, 157].

Anti-VEGF Therapy

Pegaptanib sodium (Macugen®) is the first intraocular Anti-VEGF therapy. Pegaptanib sodium is a pegylated aptamer that has high affinity to the heparin-binding domain of the EGF_{165} isoform and has demonstrated improved vision in patients with exudative AMD. Ranibizumab (Lucentis®), a humanized, recombinant, monoclonal anti-VEGF antibody fragment, demonstrated stable vision at 1 year in about 95 % of patients and improved vision in about 40 % of treated patients [158, 159]. Bevacizumab (Avastin®) is active against all VEGF-A isoforms. This drug has been approved for treatment of metastatic colon cancer [160]. Many studies demonstrated that there is no difference between ranibizumab and bevacizumab efficiencies [161, 162].

Surgical Treatments

The surgical treatment includes macular translocation, submacular surgery, and submacular hemorrhage displacement. However, these surgical procedures are not very useful in AMD, as the degenerative processes have already damaged the retina and macular tissues and have not resulted in significant improvement of vision [163].

Others

VEGF Trap-Eye (aflibercept), small interfering RNAs (siRNA), tyrosine kinase inhibitors, cytokine PEDF, epimacular brachytherapy, and combination treatment of anti-VEGF and PDT are under investigation for treatment of AMD [163].

14.2.3.4 Drug Delivery Approaches for Treatment of AMD

The treatment of posterior eye diseases such as AMD is difficult due to complexity in delivering effective doses of drugs to target tissues in the posterior eye. Various delivery systems are reported and developed to deliver drugs to the posterior segment of the eye for treatment of AMD. The standard treatment of AMD includes small amounts of intravitreal injections of anti-VEGF drugs. Repeated intravitreal injections, although effective in treatment of AMD, may lead to complications that include endophthalmitis, increased intraocular pressure, traumatic cataract, detached retina, and stroke. To overcome these problems, many sustained release formulations have been attempted using the novel particulate systems, which include the following.

14.2.3.4.1 Liposomes

Prolongation of effect on the administration of liposomal bevacizumab in the vitreous and aqueous humor has been investigated. A twofold and fivefold increase in concentrations of bevacizumab in the eye tissues was evident after the 28th day and 42nd day, respectively, after liposomal injection, compared to the levels after injection of soluble bevacizumab injection. The study proved the beneficial effects of prolonged release bevacizumab liposomes in the vitreous [164]. Prolonged liposomal formulations of SU5416 (a VEGF receptor tyrosine kinase inhibitor) [165, 166], siRNA along with PEGylation technology [167], were reported.

14.2.3.4.2 Micro-/Nanoparticles

In one of the studies on controlled release of bevacizumab, the sustained drug levels for over 90 days were obtained from nano- and microspheres fabricated from poly(ethylene glycol)-b-poly (D,L-lactic acid) and poly(DL-lactide-co-glycolide), respectively [168]. Folate-decorated polymeric nanoparticles of triamcinolone [169, 170], human serum albumin nanoparticles of Cu, Zn superoxide dismutase gene [171], and nanocarrier systems of signal peptide serine-threonine-tyrosine (ser-thr-tyr) with chitosan [172] are also reported for controlled ocular delivery.

14.2.3.4.3 Implants

Intravitreal administration of Fluocinolone acetonide conjugates with PAMAM dendrimers were selectively localized within activated outer retinal microglia in two rat models of retinal degeneration, and achieved sustained release for a period of over 90 days [173]. A novel intraocular implantable capsule drug device fabricated with polyvinyl alcohol (PVA) provided near-zero order release of Avastin® and has been reported for treatment of AMD [174]. Several animal experimentations and clinical trials have explored implantable systems of antiangiogenic steroids like triamcinolone acetonide, anercotave acetate , as well as α agonists like brimonidine; however no definite conclusions have been drawn from these studies [175, 176].

14.2.3.5 Animal Models for AMD

With the advancement of the research for treatment of the AMD, various animal models have been developed for better understanding of the underlying pathological mechanisms of AMD and replicate the features of human AMD. However it is difficult to develop the unique model which exactly resembles conditions of AMD, as it is a very complex and heterogeneous disease involving environmental and genetic factors. Animal models of pigs, rabbits, rats, mice, and nonhuman primates were reported in the literature.

14.2.3.5.1 Animal Models of Dry AMD

Complement Factor Pathway

Dry AMD is characterized by the formation of the drusens under RPE layer which leads to hypertrophy, hyperplasia, or atrophy. The complement system plays an important role in the body's defense mechanism against pathogens, apoptotic cells, immune responses, and elimination of immune complexes [177]. Several studies demonstrated the role of complement system in formation of drusen, including complement components C3a and C5a [178], C5 and C5b-9 terminal complement complex (TCC) [179, 180], as well as complement factor H-CFH, clusterin and vitronectin, and membrane-bound complement inhibitors (complement receptor 1-CR1, also called CD35, and membrane cofactor protein-MCP/CD46) [181, 182]. Dysregulation of the above complement components leads to damage and pathogenesis of AMD. Genetically engineered mice lacking complement factor H ($Cfh^{-/-}$ mice) [177, 183], transgenic CFH Y402H mice [184], and transgenic mice overexpressing C3 [185], C3a, and C5a $receptor^{-/-}$ mice [178] are the models used for the study of dry AMD.

Chemokine Models

Chemokines are the signaling proteins secreted by cells exerting their action by coupling with G protein-linked transmembrane receptors. The main functions of the chemokines are homeostasis and inflammation [186]. $Ccl2^{-/-}$ and $Ccr2^{-/-}$ mice and $Cx3cr1^{-/-}$ mice and $Ccl2^{-/-}$ $Cx3cr1^{-/-}$ double knockout mice are also reported as models used for the study of dry AMD.

Oxidative Damage Models

Oxidative stress from reactive oxygen species (ROS) is reported to be one of the key factors in the pathogenesis of aging-associated diseases, including age-related macular degeneration (AMD). Animal models with applied oxidative stress and those that lack antioxidant mechanisms express many features of AMD. Carboxyethyl pyrrole (CEP)-adducted proteins formed from docosahexaenoic acid

(DHA) in the retina are found in drusen. This could be the initiation of AMD. Hollyfield et al. demonstrated that immunization of mouse with CEP-adducted mouse serum albumin demonstrated many features of dry AMD [187, 188]. With aging iron plays an important role in the development of oxidative stress. Ceruloplasmin plays important role in cell iron export. A ceruloplasmin/hephaestin$^{-/-}$ mouse is another model of AMD in which lack of ceruloplasmin develops symptoms of AMD [189]. Sod1$^{-/-}$ mice [190, 191] and Sod2 knockdown mice [192] lacking function of superoxide dismutase which is a potent endogenous antioxidant develop AMD-like features. Exposure to cigarette smoke also plays an important role in the induction of AMD. Mice exposed to cigarette smoke demonstrated features of dry AMD. Other models such as OXYS rats, lipid/glucose metabolism, aging mice+/−high fat diet+/−light treatment, high glycemic index diet, ApoE−/−mice, APOEe2/e4 transgenic mice, APOE3-Leiden transgenic mice, APOB100 transgenic mice + high fat diet, Ldl receptor−/−mice + high fat diet, Vldl receptor−/−mice, CD36−/−mice, and Mcd/mcd mice (transgenic mutant cathepsin D) are reported in the literature for dry AMD [193].

Other Models for Dry AMD

Senescence-accelerated mice [194] and macular dystrophies by single gene mutations, e.g., Timp3$^{-/-}$mice [195], the Abcr$^{-/-}$mice [196], the ELOVL4 transgenic mouse [197], and fibulin-3 transgenic mice [198], are reported in the literature.

Nonhuman Primate Models

Animal models of rhesus and cynomolgus macaques and Japanese and cynomolgus macaques are reported in the literature [193].

14.2.3.5.2 Animal Models of Wet AMD

Laser-Induced CNV

Rodent and nonhuman primate models (cynomolgus macaques, rhesus macaques, and African green monkeys) of laser-induced CNV are reported in the literature. In these models CNV is induced by the use of laser energy [199–202].

Subretinal Injection-Induced CNV

Subretinal matrigel injection causes CNV in mice and rabbits [201, 203]. Subretinal injections of adenovirus vectors expressing VEGF [204], macrophages [205], lipid hydroperoxide [206], and polyethylene glycol [207] are also reported to produce CNV in rats.

VEGF/bFGF Pellet-Induced CNV

Zhang et al. demonstrated that implantation of VEGF/bFGF-impregnated pellets in suprachoroidal space of rabbit eye developed CNV [51].

Surgical Model of CNV

Surgical rupture of Bruch's membrane leads to development of CNV [208]. In one of the studies, surgical model of CNV was compared with CNV induced by laser and xenon lamp [209].

14.2.4 Glaucoma

Glaucoma(GL)is a condition affecting over 66 million people worldwide and responsible for causing bilateral blindness in 6.8 million people, as per WHO statistics. GL results due to slow progressive degeneration of retinal ganglion cells (RGCs) and optic nerve axons. The most common form of the disease is primary open-angle glaucoma (POAG).

14.2.4.1 Types

GL is actually a group of diseases. The most common type is hereditary.

14.2.4.1.1 Primary Open-Angle Glaucoma

This is the most common type of GL caused due to clogging of eye's drainage canal over the time. This causes an increase in inner eye pressure (also called intraocular pressure or IOP), as the correct amount of fluid cannot drain out of the eye. It shows no symptoms and no early warning signs. If undiagnosed and untreated, it can cause a gradual loss of vision. The development is slow and sometimes without noticeable sight loss for many years. It usually responds well to medication, especially in the early stages.

14.2.4.1.2 Angle-Closure Glaucoma

This is a rare and very different condition compared to open-angle GL and is also called as narrow-angle GL, with quick rise in eye pressure. Symptoms of angle-closure glaucoma may include headaches, eye pain, nausea, rainbows around lights at night, and very blurred vision. Treatment of angle-closure glaucoma usually involves either laser or conventional surgery which helps unblock the drainage

canals so that the extra fluid can drain. Success rate of surgery is high but still regular checkups are important to avoid chronic form of GL.

14.2.4.1.3 Normal-Tension Glaucoma

This condition is also called low-tension or normal-pressure glaucoma, in which the optic nerve is damaged even though the pressure in the eye is not very high. People with a family history of glaucoma, or with Japanese ancestry, and those with a history of systemic heart disease are at high risk of developing this condition. Treatment of normal tension glaucoma is by reducing the eye pressure as low as possible using medications, laser treatments, and conventional surgery.

14.2.4.1.4 Other Types of Glaucoma

There are several variations of open-angle or angle-closure types. These types can occur in one or both the eyes. It occurs as a result of an eye injury, inflammation, tumor, or in advanced cases of cataract or diabetes, or steroid drug medication. It includes secondary GL, pigmentary GL, pseudoexfoliative GL, traumatic GL, neovascular GL, iridocorneal endothelial syndrome (ICE), and congenital GL (childhood glaucoma). These forms of GL may be mild or severe. The type of treatment will depend on whether it is open-angle or angle-closure GL [210].

14.2.4.2 Pathophysiology and Treatment of GL

Underlying cause of open-angle glaucoma remains unclear and the pathophysiology of glaucoma is believed to be multifactorial. Multiple factors acting either on cell bodies or their axons are believed to lead to retinal ganglion cell (RGC) death.

14.2.4.2.1 Elevated Intraocular Pressure (IOP)

This form of GL is due to increased resistance to the draining of aqueous humor through the trabecular meshwork, which leads to an increase in IOP. This further leads to cell death from compression of the optic nerve axons [211].

14.2.4.2.2 Glutamate Excitotoxicity

A chronic increase in glutamate levels is seen in GL. This can result in activation of glutamate receptors, which further may lead to cellular apoptosis and neuronal cell death.

14.2.4.2.3 Nitric Oxide (NO) Neurotoxicity

Excessive levels of NO are associated with several degenerative aging disorders like Parkinson's disease, Alzheimer's disease, and multiple sclerosis. Studies have reported high levels of *nitric oxide synthase-2 (iNOS-2)*, *in GL*; *iNOS-2* is an inducible form of NOS, capable of releasing an excessive quantity of NO.

14.2.4.2.4 Neuroinflammation

This is a sort of autoimmune phenomenon wherein secondary antigen-mediated neurotoxicity is seen, due to sustained neurodegeneration; this is primarily due to long-term presence of lymphocytes and antigens and subsequently increased T cells, followed by release of cytokines. Marked increase in cytokine receptors has been detected in normal-pressure glaucoma (NPG) patients (67 %) and POAG patients (77 %), indicating T-cell over-activation in GL.

14.2.4.3 Drug Delivery Approaches for Treatment of GL

The major aim in GL treatment is to prevent or delay the loss of visual field. Since neuronal cell death is irreversible, no cure is available once the visual field is lost. However, since IOP is the primary risk factor, the strategies for treatment attempt to lower the raised IOP, for which several drugs are available that are effective in reducing IOP. These drugs are typically applied as eyedrops.

Different delivery systems like oral tablets (acetazolamide), topical eyedrops or gels (timolol), inserts (pilocarpine, timolol), and surgical implants (dexamethasone) are clinically available for the treatment of IOP. These have short-lived effect and need to be administered/instilled several times a day, which would be cumbersome from patient point of view. An ideal drug delivery system for GL should offer sustained release of the drug for several hours/days or months from a single application without any surgery. Using one or more of the existing IOP-lowering medications, such slow-release ocular delivery systems will circumvent patient adherence factors and may offer an attractive alternative to traditional topical eyedrops for many elderly patients. Some such novel delivery systems have been developed in the form of injectable systems, medicated contact lenses, ocuserts, and implantable devices [212].

14.2.4.3.1 Liposomes and Nanospheres

Pilocarpine-loaded liposomal dispersions, which can be instilled as eyedrops, are reported to increase the residence time of the drug to twice that obtained with conventional eyedrops. Effects of charge on the liposomes have also been studied, and the neutral uncharged systems were recommended [213].

Colloidal dispersions of neutral nanocapsules instilled as eyedrops, incorporating rhodamine as model drug, indicated that nanocapsules take an intracellular route through the corneal epithelium. Another study on polymeric nanocapsules based on diblock caprolactone copolymers for ocular delivery has compared PEG and chitosan coatings for surface modification; PEG coatings provided fast release, whereas chitosan-coated nanocapsules provided greater retention in corneal layers [214].

14.2.4.3.2 Contact Lenses as Delivery Vehicles

Contact lenses can be an attractive system to provide prolonged levels of drugs in eye. Soft contact lenses, fabricated from polymers of *N*, *N*-diethylacrylamide and methacrylic acid, have shown extended release of timolol for up to 24 h. However, with reference to elderly patients, contact lenses may be unwieldy and not suitable.

14.2.4.3.3 Sophisticated Surgical Implants

These represent advanced technological reservoir devices to be implanted in the subconjuctival space. One such example is a microelectromechanical system (MEMS) which employs electrolysis to create bubbles that push the drug out of the reservoir of the device. Surgical steps required would be similar to currently available glaucoma drainage devices. Reloading of the device and controlling the delivery rate afford flexibility to the clinician.

14.2.4.3.4 Injectable Systems

Existing drugs may be injected into the subconjunctival space to achieve localization and prolonged delivery compared with simple topical application. Formulations based on degradable and nondegradable polymers have been studied for drugs like antibiotics after cataract surgery, carboplatin for murine retinoblastoma, and celecoxib to reduce oxidative stress in the rat. Timolol encapsulated in polyester microspheres was found to afford sustained release for greater than 90 days in vitro [212].

14.2.4.3.5 Other Systems Suitable for Elderly

In general, considering the aging population, the sophisticated systems may be not very suitable. Simple eyedrops, gels, and in situ gelling systems may be more user-friendly. Studies in our group have led to the development of simple gels, in situ gelling systems, and disks of timolol maleate, based on various mucoadhesive polymers – polycarbophil and sodium alginate. In vivo studies in rabbits

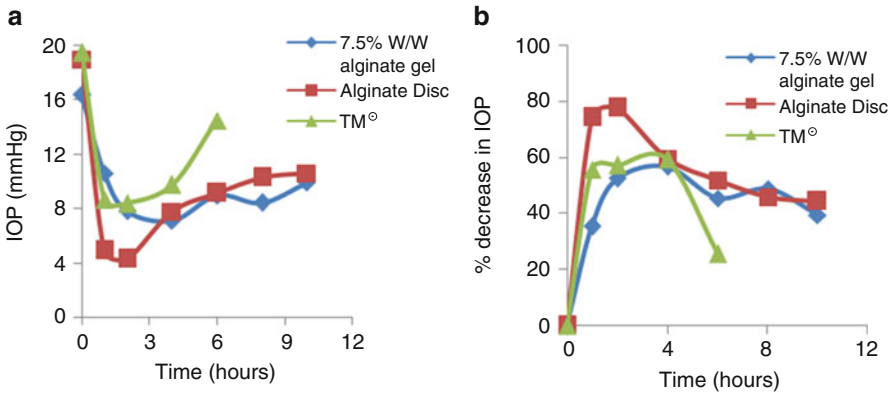

Fig. 14.3 (**a**) Effect of alginate formulation of timolol maleate and marketed eyedrops on intraocular pressure in rabbits. (**b**) Effect of alginate formulation of timolol maleate and marketed eyedrops on % reduction of intraocular pressure in rabbits

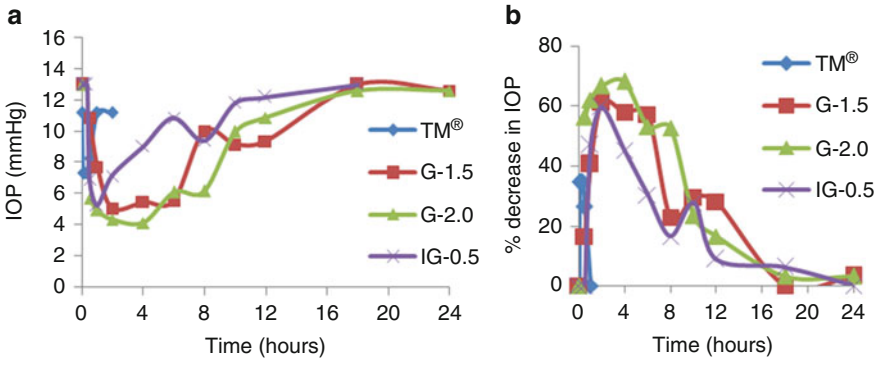

Fig. 14.4 (**a**) Effect of polycarbophil gels (G-1.5 % and G-2 %), polycarbophil 0.5 %, and methocel K4M 1 % gel (IG-0.5 %) of timolol maleate and marketed eyedrops on intraocular pressure in rabbits. (**b**) Effect of polycarbophil gels (G-1.5 % and G-2 %), polycarbophil 0.5 %, and methocel K4M 1 % gel (IG-0.5 %) of timolol maleate and marketed eyedrops on % reduction of intraocular pressure in rabbits

have revealed marked reduction in intraocular pressure (40–70 %) which was sustained for a period of up to 5 h, in the case of gels and in situ gelling systems, and up to 10 h in case of disks, as against conventional eyedrops (Figs. 14.3 and 14.4) [215, 216].

14.3 Conclusion and Future Directions

Overall, it can be summarized that the global scenario is indicative of a significant increase in the elderly population. This can have an impact on the healthcare resources and systems, which will have to gear toward the aging population.

Along with other aging disorders, visual impairment and eye problems like cataract, diabetic retinopathy, AMD, and glaucoma will be on the rise. Visual impairment dramatically reduces the ability of older people to contribute to their full capacity, which has a negative impact on society as a whole. Maintaining good vision is an important part of "active aging," a concept promoted by the WHO. Active aging means continued health, security, and participation in society as people age, in order to ensure a good quality of life in later years. Nations and communities have to gear up to this challenge to ensure that good quality eye care and therapies are available to this group. Currently the surgical cure for cataract is well established. However, surgery in the elderly is often risky and an inherent fear factor may deter people from surgical interventions, especially when they are coupled with many other concomitant diseases. In the case of other conditions, viz., glaucoma, AMD, and diabetic retinopathy, therapies and drugs are not adequate; they are simply used to provide symptomatic relief, and a great deal of research still needs to be focused in developing cures for them. Also, newer approaches based on the novel drug delivery systems (NDDS) which can overcome the formidable barriers of the eye for effective therapy need to be explored. These NDDS should be developed as simple noninvasive systems which can be easily handled, inserted, and used by the aged persons, which can ensure good patient compliance and confidence to them.

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References

1. Abdullah KN, Abdullah MT (2002) Management and planning for primary eye care of the elderly: the need to create public awareness of age-related cataract in Pakistan. Community Eye Health 15(43):45
2. Control Centers for Disease (2006) Improving the nation's vision health: a coordinated public health approach. Centre for disease control, Atlanta
3. Evans J (2008) Eye care for older people. Community Eye Health J 21(66):21–23
4. Nobili A, Garattini S, Mannucci PM (2011) Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. J Comorbidity 1(1):28–44
5. Team Ve-r (2010) Vision 2020 e-resource for eye care management worldwide. Vision 2020 e-resource team. http://www.v2020eresource.org/newsitenews.aspx?tpath=news012010

6. Wong TY, Loon SC, Saw SM (2006) The epidemiology of age related eye diseases in Asia. Br J Ophthalmol 90(4):506–511
7. Gentry LR (1998) Anatomy of the orbit. Neuroimaging Clin N Am 8(1):171–194
8. Hughes MS (1991) Dictionary of eye terminology. Arch Ophthalmol 109(9):1208
9. Alm A, Nilsson SFE (2009) Uveoscleral outflow – A review. Exp Eye Res 88(4):760–768
10. Hayreh SS (1975) Segmental nature of the choroidal vasculature. Br J Ophthalmol 59(11):631–648
11. Oyster CW (1999) The human eye: structure and function. Sinauer Associates, Inc., Sunderland
12. Hubel DH (1995) Eye, brain, and vision. Scientific American Library series (Issue 22), Henry Holt and Company, New York
13. Forrester J, Dick A, McMenamin P, Lee W (1996) The eye: basic sciences in practice. WB Saunders Company Ltd, London
14. Venes D (2013) Taber's cyclopedic medical dictionary. FA Davis, Philadelphia
15. Baerveldt G (2000) Method and apparatus for inserting a glaucoma implant in an anterior and posterior segment of the eye. Google patents
16. Kronfeld P (1962) Gross anatomy and embryology of the eye. Eye 1:1–66
17. Salvi SM, Akhtar S, Currie Z (2006) Ageing changes in the eye. Postgrad Med J 82(971):581–587
18. Van Haeringen NJ (1997) Aging and the lacrimal system. Br J Ophthalmol 81(10):824–826
19. Faragher RGA, Mulholland B, Tuft SJ, Sandeman S, Khaw PT (1997) Aging and the cornea. Br J Ophthalmol 81(10):814–817
20. Duncan G, Wormstone IM, Davies P (1997) The aging human lens: structure, growth, and physiological behaviour. Br J Ophthalmol 81(10):818–823
21. Le Goff MM, Bishop PN (2008) Adult vitreous structure and postnatal changes. Eye 22(10):1214–1222
22. Grunwald JE, Metelitsina TI, DuPont JC, Ying G-S, Maguire MG (2005) Reduced foveolar choroidal blood flow in eyes with increasing AMD severity. Invest Ophthalmol Vis Sci 46(3):1033–1038
23. Grunwald JE, Piltz J, Patel N, Bose S, Riva CE (1993) Effect of aging on retinal macular microcirculation: a blue field simulation study. Invest Ophthalmol Vis Sci 34(13):3609–3613
24. Brian G, Taylor H (2001) Cataract blindness: challenges for the 21st century. Bull World Health Organ 79(3):249–256
25. Rao GN, Sadasivudu B, Cotlier E (1983) Studies on glutathione S-transferase, glutathione peroxidase and glutathione reductase in human normal and cataractous lenses. Ophthalmic Res 15(4):173–179
26. Beers MH, Berkow R (1999) The Merck manual of diagnosis and therapy. Merck and Co. Inc., Whitehouse Station
27. Cejková J, Stípek S, Crkovska J, Ardan T, Platenik J, Cejka C, Midelfart A (2004) UV rays, the prooxidant/antioxidant imbalance in the cornea and oxidative eye damage. Physiol Res 53:1–10
28. Cumming RG, Mitchell P (1997) Alcohol, smoking, and cataracts: the Blue Mountains eye study. Arch Ophthalmol 115(10):1296–1303
29. Auricchio G, Libondi T (1982) The physiologic and pharmacologic factors protecting the lens transparency and the update approach to the prevention of experimental cataracts: a review. Metab Pediatr Syst Ophthalmol 7(2):115–124
30. Spector A, Garner WH (1981) Hydrogen peroxide and human cataract. Exp Eye Res 33(6):673–681
31. Wakamatsu TH, Dogru M, Tsubota K (2008) Tearful relations: oxidative stress, inflammation and eye diseases. Arq Bras Oftalmol 71(6):72–79
32. Brown L, Rimm EB, Seddon JM, Giovannucci EL, Chasan-Taber L, Spiegelman D, Willett WC, Hankinson SE (1999) A prospective study of carotenoid intake and risk of cataract extraction in US men. Am J Clin Nutr 70(4):517–524

33. Gritz DC, Srinivasan M, Smith SD, Kim U, Lietman TM, Wilkins JH, Priyadharshini B, John RK, Aravind S, Prajna NV (2006) The antioxidants in prevention of cataracts study: effects of antioxidant supplements on cataract progression in South India. Br J Ophthalmol 90(7):847–851
34. Jacques PF, Chylack LT (1991) Epidemiologic evidence of a role for the antioxidant vitamins and carotenoids in cataract prevention. Am J Clin Nutr 53(1):352S–355S
35. Calladine D, Evans JR, Shah S, Leyland M (2012) Multifocal versus monofocal intraocular lenses after cataract extraction. Cochrane Database Syst Rev 9
36. Leung TG, Lindsley K, Kuo IC (2014) Types of intraocular lenses for cataract surgery in eyes with uveitis. Cochrane Database Syst Rev 3:Cd007284
37. Chanalet L, Lapalus P (1994) Drugs designed to maintain the transparence of the ocular lens. Fundam Clin Pharmacol 8(4):322–341
38. Testa M, Iuliano G, Marino E, Buongiovanni C, Paolercio F, Trapanese A, Mortow P (1986) Bendazac and benzydamine for treatment of cataract: individualized therapy by the "BLOA test". J Ocul Pharmacol Ther 2(3):251–266
39. Toh TY, Morton J, Coxon J, Elder MJ (2007) Medical treatment of cataract. Clin Experiment Ophthalmol 35(7):664–671
40. Balfour JA, Clissold SP (1990) Bendazac lysine. Drugs 39(4):575–596
41. Testa M, Iuliano G, Morton P, Longoni A (1987) Topical benzyl alcohol reduces cataract surgery need: two long-term double blind studies. J Ocul Pharmacol Ther 3(3):211–225
42. Hu C-C, Liao J-H, Hsu K-Y, Lin IL, Tsai M-H, Wu W-H, Wei T-T, Huang Y-S, Chiu S-J, Chen H-Y (2011) Role of pirenoxine in the effects of catalin on in vitro ultraviolet-induced lens protein turbidity and selenite-induced cataractogenesis in vivo. Mol Vis 17: 1862
43. Kociecki J, Załecki K, Wasiewicz-Rager J, Pecold K (2003) Evaluation of effectiveness of Catalin eyedrops in patients with presenile and senile cataract. Klinika oczna 106(6): 778–782
44. Angra SK, Mohan M, Saini JS (1983) Medical therapy of cataract (evaluation of Catalin). Indian J Ophthalmol 31(1):5
45. Hockwin O, Laser H, De Gregorio M, Carrieri MP (1989) Bendazac lysine in selected types of human senile cataract. Ophthalmic Res 21(3):141–154
46. Leuschen J, Mortensen EM, Frei CR, Mansi EA, Panday V, Mansi I (2013) Association of statin use with cataracts: a propensity score-matched analysis. JAMA Ophthalmol 131(11):1427–1434
47. Bonnefont-Rousselot D (2000) Antioxidant and anti-AGE therapeutics: evaluation and perspectives. J Soc Biol 195(4):391–398
48. Babizhayev MA, Deyev AI, Yermakova VN, Semiletov YA, Davydova NG, Doroshenko VS, Zhukotskii AV, Goldman IM (2002) Efficacy of *N*-acetylcarnosine in the treatment of cataracts. Drugs R&D 3(2):87–103
49. Stankiewicz A, Poppe E, Stasiewicz B, Gołebiowska-Hrycukowa A (1990) Evaluation of the effectiveness of Quinax in the prevention of the development of senile cataract. Klinika oczna 92(3–4):52–54
50. Ito Y et al (1999) Correlation between prevention of cataract development by disulfiram and fates of selenium in selenium-treated rats. Curr Eye Res 18(4):292–299
51. Zhang J, Guan P, Wang T, Chang D, Jiang T, Wang S (2009) Freeze-dried liposomes as potential carriers for ocular administration of cytochrome c against selenite cataract formation. J Pharm Pharmacol 61(9):1171–1178
52. Grama CN, Suryanarayana P, Patil MA, Raghu G, Balakrishna N, Kumar MNVR, Reddy GB (2013) Efficacy of biodegradable curcumin nanoparticles in delaying cataract in diabetic rat model. PLoS One 8(10), e78217
53. Sunkireddy P, Jha SN, Kanwar JR, Yadav SC (2013) Natural antioxidant biomolecules promises future nanomedicine based therapy for cataract. Colloids Surf B Biointerfaces 112:554–562

54. Ito Y, Nagai N, Cai H, Takeda M, Koizumi Y (2006) Preventive effect of eye drops of liposomes containing disulfiram and cefmetazole on selenite-induced cataract in rat pups. J Oleo Sci 55(1):15–22
55. Hazare SA (2010) Studies in the development of novel carrier systems for enzymes. University of Mumbai, Mumbai
56. Ramos D, Carretero A, Navarro M, Mendes-Jorge L, Rodriguez-Baeza A, Nacher V, Ruberte J (2014) Mouse models of diabetic retinopathy. Drug Discov Today Dis Models. doi:10.1016/j.ddmod.2014.02.002
57. Macleod S, Forrester JV (2002) Diabetic retinopathy. Medicine 30(2):41–44. doi:10.1383/medc.30.2.41.28272
58. Scanlon PH (2010) Diabetic retinopathy. Medicine 38(12):656–660. doi:10.1016/j.mpmed.2010.08.010
59. Alghadyan AA (2011) Diabetic retinopathy – an update. Saudi J Ophthalmol 25(2):99–111. doi:10.1016/j.sjopt.2011.01.009
60. Fante RJ, Durairaj VD, Oliver SC (2010) Diabetic retinopathy: an update on treatment. Am J Med 123(3):213–216. doi:10.1016/j.amjmed.2009.09.020
61. National Eye Institute (2003) Diabetic retinopathy: what you should know. National Eye Institute, Bethesda
62. Laatikainen L (1977) Preliminary report on effect of retinal panphotocoagulation on rubeosis iridis and neovascular glaucoma. Br J Ophthalmol 61(4):278–284
63. Turner R, Holman R (1995) Lessons from UK prospective diabetes study. Diabetes Res Clin Pract 28:S151–S157
64. Cunha-Vaz J (1978) Pathophysiology of diabetic retinopathy. Br J Ophthalmol 62(6):351–355
65. Tarr JM, Kaul K, Chopra M, Kohner EM, Chibber R (2013) Pathophysiology of diabetic retinopathy. ISRN Ophthalmol. http://dx.doi.org/10.1155/2013/343560
66. Dagher Z, Park YS, Asnaghi V, Hoehn T, Gerhardinger C, Lorenzi M (2004) Studies of rat and human retinas predict a role for the polyol pathway in human diabetic retinopathy. Diabetes 53(9):2404–2411
67. Lorenzi M (2007) The polyol pathway as a mechanism for diabetic retinopathy: attractive, elusive, and resilient. Exp Diabetes Res 2007:61038. doi: 10.1155/2007/61038
68. Van den Enden MK, Nyengaard JR, Ostrow E, Burgan JH, Williamson JR (1995) Elevated glucose levels increase retinal glycolysis and sorbitol pathway metabolism. Implications for diabetic retinopathy. Invest Ophthalmol Vis Sci 36(8):1675–1685
69. Hammes H-P, Du X, Edelstein D, Taguchi T, Matsumura T, Ju Q, Lin J, Bierhaus A, Nawroth P, Hannak D (2003) Benfotiamine blocks three major pathways of hyperglycemic damage and prevents experimental diabetic retinopathy. Nat Med 9(3):294–299
70. Kern TS, Kowluru RA, Engerman RL (1994) Abnormalities of retinal metabolism in diabetes or galactosemia: ATPases and glutathione. Invest Ophthalmol Vis Sci 35(7):2962–2967
71. Robison W, Nagata M, Laver N, Hohman T, Kinoshita J (1989) Diabetic-like retinopathy in rats prevented with an aldose reductase inhibitor. Invest Ophthalmol Vis Sci 30(11):2285–2292
72. Hotta N, Akanuma Y, Kawamori R, Matsuoka K, Oka Y, Shichiri M, Toyota T, Nakashima M, Yoshimura I, Sakamoto N (2006) Long-term clinical effects of epalrestat, an aldose reductase inhibitor, on diabetic peripheral neuropathy the 3-year, multicenter, comparative aldose reductase inhibitor-diabetes complications trial. Diabetes Care 29(7):1538–1544
73. Sun W, Oates PJ, Coutcher JB, Gerhardinger C, Lorenzi M (2006) A selective aldose reductase inhibitor of a new structural class prevents or reverses early retinal abnormalities in experimental diabetic retinopathy. Diabetes 55(10):2757–2762
74. Amano S, S-i Y, Kato N, Inagaki Y, Okamoto T, Makino M, Taniko K, Hirooka H, Jomori T, Takeuchi M (2002) Sorbitol dehydrogenase overexpression potentiates glucose toxicity to cultured retinal pericytes. Biochem Biophys Res Commun 299(2):183–188
75. Stitt AW (2003) The role of advanced glycation in the pathogenesis of diabetic retinopathy. Exp Mol Pathol 75(1):95–108

76. Stitt AW, Li YM, Gardiner TA, Bucala R, Archer DB, Vlassara H (1997) Advanced glycation end products (AGEs) co-localize with AGE receptors in the retinal vasculature of diabetic and of AGE-infused rats. Am J Pathol 150(2):523
77. Grossin N, Wautier MP, Mes T, Guillausseau PJ et al (2008) Severity of diabetic microvascular complications is associated with low soluble RAGE level. Diabetes Metab 34:392–395
78. Zong H, Ward M, Stitt AW (2011) AGEs, RAGE, and diabetic retinopathy. Curr Diab Rep 11(4):244–252
79. Ahmed N, Thornalley P (2007) Advanced glycation end products: what is their relevance to diabetic complications? Diabetes Obes Metab 9(3):233–245
80. Thallas-Bonke V, Lindschau C, Rizkalla B, Bach LA, Boner G, Meier M, Haller H, Cooper ME, Forbes JM (2004) Attenuation of extracellular matrix accumulation in diabetic nephropathy by the advanced glycation end product cross-link breaker ALT-711 via a protein kinase C-α-dependent pathway. Diabetes 53(11):2921–2930
81. Koya D, King GL (1998) Protein kinase C activation and the development of diabetic complications. Diabetes 47(6):859–866
82. Aiello LP, Bursell S-E, Clermont A, Duh E, Ishii H, Takagi C, Mori F, Ciulla TA, Ways K, Jirousek M (1997) Vascular endothelial growth factor–induced retinal permeability is mediated by protein kinase C in vivo and suppressed by an orally effective β-isoform–selective inhibitor. Diabetes 46(9):1473–1480
83. Aiello LP, Clermont A, Arora V, Davis MD, Sheetz MJ, Bursell S-E (2006) Inhibition of PKC β by oral administration of ruboxistaurin is well tolerated and ameliorates diabetes-induced retinal hemodynamic abnormalities in patients. Invest Ophthalmol Vis Sci 47(1):86–92
84. Strøm C, Sander B, Klemp K, Aiello LP, Lund-Andersen H, Larsen M (2005) Effect of ruboxistaurin on blood–retinal barrier permeability in relation to severity of leakage in diabetic macular edema. Invest Ophthalmol Vis Sci 46(10):3855–3858
85. Klein BE, Knudtson MD, Tsai MY, Klein R (2009) The relation of markers of inflammation and endothelial dysfunction to the prevalence and progression of diabetic retinopathy: Wisconsin epidemiologic study of diabetic retinopathy. Arch Ophthalmol 127(9): 1175–1182
86. Tang J, Kern TS (2011) Inflammation in diabetic retinopathy. Prog Retin Eye Res 30(5):343–358. doi:10.1016/j.preteyeres.2011.05.002
87. Chibber R, Ben-Mahmud BM, Mann GE, Zhang JJ, Kohner EM (2003) Protein kinase C β2-dependent phosphorylation of core 2 GlcNAc-T promotes leukocyte-endothelial cell adhesion a mechanism underlying capillary occlusion in diabetic retinopathy. Diabetes 52(6):1519–1527
88. Gillies MC, Sutter FK, Simpson JM, Larsson J, Ali H, Zhu M (2006) Intravitreal triamcinolone for refractory diabetic macular edema: two-year results of a double-masked, placebo-controlled, randomized clinical trial. Ophthalmology 113(9):1533–1538
89. Kuppermann BD, Blumenkranz MS, Haller JA, Williams GA, Weinberg DV, Chou C, Whitcup SM (2007) Randomized controlled study of an intravitreous dexamethasone drug delivery system in patients with persistent macular edema. Arch Ophthalmol 125(3):309–317
90. Baynes JW, Thorpe SR (1999) Role of oxidative stress in diabetic complications: a new perspective on an old paradigm. Diabetes 48(1):1–9
91. Mohammad G, Kowluru RA (2011) Novel role of mitochondrial matrix metalloproteinase-2 in the development of diabetic retinopathy. Invest Ophthalmol Vis Sci 52(6):3832–3841
92. Kowluru RA (2003) Effect of reinstitution of good glycemic control on retinal oxidative stress and nitrative stress in diabetic rats. Diabetes 52(3):818–823
93. Haskins K, Bradley B, Powers K, Fadok V, Flores S, Ling X, Pugazhenthi S, Reusch J, Kench J (2003) Oxidative stress in type 1 diabetes. Ann N Y Acad Sci 1005(1):43–54
94. Hueber A, Wiedemann P, Esser P, Heimann K (1997) Basic fibroblast growth factor mRNA, bFGF peptide and FGF receptor in epiretinal membranes of intraocular proliferative disorders (PVR and PDR). Int Ophthalmol 20(6):345–350
95. Haurigot V, Villacampa P, Ribera A, Llombart C, Bosch A, Nacher V, Ramos D, Ayuso E, Segovia JC, Bueren JA (2009) Increased intraocular insulin-like growth factor-I triggers blood-retinal barrier breakdown. J Biol Chem 284(34):22961–22969

96. Rangasamy S, Srinivasan R, Maestas J, McGuire PG, Das A (2011) A potential role for angiopoietin 2 in the regulation of the blood–retinal barrier in diabetic retinopathy. Invest Ophthalmol Vis Sci 52(6):3784–3791
97. Brooks HL, Caballero S, Newell CK, Steinmetz RL, Watson D, Segal MS, Harrison JK, Scott EW, Grant MB (2004) Vitreous levels of vascular endothelial growth factor and stromal-derived factor 1 in patients with diabetic retinopathy and cystoid macular edema before and after intraocular injection of triamcinolone. Arch Ophthalmol 122(12):1801–1807
98. Lev-Ran A, Hwang DL, Miller JD, Josefsberg Z (1990) Excretion of epidermal growth factor (EGF) in diabetes. Clin Chim Acta 192(3):201–206
99. Ie D, Gordon LW, Glaser BM, Pena RA (1994) Transforming growth factor-beta 2 levels increase following retinal laser photocoagulation. Curr Eye Res 13(10):743–746
100. Praidou A, Klangas I, Papakonstantinou E, Androudi S, Georgiadis N, Karakiulakis G, Dimitrakos S (2009) Vitreous and serum levels of platelet-derived growth factor and their correlation in patients with proliferative diabetic retinopathy. Curr Eye Res 34(2):152–161
101. Eckardt K-U (2009) Erythropoietin and microvascular diabetic complications. Nephrol Dial Transplant 24(2):388–390
102. Awata T, Inoue K, Kurihara S, Ohkubo T, Watanabe M, Inukai K, Inoue I, Katayama S (2002) A common polymorphism in the 5′-untranslated region of the VEGF gene is associated with diabetic retinopathy in type 2 diabetes. Diabetes 51(5):1635–1639
103. Boulton M, Foreman D, Williams G, McLeod D (1998) VEGF localisation in diabetic retinopathy. Br J Ophthalmol 82(5):561–568
104. Joussen AM, Poulaki V, Qin W, Kirchhof B, Mitsiades N, Wiegand SJ, Rudge J, Yancopoulos GD, Adamis AP (2002) Retinal vascular endothelial growth factor induces intercellular adhesion molecule-1 and endothelial nitric oxide synthase expression and initiates early diabetic retinal leukocyte adhesion in vivo. Am J Pathol 160(2):501–509
105. Ray D, Mishra M, Ralph S, Read I, Davies R, Brenchley P (2004) Association of the VEGF gene with proliferative diabetic retinopathy but not proteinuria in diabetes. Diabetes 53(3):861–864
106. Park Y, Freedman B, Lee E, Park S, Jameson J (2003) A dominant negative PPARγ mutant shows altered cofactor recruitment and inhibits adipogenesis in 3T3-L1 cells. Diabetologia 46(3):365–377
107. Estacio R, Jeffers B, Gifford N, Schrier R (2000) Effect of blood pressure control on diabetic microvascular complications in patients with hypertension and type 2 diabetes. Diabetes Care 23:B54–B64
108. Rassam S, Patel V, Kohner E (1995) The effect of experimental hypertension on retinal vascular autoregulation in humans: a mechanism for the progression of diabetic retinopathy. Exp Physiol 80(1):53–68
109. Suzuma I, Hata Y, Clermont A, Pokras F, Rook SL, Suzuma K, Feener EP, Aiello LP (2001) Cyclic stretch and hypertension induce retinal expression of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 potential mechanisms for exacerbation of diabetic retinopathy by hypertension. Diabetes 50(2):444–454
110. DPS Group (2005) The DIabetic REtinopathy Candesartan Trials (DIRECT) programme: baseline characteristics. J Renin Angiotensin Aldosterone Syst 6(1):25–32
111. Corneli HM, Zorc JJ, Mahajan P, Shaw KN, Holubkov R, Reeves SD, Ruddy RM, Malik B, Nelson KA, Bregstein JS (2007) A multicenter, randomized, controlled trial of dexamethasone for bronchiolitis. New Engl J Med 357(4):331–339
112. Makadia HK, Siegel SJ (2011) Poly lactic-co-glycolic acid (PLGA) as biodegradable controlled drug delivery carrier. Polymers 3(3):1377–1397
113. Boyer DS, Faber D, Gupta S, Patel SS, Tabandeh H, Li X-Y, Liu CC, Lou J, Whitcup SM, OCS Group (2011) Dexamethasone intravitreal implant for treatment of diabetic macular edema in vitrectomized patients. Retina 31(5):915–923
114. Pacella E, Vestri AR, Muscella R, Carbotti MR, Castellucci M, Coi L, Turchetti P, Pacella F (2013) Preliminary results of an intravitreal dexamethasone implant (Ozurdex®) in patients with persistent diabetic macular edema. Clin Ophthalmol 7:1423

115. Pearson P, Levy B, Comstock T, Group FAIS (2006) Fluocinolone acetonide intravitreal implant to treat diabetic macular edema: 3-year results of a multi-center clinical trial. Invest Ophthalmol Vis Sci 47(5):5442
116. Pearson PA, Comstock TL, Ip M, Callanan D, Morse LS, Ashton P, Levy B, Mann ES, Eliott D (2011) Fluocinolone acetonide intravitreal implant for diabetic macular edema: a 3-year multicenter, randomized, controlled clinical trial. Ophthalmology 118(8):1580–1587
117. Campochiaro PA, Brown DM, Pearson A, Ciulla T, Boyer D, Holz FG, Tolentino M, Gupta A, Duarte L, Madreperla S (2011) Long-term benefit of sustained-delivery fluocinolone acetonide vitreous inserts for diabetic macular edema. Ophthalmology 118(4):626–635. e622
118. Chew EY, Kim J, Coleman HR, Aiello LP, Fish G, Ip M, Haller JA, Figueroa M, Martin D, Callanan D (2010) Preliminary assessment of celecoxib and microdiode pulse laser treatment of diabetic macular edema. Retina 30(3):459
119. Ayalasomayajula SP, Kompella UB (2005) Subconjunctivally administered celecoxib-PLGA microparticles sustain retinal drug levels and alleviate diabetes-induced oxidative stress in a rat model. Eur J Pharmacol 511(2):191–198
120. Felinski EA, Antonetti DA (2005) Glucocorticoid regulation of endothelial cell tight junction gene expression: novel treatments for diabetic retinopathy. Curr Eye Res 30(11):949–957
121. Kompella UB, Bandi N, Ayalasomayajula SP (2003) Subconjunctival nano-and microparticles sustain retinal delivery of budesonide, a corticosteroid capable of inhibiting VEGF expression. Invest Ophthalmol Vis Sci 44(3):1192–1201
122. Prasad PS, Schwartz SD, Hubschman J-P (2010) Age-related macular degeneration: current and novel therapies. Maturitas 66(1):46–50
123. Swaroop A, Branham KEH, Chen W, Abecasis G (2007) Genetic susceptibility to age-related macular degeneration: a paradigm for dissecting complex disease traits. Hum Mol Genet 16(R2):R174–R182
124. Friedman DS, O'Colmain BJ, Munoz B, Tomany SC, McCarty C, De Jong PT, Nemesure B, Mitchell P, Kempen J (2004) Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol 122(4):564–572
125. Kowluru RA, Zhong Q (2011) Beyond AREDS: is there a place for antioxidant therapy in the prevention/treatment of eye disease? Invest Ophthalmol Vis Sci 52(12):8665–8671
126. Evans JR (2001) Risk factors for age-related macular degeneration. Prog Retin Eye Res 20(2):227–253
127. Seddon JM, Reynolds R, Rosner B (2010) Associations of smoking, body mass index, dietary lutein, and the LIPC gene variant rs10468017 with advanced age-related macular degeneration. Mol Vis 16:2412
128. Vingerling JR, Hofman A, Grobbee DE, De Jong PTVM (1996) Age-related macular degeneration and smoking: the Rotterdam study. Arch Ophthalmol 114(10):1193–1196
129. Chakravarthy U, Augood C, Bentham GC, de Jong P, Rahu M, Seland J, Soubrane G, Tomazzoli L, Topouzis F, Vingerling JR (2007) Cigarette smoking and age-related macular degeneration in the EUREYE Study. Ophthalmology 114(6):1157–1163
130. Seddon JM, George S, Rosner B, Klein ML (2006) CFH gene variant, Y402H, and smoking, body mass index, environmental associations with advanced age-related macular degeneration. Hum Hered 61(3):157–165
131. Francis PJ, George S, Schultz DW, Rosner B, Hamon S, Ott J, Weleber RG, Klein ML, Seddon JM (2007) The LOC387715 gene, smoking, body mass index, environmental associations with advanced age-related macular degeneration. Hum Hered 63(3–4):212–218
132. Schmidt S, Hauser MA, Scott WK, Postel EA, Agarwal A, Gallins P, Wong F, Chen YS, Spencer K, Schnetz-Boutaud N (2006) Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. Am J Hum Genet 78(5):852–864
133. Algvere PV, Marshall J, Seregard S (2006) Age related maculopathy and the impact of blue light hazard. Acta Ophthalmol Scand 84(1):4–15
134. Cruickshanks KJ, Klein R, Klein BEK (1993) Sunlight and age-related macular degeneration: the Beaver Dam eye study. Arch Ophthalmol 111(4):514–518

135. Darzins P, Mitchell P, Heller RF (1997) Sun exposure and age-related macular degeneration: an Australian case-control study. Ophthalmology 104(5):770–776
136. Delcourt C, Carriere I, Ponton-Sanchez A, Fourrey S, Lacroux A, Papoz L (2001) Light exposure and the risk of age-related macular degeneration: the Pathologies Oculaires Liees a l'Age (POLA) study. Arch Ophthalmol 119(10):1463–1468
137. McCarty CA, Mukesh BN, Fu CL, Mitchell P, Wang JJ, Taylor HR (2001) Risk factors for age-related maculopathy: the visual impairment project. Arch Ophthalmol 119(10):1455–1462
138. Pham TQ, Rochtchina E, Mitchell P, Smith W, Wang JJ (2009) Sunlight-related factors and the 10-year incidence of age-related maculopathy. Ophthalmic Epidemiol 16(2):136–141
139. Taylor HR, West S, Muñoz B, Rosenthal FS, Bressler SB, Bressler NM (1992) The long-term effects of visible light on the eye. Archives Ophthalmol 110(1):99–04
140. Tomany SC, Cruickshanks KJ, Klein R, Klein BEK, Knudtson MD (2004) Sunlight and the 10-year incidence of age-related maculopathy: the Beaver Dam eye study. Arch Ophthalmol 122(5):750–757
141. Whitehead AJ, Mares JA, Danis RP (2006) Macular pigment: a review of current knowledge. Arch Ophthalmol 124(7):1038–1045
142. Fletcher AE, Bentham GC, Agnew M, Young IS, Augood C, Chakravarthy U, de Jong PTVM, Rahu M, Seland J, Soubrane G (2008) Sunlight exposure, antioxidants, and age-related macular degeneration. Arch Ophthalmol 126(10):1396–1403
143. Johnson EJ (2005) Obesity, lutein metabolism, and age-related macular degeneration: a web of connections. Nutr Rev 63(1):9–15
144. Klein R, Klein BEK, Tomany SC, Cruickshanks KJ (2003) The association of cardiovascular disease with the long-term incidence of age-related maculopathy: the Beaver Dam eye study. Ophthalmology 110(4):636–643
145. Krishnaiah S, Das T, Nirmalan PK, Nutheti R, Shamanna BR, Rao GN, Thomas R (2005) Risk factors for age-related macular degeneration: findings from the Andhra Pradesh eye disease study in South India. Invest Ophthalmol Vis Sci 46(12):4442–4449
146. Cugati S, Mitchell P, Rochtchina E, Tan AG, Smith W, Wang JJ (2006) Cataract surgery and the 10-year incidence of age-related maculopathy: the Blue Mountains eye study. Ophthalmology 113(11):2020–2025
147. Ho L, Boekhoorn SS, van Duijn CM, Uitterlinden AG, Hofman A, de Jong PTVM, Stijnen T, Vingerling JR (2008) Cataract surgery and the risk of aging macula disorder: the Rotterdam study. Invest Ophthalmol Vis Sci 49(11):4795–4800
148. Kaiserman I, Kaiserman N, Elhayany A, Vinker S (2007) Cataract surgery is associated with a higher rate of photodynamic therapy for age-related macular degeneration. Ophthalmology 114(2):278–282
149. Klein R, Klein BEK, Wong TY, Tomany SC, Cruickshanks KJ (2002) The association of cataract and cataract surgery with the long-term incidence of age-related maculopathy: the Beaver Dam eye study. Arch Ophthalmol 120(11):1551–1558
150. Pham TQ, Cugati S, Rochtchina E, Mitchell P, Maloof A, Wang JJ (2006) Early age-related maculopathy in eyes after cataract surgery. Eye 21(4):512–517
151. Pollack A, Marcovich A, Bukelman A, Oliver M (1996) Age-related macular degeneration after extracapsular cataract extraction with intraocular lens implantation. Ophthalmology 103(10):1546–1554
152. Wang JJ, Klein R, Smith W, Klein BEK, Tomany S, Mitchell P (2003) Cataract surgery and the 5-year incidence of late-stage age-related maculopathy: pooled findings from the Beaver Dam and Blue Mountains eye studies. Ophthalmology 110(10):1960–1967
153. Jarrett SG, Boulton ME (2012) Consequences of oxidative stress in age-related macular degeneration. Mol Aspects Med 33(4):399
154. Group A-REDSR (2001) 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 119(10):1417

155. Macular Photocoagulation Study Group (1991) Argon laser photocoagulation for neovascular maculopathy: five-year results from randomized clinical trials. Arch Ophthalmol 109(8):1109
156. Bressler NM (2002) Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization-verteporfin in photodynamic therapy report 2. Am J Ophthalmol 133(1):168–169
157. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group (1999) Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials – TAP report 1. Arch Ophthalmol 117(10):1329
158. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, Sy JP, Schneider S (2006) Ranibizumab versus verteporfin for neovascular age-related macular degeneration. New Engl J Med 355(14):1432–1444
159. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, Kim RY (2006) Ranibizumab for neovascular age-related macular degeneration. New Engl J Med 355(14):1419–1431
160. Kabbinavar F, Hurwitz HI, Fehrenbacher L, Meropol NJ, Novotny WF, Lieberman G, Griffing S, Bergsland E (2003) Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. J Clin Oncol 21(1):60–65
161. Fong DS, Custis P, Howes J, Hsu J-W (2010) Intravitreal bevacizumab and ranibizumab for age-related macular degeneration: a multicenter, retrospective study. Ophthalmology 117(2):298–302
162. Landa G, Amde W, Doshi V, Ali A, McGevna L, Gentile RC, Muldoon TO, Walsh JB, Rosen RB (2009) Comparative study of intravitreal bevacizumab (Avastin) versus ranibizumab (Lucentis) in the treatment of neovascular age-related macular degeneration. Ophthalmologica 223(6):370–375
163. Thomas L, Berenberg MD, Ying GS et al (2012) The association between Drusen extent and foveolar choroidal blood flow in AMD. Retina 32(1):25–31
164. Abrishami M, Ghanavati SZ, Soroush D, Rouhbakhsh M, Jaafari MR, Malaekeh-Nikouei B (2009) Preparation, characterization, and in vivo evaluation of nanoliposomes-encapsulated bevacizumab (avastin) for intravitreal administration. Retina 29(5):699–703
165. Honda M, Asai T, Umemoto T, Araki Y, Oku N, Tanaka M (2011) Suppression of choroidal neovascularization by intravitreal injection of liposomal SU5416. Arch Ophthalmol 129(3):317–321
166. Katanasaka Y, Ida T, Asai T, Shimizu K, Koizumi F, Maeda N, Baba K, Oku N (2008) Antiangiogenic cancer therapy using tumor vasculature-targeted liposomes encapsulating 3-(3, 5-dimethyl-1H-pyrrol-2-ylmethylene)-1, 3-dihydro-indol-2-one, SU5416. Cancer Lett 270(2):260–268
167. Wang C-H, Lu D-W, Chiang C-H (2010) Gene therapy using SiRNA for treatment of ocular neovascularization. J Med Sci 30(3):79–84
168. Li F, Hurley B, Liu Y, Leonard B, Griffith M (2012) Controlled release of bevacizumab through nanospheres for extended treatment of age-related macular degeneration. Open Ophthalmol J 6:54
169. Kadam RS, Tyagi P, Edelhauser HF, Kompella UB (2012) Influence of choroidal neovascularization and biodegradable polymeric particle size on transscleral sustained delivery of triamcinolone acetonide. Int J Pharm 434(1):140–147
170. Suen W-LL, Chau Y (2013) Specific uptake of folate-decorated triamcinolone-encapsulating nanoparticles by retinal pigment epithelium cells enhances and prolongs antiangiogenic activity. J Control Release 167(1):21–28
171. Mo Y, Barnett ME, Takemoto D, Davidson H, Kompella UB (2007) Human serum albumin nanoparticles for efficient delivery of Cu, Zn superoxide dismutase gene. Mol Vis 13:746

172. Jayaraman MS, Bharali DJ, Sudha T, Mousa SA (2012) Nano chitosan peptide as a potential therapeutic carrier for retinal delivery to treat age-related macular degeneration. Mol Vis 18:2300
173. Iezzi R, Guru BR, Glybina IV, Mishra MK, Kennedy A, Kannan RM (2012) Dendrimer-based targeted intravitreal therapy for sustained attenuation of neuroinflammation in retinal degeneration. Biomaterials 33(3):979–988
174. Molokhia SA, Sant H, Simonis J, Bishop CJ, Burr RM, Gale BK, Ambati BK (2010) The capsule drug device: novel approach for drug delivery to the eye. Vision Res 50(7):680–685
175. Geltzer A, Turalba A, Vedula SS (2007) Surgical implantation of steroids with antiangiogenic characteristics for treating neovascular age-related macular degeneration. Cochrane Database Syst Rev 4, 2013 Jan 31;1:CD005022. doi: 10.1002/14651858.CD005022.pub3
176. Cantor LB (2006) Brimonidine in the treatment of glaucoma and ocular hypertension. Ther Clin Risk Manag 2(4):337
177. Pickering MC, Cook HT, Warren J, Bygrave AE, Moss J, Walport MJ, Botto M (2002) Uncontrolled C3 activation causes membranoproliferative glomerulonephritis in mice deficient in complement factor H. Nat Genet 31(4):424–428
178. Nozaki M, Raisler BJ, Sakurai E, Sarma JV, Barnum SR, Lambris JD, Chen Y, Zhang K, Ambati BK, Baffi JZ (2006) Drusen complement components C3a and C5a promote choroidal neovascularization. Proc Natl Acad Sci 103(7):2328–2333
179. Johnson LV, Ozaki S, Staples MK, Erickson PA, Anderson DH (2000) A potential role for immune complex pathogenesis in drusen formation. Exp Eye Res 70(4):441–449
180. Mullins RF, Russell SR, Anderson DH, Hageman GS (2000) Drusen associated with aging and age-related macular degeneration contain proteins common to extracellular deposits associated with atherosclerosis, elastosis, amyloidosis, and dense deposit disease. FASEB J 14(7):835–846
181. Hageman GS, Anderson DH, Johnson LV, Hancox LS, Taiber AJ, Hardisty LI, Hageman JL, Stockman HA, Borchardt JD, Gehrs KM (2005) A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci 102(20):7227–7232
182. Johnson LV, Leitner WP, Staples MK, Anderson DH (2001) Complement activation and inflammatory processes in drusen formation and age related macular degeneration. Exp Eye Res 73(6):887–896
183. Coffey PJ, Gias C, McDermott CJ, Lundh P, Pickering MC, Sethi C, Bird A, Fitzke FW, Maass A, Chen LL (2007) Complement factor H deficiency in aged mice causes retinal abnormalities and visual dysfunction. Proc Natl Acad Sci 104(42):16651–16656
184. Ufret-Vincenty RL, Aredo B, Liu X, McMahon A, Chen PW, Sun H, Niederkorn JY, Kedzierski W (2010) Transgenic mice expressing variants of complement factor H develop AMD-like retinal findings. Invest Ophthalmol Vis Sci 51(11):5878–5887
185. Cashman SM, Desai A, Ramo K, Kumar-Singh R (2011) Expression of complement component 3 (C3) from an adenovirus leads to pathology in the murine retina. Invest Ophthalmol Vis Sci 52(6):3436–3445
186. Mélik-Parsadaniantz S, Rostène W (2008) Chemokines and neuromodulation. J Neuroimmunol 198(1):62–68
187. Hollyfield JG, Bonilha VL, Rayborn ME, Yang X, Shadrach KG, Lu L, Ufret RL, Salomon RG, Perez VL (2008) Oxidative damage-induced inflammation initiates age-related macular degeneration. Nat Med 14(2):194–198
188. Hollyfield JG, Perez VL, Salomon RG (2010) A hapten generated from an oxidation fragment of docosahexaenoic acid is sufficient to initiate age-related macular degeneration. Mol Neurobiol 41(2–3):290–298
189. Hahn P, Qian Y, Dentchev T, Chen L, Beard J, Harris ZL, Dunaief JL (2004) Disruption of ceruloplasmin and hephaestin in mice causes retinal iron overload and retinal degeneration with features of age-related macular degeneration. Proc Natl Acad Sci 101(38):13850–13855

190. Crabb JW, Miyagi M, Gu X, Shadrach K, West KA, Sakaguchi H, Kamei M, Hasan A, Yan L, Rayborn ME (2002) Drusen proteome analysis: an approach to the etiology of age-related macular degeneration. Proc Natl Acad Sci 99(23):14682–14687
191. Imamura Y, Noda S, Hashizume K, Shinoda K, Yamaguchi M, Uchiyama S, Shimizu T, Mizushima Y, Shirasawa T, Tsubota K (2006) Drusen, choroidal neovascularization, and retinal pigment epithelium dysfunction in SOD1-deficient mice: a model of age-related macular degeneration. Proc Natl Acad Sci 103(30):11282–11287
192. Justilien V, Pang J-J, Renganathan K, Zhan X, Crabb JW, Kim SR, Sparrow JR, Hauswirth WW, Lewin AS (2007) SOD2 knockdown mouse model of early AMD. Invest Ophthalmol Vis Sci 48(10):4407–4420
193. Pennesi ME, Neuringer M, Courtney RJ (2012) Animal models of age related macular degeneration. Mol Aspects Med 33(4):487–509
194. Majji AB, Cao J, Chang KY, Hayashi A, Aggarwal S, Grebe RR, de Juan E (2000) Age-related retinal pigment epithelium and Bruch's membrane degeneration in senescence-accelerated mouse. Invest Ophthalmol Vis Sci 41(12):3936–3942
195. Weber BHF, Lin B, White K, Kohler K, Soboleva G, Herterich S, Seeliger MW, Jaissle GB, Grimm C, Reme C (2002) A mouse model for Sorsby fundus dystrophy. Invest Ophthalmol Vis Sci 43(8):2732–2740
196. Mata NL, Weng J, Travis GH (2000) Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration. Proc Natl Acad Sci 97(13):7154–7159
197. Karan G, Lillo C, Yang Z, Cameron DJ, Locke KG, Zhao Y, Thirumalaichary S, Li C, Birch DG, Vollmer-Snarr HR (2005) Lipofuscin accumulation, abnormal electrophysiology, and photoreceptor degeneration in mutant ELOVL4 transgenic mice: a model for macular degeneration. Proc Natl Acad Sci 102(11):4164–4169
198. Marmorstein LY, McLaughlin PJ, Peachey NS, Sasaki T, Marmorstein AD (2007) Formation and progression of sub-retinal pigment epithelium deposits in Efemp1 mutation knock-in mice: a model for the early pathogenic course of macular degeneration. Hum Mol Genet 16(20):2423–2432
199. Dobi ET, Puliafito CA, Destro M (1989) A new model of experimental choroidal neovascularization in the rat. Arch Ophthalmol 107(2):264–269
200. Ryan S (1979) The development of an experimental model of subretinal neovascularization in disciform macular degeneration. Trans Am Ophthalmol Soc 77:707
201. Shen D, Wen R, Tuo J, Bojanowski CM, Chan CC (2006) Exacerbation of retinal degeneration and choroidal neovascularization induced by subretinal injection of Matrigel in CCL2/MCP-1-deficient mice. Ophthalmic Res 38(2):71–73
202. Tobe T, Ortega S, Luna JD, Ozaki H, Okamoto N, Derevjanik NL, Vinores SA, Basilico C, Campochiaro PA (1998) Targeted disruption of the FGF2 gene does not prevent choroidal neovascularization in a murine model. Am J Pathol 153(5):1641–1646
203. Qiu G, Stewart JM, Sadda S, Freda R, Lee S, Guven D (2006) A new model of experimental subretinal neovascularization in the rabbit. Exp Eye Res 83(1):141–152
204. Baffi J, Byrnes G, Chan CC, Csaky KG (2000) Choroidal neovascularization in the rat induced by adenovirus mediated expression of vascular endothelial growth factor. Invest Ophthalmol Vis Sci 41(11):3582–3589
205. Grossniklaus HE, Ling JX, Wallace TM, Dithmar S, Lawson DH, Cohen C, Elner VM, Elner SG, Sternberg P Jr (2002) Macrophage and retinal pigment epithelium expression of angiogenic cytokines in choroidal neovascularization. Mol Vis 8(8):119–126
206. Tamai K, Spaide RF, Ellis E, Iwabuchi S, Ogura Y, Armstrong D (2002) Lipid hydroperoxide stimulates subretinal choroidal neovascularization in the rabbit. Exp Eye Res 74(2):301–308
207. Lyzogubov VV, Tytarenko RG, Liu J, Bora NS, Bora PS (2011) Polyethylene glycol (PEG)-induced mouse model of choroidal neovascularization. J Biol Chem 286(18):16229–16237
208. Goldberg MF (1976) Bruch's membrane and vascular growth. Invest Ophthalmol Vis Sci 15(6):443–446

209. Kiilgaard JF, Andersen MVN, Wiencke AK, Scherfig E, La Cour M, Tezel TH, Prause JU (2005) A new animal model of choroidal neovascularization. Acta Ophthalmol Scand 83(6):697–704
210. Glaucoma Research Foundation (2014) Types of glaucoma. Glaucoma Research Foundation. Accessed Sept 2014
211. Kumarasamy NA, Lam FS, Wang AL, Theoharides TC (2006) Glaucoma: current and developing concepts for inflammation, pathogenesis and treatment. Eur J Inflamm 4(3):129
212. Lavik E, Kuehn MH, Kwon YH (2011) Novel drug delivery systems for glaucoma. Eye 25(5):578–586
213. Monem AS, Ali FM, Ismail MW (2000) Prolonged effect of liposomes encapsulating pilocarpine HCl in normal and glaucomatous rabbits. Int J Pharm 198(1):29–38
214. De Campos AM, Sánchez A, Gref R, Calvo P, Alonso MJ (2003) The effect of a PEG versus a chitosan coating on the interaction of drug colloidal carriers with the ocular mucosa. Eur J Pharm Sci 20(1):73–81
215. Date RD (1999) Studies in the development of new drug delivery systems- mucoadhesive systems. University of Mumbai, Mumbai
216. Gaikwad DD (2000) New drug delivery systems: mucoadhesive opthalmic formulations. University of Mumbai, Mumbai