What is Glaucoma

Glaucoma is a complex eye condition characterized by elevated intraocular pressure (IOP) that may progress to vision loss over time. Glaucoma is the second leading cause of permanent blindness in the United States and occurs most often in older adults.[1] Glaucoma can be categorized into either primary or secondary types and further into open-angle or closed-angle variants within each type of glaucoma. Adult glaucoma includes primary open-angle glaucoma (POAG) and angle-closure glaucoma, as well as secondary open and angle-closure glaucoma,[2][3] with a specific focus on the most prevalent type, POAG.[4][5]

Glaucoma is an acquired loss of retinal ganglion cells and axons within the optic nerve or optic neuropathy that results in a characteristic optic nerve head appearance and a corresponding progressive loss of vision.[6] This unique pattern of peripheral vision loss serves as a distinguishing feature from other types of vision impairment.[7]

Patients with POAG are often asymptomatic until significant optic nerve damage occurs unless early signs of glaucoma are identified during routine eye examinations.[8] On the other hand, acute angle-closure glaucoma can develop suddenly and lead to a rapid decline in vision, accompanied by symptoms such as corneal edema, eye pain, headache, nausea, and emesis.[9][10] Secondary glaucoma often arises due to a previous eye injury or underlying medical conditions, resulting in elevated IOP and subsequent optic neuropathy. This category encompasses various subtypes, including congenital, pigmentary, neovascular, exfoliative, traumatic, and uveitic glaucoma.[11] Normal or low-tension type of glaucoma presents as an optic neuropathy with glaucomatous visual loss despite normal or unremarkable IOP readings.[12]

Although congenital, infantile, and developmental glaucoma, along with a juvenile variant of POAG, primarily affect younger individuals, most types of glaucoma are commonly diagnosed in individuals aged 40 and older. While IOP is often associated with glaucoma, a direct causal relationship has not been definitively established. Researchers are investigating genetic and environmental factors contributing to glaucoma development. Evidence from studies involving monozygotic twin pairs, who exhibit a higher concordance rate compared to dizygotic pairs, suggests that environmental factors also have a significant role in the disease's development.[13]

Although the available treatments cannot cure existing optic nerve damage or reverse visual field loss, they can help control the disease progression through medication, laser treatment, or incisional glaucoma surgeries to prevent further vision loss. All therapeutic interventions are focused on lowering IOP and minimizing the impact of this vision-threatening condition. This approach aims to prevent the onset of glaucoma in patients with risk factors and to manage the condition effectively to limit its progression in affected individuals

Treatment of Glaucoma :

Managing glaucoma involves personalized strategies based on the type and severity of the condition. Available treatments cannot reverse vision loss; they aim to lower IOP, a key risk factor, to prevent further damage and vision loss. Therapeutic options such as eye drops, laser procedures, and surgeries are focused on reducing IOP. Monitoring disease progression involves using tools like tonometry, visual field tests, OCT, and vision loss mapping.

Open-angle glaucoma is typically managed initially with medications aimed at reducing eye pressure. Common medication classes include prostaglandin analogs, β-blockers, carbonic anhydrase

inhibitors, α-2 agonists, miotic agents, and more recently, Rho-kinase inhibitors and nitric oxide-donating medications.[90][91] Laser trabeculoplasty, such as argon laser trabeculoplasty, selective laser trabeculoplasty, and multipulse laser trabeculoplasty, may also be considered in certain cases. However, the benefits of lowering IOP with laser trabeculoplasty often last several months, and retreatments are commonly necessary.[92]

If medical and/or laser management is unsuccessful, procedures such as trabeculectomy, deep sclerectomy, canaloplasty, insertion of a drainage valve/tube shunt, and laser treatment to the ciliary body to reduce aqueous production can help achieve better control of IOP.[93][94][95] Minimally invasive glaucoma surgery (MIGS) is an emerging option for individuals with mild-to-moderate glaucoma.[96] Compared to traditional trabeculectomy and tube shunts, MIGS offers a more favorable safety profile, quicker recovery time, and effective reduction of IOP to the mid-high teens. Studies also indicate that MIGS placement can decrease the number of pressure-lowering medications needed to maintain target IOP levels.[97]

Normal-tension glaucoma can be managed with medications to reduce IOP and address any underlying medical conditions. Treatment options include prostaglandin analogs, α-2 agonists, carbonic anhydrase inhibitors, and miotics. The use of β-blockers is debated due to concerns about reduced optic nerve head perfusion, particularly regarding the potential exacerbation of the early morning nadir in blood pressure. If medical therapy proves ineffective, laser trabeculoplasty or filtration surgery may be necessary, especially in cases of progressive vision loss. The collaborative normal-tension glaucoma study demonstrated that patients with this condition can slow or stabilize their field loss after achieving a 30% reduction in IOP.[98]

Angle-closure glaucoma is considered a medical emergency due to the potential for elevated pressures leading to glaucomatous optic nerve damage, ischemic nerve damage, or retinal vascular occlusion. Patients can take medications to reduce eye pressure as quickly as possible but usually require a laser procedure called laser peripheral iridotomy. This procedure involves creating a small hole in the iris to alleviate pupillary blockage. By equalizing the pressure gradient between the posterior and anterior chambers, laser iridotomy resolves the iris bombe and opens up the drainage angle in the anterior chamber, relieving the condition. The peripheral iris can be flattened with laser iridoplasty and, less commonly, with laser pupilloplasty.

A decrease in IOP does not always indicate that the angle has reopened. Ischemic damage to the ciliary body during an attack can reduce aqueous humor production for several weeks. Therefore, it is crucial to perform a follow-up gonioscopy to confirm angle patency. This evaluation also helps assess the percentage of the angle with peripheral anterior synechia from acute or prior subacute attacks. After resolving the acute crisis, patients are at a high risk of experiencing an attack in the contralateral eye. Therefore, they should undergo gonioscopy to assess the angle and consider prophylactic iridotomy in the other eye if the angle is narrow.[99] Treatment for secondary glaucoma should focus on addressing the underlying cause along with the possible inclusion of medications to reduce IOP.

CAUSES OF GLAUCOMA

Open-angle glaucoma symptoms

With open-angle glaucoma, there are no warning signs or obvious symptoms in the early stages. As the disease progresses, blind spots develop in your peripheral (side) vision.

Most people with open-angle glaucoma do not notice any change in their vision until the damage is quite severe. This is why glaucoma is called the “silent thief of sight.” Having regular eye exams can help your ophthalmologist find this disease before you lose vision. Your ophthalmologist can tell you how often you should be examined.

Angle-closure glaucoma symptoms

People at risk for angle-closure glaucoma usually show no symptoms before an attack. Some early symptoms of an attack may include blurred vision, halos, mild headaches or eye pain. People with these symptoms should be checked by their ophthalmologist as soon as possible. An attack of angle-closure glaucoma includes the following:

- severe pain in the eye or forehead
- redness of the eye
- decreased vision or blurred vision
- seeing rainbows or halos
- headache
- nausea
- vomiting

Normal tension glaucoma symptoms

People with "normal tension glaucoma" have eye pressure that is within normal ranges, but show signs of glaucoma, such as blind spots in their field of vision and optic nerve damage.

Do glaucoma suspects have symptoms?

Some people have no signs of damage but have higher than normal eye pressure (called ocular hypertension). These patients are considered "glaucoma suspects" and have a higher risk of eventually developing glaucoma. Some people are considered glaucoma suspects even if their eye pressure is normal. For example, their ophthalmologist may notice something different about their optic nerve. Most glaucoma suspects have no symptoms. That is why you need to be carefully monitored by your ophthalmologist if you are a glaucoma suspect. An ophthalmologist can check for any changes over time and begin treatment if needed.

Pigment dispersion syndrome and pigmentary glaucoma symptoms

Pigment dispersion syndrome (PDS) happens when the pigment rubs off the back of your iris. This pigment can raise eye pressure and
lead to pigmentary glaucoma. Some people with PDS or pigmentary glaucoma may see halos or have blurry vision after activities like jogging or playing basketball

See your ophthalmologist if you have these or other symptoms.

WHAT is Cataract?

Cataract, the clinical correlate of opacity or light scattering in the eye lens, is usually caused by the presence of high molecular weight protein aggregates or disruption of the lens microarchitecture. In general, genes involved in inherited cataract reflect important processes and pathways in the lens including lens crystallins, connexins, growth factors, membrane proteins, intermediate filament proteins, and chaperones. Usually, mutations causing severe damage to proteins cause congenital cataracts, while milder variants increasing susceptibility to environmental insults are associated with age-related cataracts. These might have different pathogenic mechanisms, with congenital cataracts inducing the UPR and apoptosis, while in age-related cataract denatured crystallins are bound by α-crystallin and form light scattering high molecular weight aggregates. New therapeutic approaches to age related cataracts involve using chemical chaperones to solubilize high molecular weight aggregates, while attempts are being made to regenerate lenses using endogenous stem cells to treat congenital cataracts.

Introduction

Overview of the eye lens

The eye lens transmits and focuses light on the retina, where photoreceptors detect it and along with the other retinal cell types convert it into visual signals which then undergo initial processing before being transmitted through the optic nerve to the optic cortex. This function is facilitated by the lens structure, which consists of a single layer of anterior epithelial cells that migrate laterally during development towards the lens equator where they invert, elongate, synthesize large amounts of proteins specific to the lens including the lens crystallins, and finally degrade their organelles so as to increase their transparency. They are then overlayed by succeeding lens epithelial cells so that they eventually form an onion like structure of mature fiber cells called the lens nucleus. While this process begins during

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embryogenesis and is most active during development, it continues more gradually throughout life, so that older fiber cells reside in the lens nucleus, around which younger cortical fiber cells continue to be layered at the equator.

The mechanisms through which lens epithelial cells are transformed to elongated fiber cells lacking organelles is an area of active investigation. There is strong evidence that as the epithelial cells reach the equator they are exposed to increased levels of FGF (Dawes et al. 2018) and possibly oxidative stress (Brennan et al. 2018) to induce lens fiber differentiation. Mechanistically, the loss of organelles has been shown to involve the ubiquitin-proteasome pathway (Wride 2011), although there is increasing evidence that autophagy has an essential role in this process (Costello et al. 2013), However, both the organelle-free nature of lens fiber cells and their precise organization within the lens are critical to lens transparency and vision, as deviations from either can scatter light.

Since lens fiber cells lack ribosomes and other organelles, they cannot repair or replace damaged or modified proteins. This requires that lens crystallins be extremely stable so that they can last the lifetime of the organism, and also requires that the lens maintain strong homeostatic metabolic systems, especially those that contribute to maintenance of a reducing environment, to minimize damage to crystallins and other lens components (Ganea & Harding 2006) or reduce oxidative damage once it occurs (Kantorow et al. 2004), and avoid glycation and osmotic damage to the lens (Linetsky et al. 2008). The central nuclear fiber cells, are mostly dependent on glycolysis as an intrinsic energy source, which limits the energy available to them for these homeostatic activities. However, they receive considerable metabolic support from the anterior epithelia through an intrinsic circulation of fluid that appears to be critical for maintenance of lens homeostasis and transparency (Gao et al. 2018). Thus, the lens represents a delicately balanced anatomical and biochemical system, disruption of any part of which can result in loss of lens transparency or cataracts.

Overview of lens opacity

Opacity or cloudiness of the eye lens, the optical basis of cataract result when the refractive

index within the lens varies significantly over distances approximating the wavelength of the transmitted light (Benedek 1971, Delaye & Tardieu 1983). Lens transparency requires both the orderly arrangement of lens cells and the high density and close packing of their protein constituents, primarily the lens crystallins. Variation in the refractive index and hence light scattering can result from changes in lens microarchitecture, the protein constituents, or both (Shiels & Hejtmancik 2017). Breakdown of the lens microarchitecture, including vacuole formation and disarray and degeneration of the lens fiber cells, results in large fluctuations in optical density, causing light scattering and hence cataract. Similarly, light scattering and opacity also can result from increased concentrations of high molecular weight protein aggregates (HMW) larger than 1000 Å in size. As lens crystallins make up over 90% of soluble lens proteins, their short-range ordered packing in a homogeneous phase is critical for lens transparency.

For patients, cataracts become important when they begin to interfere with vision, and they can be categorized by the age at which this occurs, even though some lens opacity probably precedes the clinical recognition. Congenital cataracts are diagnosed in the first year of life,

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while juvenile cataracts declare themselves between one and ten years of life. Presenile cataracts come to clinical attention before the age of 45–55 years, and cataracts diagnosed after that time are classified as senile or age-related cataract. These definitions are approximate and somewhat arbitrary, so that different studies might shift the limits by 5–10 years. Also, as mentioned, asymptomatic mild cataracts might not be diagnosed for years after they occur. The age of onset of a cataract does not necessarily imply a specific cause. Congenital cataracts might be inherited or secondary to an intrauterine insult (e.g. viral or parasitic disease). Cataracts associated with a systemic metabolic disease such as diabetes or an ophthalmic genetic disease such as retinitis pigmentosa may not occur until the later in life. Age-related cataracts are almost always associated with both a variety of environmental insults accumulated over many years, and the susceptibility to these insults may be modulated directly or indirectly by genetic risk factors (1994, Hammond et al. 2001,

Hammond et al. 2000, Heiba et al. 1993, Heiba et al. 1995, Leske et al. 1998, Yonova-Doing et al. 2016).

The genetic origin of an inherited cataract can be suggested by the time it first appears and the specific region of the lens in which it occurs. Opacity should present in lens cells synthesizing large amounts of a mutant protein at the time at which it is being synthesized. One example of this principle is the γ-crystallins, which are synthesized at high levels early in development in fiber cells which are destined to populate the embryonic or central nucleus. For this reason, mutations in γ-crystallins often tend to cause nuclear cataracts, with ~49% of mutations in γ-crystallins listed in CAT-MAP (Shiels et al. 2010) being nuclear and ~15% nuclear lamellar. In spite of these general tendencies, mutations in a variety of genes can cause clinically indistinguishable cataracts and identical mutations in the same gene can cause varying cataract phenotypes. However, one general principle seems to be that mutations in crystallins or other lens proteins are sufficiently severe to cause protein aggregation or directly damage lens cells by themselves, thereby resulting in congenital cataract. In contrast, if mutations merely increase susceptibility to damage from light, hyperglycemia, oxidative stress, or other environmental insults they might contribute to age related cataract.(Hejtmancik & Smaoui 2003) Thus, hereditary congenital cataracts tend to be inherited in a Mendelian fashion with high penetrance, while age-related cataracts tend to be multifactorial, with both multiple genes and environmental factors influencing the phenotype, making them significantly less amenable to classical genetic and biochemical analysis.

Congenital cataract

Estimates of the incidence of congenital cataracts vary from 12 to 136 per 100,000 births, with most countries showing about 72 per 100,000 children. The incidence tends to be higher in less developed countries, probably because of a higher risk of infectious disease and other environmental causes (Gilbert & Foster 2001, Haargaard et al. 2004, Stoll et al. 1992). Overall, between 8.3 and 25 percent of congenital or infantile cataracts are inherited (Francois 1982, Haargaard et al. 2005, Merin 1991). They may be isolated cataracts or may be accompanied by anterior chamber developmental anomalies including microphthalmia, microcornea, or aniridia. Cataracts may also occur as part of multisystem genetic problems including chromosome disorders, developmental defects, or metabolic disorders. There can

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because of defects in many growth factors. In some patients these may cause cataracts associated with defects in the anterior segment or optic disc in some family members while resulting in isolated cataracts in other members of the same family.

Hereditary Mendelian cataracts are most frequently inherited as an autosomal dominant trait, ~85% in CAT-MAP (Shiels et al. 2010) but can also show autosomal recessive, or X-linked inheritance. As mentioned above clinically similar cataracts can result from mutations in different genes and also may show different inheritance patterns, while phenotypically variable cataracts can result from the same mutation in a single gene, and even be found in a single family (Scott et al. 1994). Several classification systems have been developed based on the clinical presentation and anatomic location of the opacity, with the one proposed by Merin being the most commonly used. In this system cataracts are classified as polar (anterior or posterior), zonular (nuclear, lamellar, sutural, etc.), total (mature or complete), and capsular or membranous (Merin & Crawford 1971). A revision of this system taking anterior segment characteristics into account has recently been proposed (Lin et al. 2016a).

Age-related cataract

Age-related or senile cataracts present after the age of 45–55 years, with the lens clear before that time. They tend to be progressive in nature and are extremely common. Age related cataracts usually represent the effects of various combinations and cumulative damage of environmental effects acting in concert with the genetic predisposition encoded in genes for lens proteins (1994, Hammond et al. 2001, Hammond et al. 2000, Heiba et al. 1993, Heiba et al. 1995, Leske et al. 1998, Yonova-Doing et al. 2016).

Lens crystallins show multiple types of modifications with aging of the lens. Most of the changes are caused or accelerated by oxidative, UV, osmotic, or other types of damage, and these environmental risks are independently associated with cataractogenesis in epidemiological studies (Sharma & Santhoshkumar 2009). Alterations of lens crystallins include proteolysis, an increase in disulfide bridges, phosphorylation, nonenzymatic

glycosylation, carbamylation, deamidation of asparagine and glutamine residues, and racemization of aspartic acid residues among others (Sharma & Santhoshkumar 2009). Just as the environmental stresses that cause these changes have been linked epidemiologically to age related cataracts in human populations, the chemical modifications themselves are increased in lenses with cataracts as well as in *in vitro* or in model systems in which the model animals are subjected to similar environmental insults as seen in human age related cataract (Ottonello et al. 2000).

Crystallins comprise over 90% of the soluble proteins in the eye lens and are the most studied proteins in the aging lens. In humans there are three major classis of lens, α-, β- and γ-crystallins, each of which consist of gene families, the latter two of which share a very stable structure composed of two domains, each comprising two very stable Greek key motifs (Jaenicke & Slingsby 2001). As individuals age, the β- and γ-crystallins are modified, especially under the influence of environmental stress, and start to lose their normally stable protein fold and form irreversible aggregates. The slowly denaturing β- and γ-crystallins are bound by α-crystallins, which have a chaperone-like activity (Rao et al.

1995). However, complexing of the denatured βγ-crystallins by α-crystallins maintains their solubility and thus reduces light scattering, it does not result in their being recycled into the cytoplasm as would happen with true chaperones. Instead, the denatured crystallins are held in complexes with α-crystallins that increase in size over time as increasing amounts of damaged protein are bound until they become high molecular weight aggregates that are large enough to scatter light (Datiles et al. 2008, Rao et al. 1995). With sufficient time and insults, even the high level of α-crystallin in the lens is exhausted and the high molecular weight aggregates precipitate, joining the insoluble protein that increases with age and in cataractous lenses. Whether this process involves complete or partial denaturation or the modified crystallins simply have decreased solubility but intact protein folds is not known currently, and might vary for each crystallin and mutation. However, both mouse models and cell culture studies of mutant proteins associated with human cataracts strongly suggest that

the presence of large amounts of denatured protein damages the lens cell, and contributes to cataracts not only through light scattering by protein aggregates, but eventually also through toxicity to lens fiber cells and resultant disruption of cellular architecture (Ma et al. 2011, Wang et al. 2007). Similarly mutations in proteins that maintain intracellular homeostasis can disrupt the intracellular environment of lens cells and eventually cause damage to their constituents, contributing to age related cataract.

Age-related cataracts, while not having as severe an impact on each affected individual as congenital cataracts, have a much greater overall burden on the population because they are extremely common. They are responsible for blinding 17 million persons worldwide, causing just under half of all blindness (Congdon et al. 2003), and are the leading cause of low vision in the United States (Congdon et al. 2003). Cataract surgery is required by about 5% of the American population over 40 years old, making it the most frequently performed surgical procedure. It has been pointed out that due to the advanced age at which age related cataracts are found, delaying their age of onset by only ten years would decrease cataract surgery in the United States by about 45% (Kupfer 1984).

The risk of age-related nuclear cataract is increased by exposure to certain environmental factors such as elevated blood glucose levels, cigarette smoking or chronic exposure to wood smoke, or obesity (Chang et al. 2011, Foster et al. 2003, Leske et al. 1991, Lu et al. 2012, Ye et al. 2012). Similarly, the risk of age related cortical cataracts is increased by ultraviolet light and elevated glucose levels (Brown & Hill 1987, Foster et al. 2003, Group 1991, Hennis et al. 2004, Machan et al. 2012), and the risk of age related PSC is increased by smoking, diabetes, radiation, corticosteroids, and some other drugs (Abe et al. 2012). Alcohol consumption has been suggested to be associated with age-related cataract, but the relationship appears to be complicated and results are somewhat inconsistent (1991, Kanthan et al. 2010). Conversely, exercise, vitamin D, and antioxidant vitamins might have a protective effect, although this has not been borne out by all studies (Chang et al. 2011, West & Valmadrid 1995, Williams 2012) (Park & Choi 2017). One interesting aspect of these studies is that not only have they identified a number of potentially correctable environmental risk factors for age related cataract, but the different risk factors for nuclear, cortical and posterior subcapsular cataracts suggest that they might have distinct pathogenic mechanisms that begin to converge in the final steps of cataractogenesis.

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Many epidemiological studies also support a role for genetic factors in age-related cataract

(Group 1991, McCarty & Taylor 2001). The Italian American cataract study group (1991)

and the Lens Opacity Case Control Study (Leske et al. 1991) both suggest that family

history is a risk factor for cortical, combined nuclear and cortical, and posterior subcapsular

cataracts. The Framingham Offspring Eye Study (1994) found a threefold increased risk for

cataract in individuals with a sibling having a cataract. Results from the Beaver Dam Eye

Study (Klein et al. 2001) and Twin Eye Study (Hammond et al. 2001) both suggest that

genetic factors could account for as much as 35–48% of the risk for nuclear and 53–75% of

the risk for nuclear and cortical cataract, respectively. Finally, a recent twin study suggests

that genetic factors might account for 20–39% of intraocular light scattering that didn’t

reach the stage of cataract (Benito et al. 2016).

o determine whether you have a cataract, your eye doctor will review your medical history and symptoms. They also will perform an eye exam. Your doctor may do several tests, including:

- **Vision test.** A vision test, also called a visual acuity test, uses an eye chart to measure how well you can read a series of letters. One eye is tested at a time, while the other eye is covered. A chart or a viewing device with letters that get smaller is used. With this, your eye doctor determines if you have 20/20 vision or if you have trouble seeing.
- **Eye structure exam.** An eye structure exam, also called a slit lamp, allows your eye doctor to see the structures at the front of your eye up close. It's called a slit lamp because it uses an intense line of light, a slit, to light up the structures in your eye. The slit allows your doctor to view these structures in small sections. This makes it easier to find anything that may be wrong.
- **Retinal exam.** A retinal exam looks at the back of your eyes, called the retina. To prepare for a retinal exam, your eye doctor puts drops in your eyes to open your pupils wide, called dilation. This makes it easier to see the retina. Using a slit lamp or a special device called an ophthalmoscope, your eye doctor can examine your lens for signs of a cataract.
- **Fluid pressure test.** This test, also called applanation tonometry, measures fluid pressure in your eye. There are multiple different devices available to do this.

Treatment

When your prescription glasses can't clear your vision, the only effective treatment for cataracts is surgery.

When to consider cataract surgery

Talk with your eye doctor about whether surgery is right for you. Most eye doctors suggest considering cataract surgery when your cataracts begin to affect your quality of life. This may include your ability to perform daily activities, such as reading or driving at night.

For most people, there is no rush to remove cataracts because they usually don't harm the eyes. But cataracts can worsen faster in people with certain conditions. These include diabetes, high blood pressure or obesity.

Waiting to do cataract surgery typically won't affect how well your vision recovers. Take time to consider the benefits and risks of cataract surgery with your doctor.

If you choose not to have cataract surgery now, your eye doctor may recommend periodic follow-up exams to see if your cataracts are getting worse. How often you'll see your eye doctor depends on your situation.

What happens during cataract surgery

Cataract surgery Enlarge image

Cataract surgery involves removing the clouded lens and replacing it with a clear artificial lens. The artificial lens, called an intraocular lens, is put in the same place as your natural lens. It remains a permanent part of your eye.

For some people, artificial lenses can't be used. In these situations, once the cataract is removed, vision may be corrected with eyeglasses or contact lenses.

Cataract surgery is typically done on an outpatient basis. This means you won't need to stay in a hospital after the surgery. During surgery, your eye doctor uses a medicine to numb the area around your eye. You usually stay awake during the procedure.

Cataract surgery is generally safe. However, it carries a risk of infection and bleeding. Cataract surgery also increases the risk of the retina being pulled out of place. This is called retinal detachment.

After the procedure, you may be sore for a few days. Healing usually happens within a few weeks.

If you need cataract surgery in both eyes, your doctor will schedule surgery to remove the cataract in the second eye after you've healed from the first surgery.

Diabetic retinopathy

Diabetic retinopathy (DR) is a leading cause of visual impairment and blindness

worldwide. Since DR was first recognized as an important complication of

diabetes, there have been many attempts to accurately classify the severity and

stages of disease. These historical classification systems evolved as

understanding of disease pathophysiology improved, methods of imaging and assessing DR changed, and effective treatments were developed. Current DR classification systems are effective, and have been the basis of major research trials and clinical management guidelines for decades. However, with further new developments such as recognition of diabetic retinal neurodegeneration, new imaging platforms such as optical coherence tomography and ultra wide-field retinal imaging, artificial intelligence and new treatments, our current classification systems have significant limitations that need to be addressed. In this paper, we provide a historical review of different classification systems for DR, and discuss the limitations of our current classification systems in the context of new developments. We also review the implications of new developments in the field, to see how they might feature in a future, updated classification.

Past: A historical review of classification systems for diabetic retinopathy

Early classifications of DR

Diabetic retinal lesions such as hemorrhages and exudates were first observed by Eduard Jaeger using the direct ophthalmoscope in 1856 (14). However, there was limited evidence of a causal relationship between diabetes mellitus and retinopathy at the time, and many prominent ophthalmologists, such as Albrecht von Graefe, questioned the link (15). In the years that followed, more evidence linking diabetes and retinal complications began to emerge, including reports by Louis Desmarres in 1858 (16) and Henry Noyes in 1869 (17). In 1872, Edward Nettleship published a histopathological study

demonstrating “cystoid degeneration of the macula” in diabetes (18). In 1876, German ophthalmologist Wilhelm Manz described fibrovascular proliferations along the blood vessels in a patient with proliferative diabetic retinopathy, which he termed “retinitis proliferans” at the time (19). Julius Hirschberg proposed the first classification of DR in 1890, which he sub divided into 3 types: retinitis centralis punctata (which affected mainly the posterior pole), retinitis hemorrhagica, and other retinal manifestations (20). “Diabetic retinitis” was a frequently used term at the time, because it was presumed that exudation was related to inflammation. In 1934, Wagener, Dry and Wilder proposed an expanded classification which included 5 stages and incorporated lesions such as hemorrhages, punctate exudates, cotton-wool exudates and venous changes, with proliferative retinopathy being the most severe stage of disease (21). Subsequently in the 1940s, Arthur James Ballantyne described capillary wall alterations and microaneurysms in DR, and included them in a classification of DR (22).

As DR was studied in greater depth, more classification systems for DR were proposed over the next decades. In the early 1950s, Scott suggested a six-stage clinical classification of DR (23). In stages I to III, various lesions that we now understand as pre-proliferative disease were described, including capillary

microaneurysms, intraretinal hemorrhages, exudates and venous changes. At the time, it was not recognized that vitreous hemorrhage was a direct consequence of neovascularization, and so vitreous hemorrhage was classified as a separate stage IV,

which was thought to subsequently progress to proliferative disease. Stage V was “retinitis proliferans”, which was subdivided into V(a), retinitis proliferans, and V(b), the “vascular type” of retinitis proliferans, while stage VI was retinal detachment and “gross degenerative changes”, representing end-stage diabetic retinal disease. One of the major drawbacks of this classification system was the fact that the pre-proliferative stages of disease were still divided primarily by specific lesion type – for example, the presence of exudates necessitated classification as stage III, whereas we now know that the development of hard exudates or macular edema can progress independently of overall retinopathy status.

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What are the symptoms of diabetic retinopathy?

The early stages of diabetic retinopathy usually don’t have any symptoms. Some people notice changes in their vision, like trouble reading or seeing faraway objects. These changes may come and go.

In later stages of the disease, blood vessels in the retina start to bleed into the vitreous (gel-like fluid that fills your eye). If this happens, you may see dark, floating spots or streaks that look like cobwebs. Sometimes, the spots clear up on their own — but it’s important to get treatment right away. Without treatment, scars can form in the back of the eye. Blood vessels may also start to bleed again, or the bleeding may get worse.

What other problems can diabetic retinopathy cause?

Diabetic retinopathy can lead to other serious eye conditions:

- **Diabetic macular edema (DME).** Over time, about 1 in 15 people with diabetes will develop DME. DME happens when blood vessels in the retina leak fluid into the macula (a part of the retina needed for sharp, central vision). This causes blurry vision.
- **Neovascular glaucoma.** Diabetic retinopathy can cause abnormal blood vessels to grow out of the retina and block fluid from draining out of the eye. This causes a type of glaucoma (a group of eye diseases that can cause vision loss and blindness).

Learn more about types of glaucoma

- **Retinal detachment.** Diabetic retinopathy can cause scars to form in the back of your eye. When the scars pull your retina away from the back of your eye, it’s called tractional retinal detachment.

Learn more about types of retinal detachment

Am I at risk for diabetic retinopathy?

Anyone with any kind of diabetes can get diabetic retinopathy — including people with type 1, type 2, and gestational diabetes (a type of diabetes that can develop during pregnancy).

Your risk increases the longer you have diabetes. Over time, more than half of people with diabetes will develop diabetic retinopathy. The good news is that you can lower your risk of developing diabetic retinopathy by controlling your diabetes.

Women with diabetes who become pregnant — or women who develop gestational diabetes — are at high risk for getting diabetic retinopathy. If you have diabetes and are pregnant, have a comprehensive dilated eye exam as soon as possible. Ask your doctor if you'll need additional eye exams during your pregnancy.

What causes diabetic retinopathy?

Diabetic retinopathy is caused by high blood sugar due to diabetes. Over time, having too much sugar in your blood can damage your retina — the part of your eye that detects light and sends signals to your brain through a nerve in the back of your eye (optic nerve).

Diabetes damages blood vessels all over the body. The damage to your eyes starts when the sugar in your blood causes changes to the tiny blood vessels that go to your retina. These changes make it harder for the blood to flow, leading to blocked blood vessels that leak fluid or bleed. To make up for these blocked blood vessels, your eyes then grow new blood vessels that don't work well. These new blood vessels can leak or bleed easily.

How will my eye doctor check for diabetic retinopathy?

Eye doctors can check for diabetic retinopathy as part of a dilated eye exam. The exam is simple and painless — your doctor will give you some eye drops to dilate (widen) your pupil and then check your eyes for diabetic retinopathy and other eye problems.

Learn what to expect from a dilated eye exam

If you have diabetes, it's very important to get regular eye exams. If you do develop diabetic retinopathy, early treatment can stop the damage and prevent blindness.

If your eye doctor thinks you may have severe diabetic retinopathy or DME, they may do a test called a fluorescein angiogram. This test lets the doctor see pictures of the blood vessels in your retina.

What can I do to prevent diabetic retinopathy?

Managing your diabetes is the best way to lower your risk of diabetic retinopathy. That means keeping your blood sugar levels in a healthy range. You can do this by getting regular physical activity, eating healthy, and carefully following your doctor's instructions for your insulin or other diabetes medicines.

To make sure your diabetes treatment plan is working, you'll need a special lab test called an A1C test. This test shows your average blood sugar level over the past 3 months. You can work with your doctor to set a personal A1C goal. Meeting your A1C goal can help prevent or manage diabetic retinopathy.

Learn more about the A1c test

Having high blood pressure or high cholesterol along with diabetes increases your risk for diabetic retinopathy. So controlling your blood pressure and cholesterol can also help lower your risk for vision loss.

What's the treatment for diabetic retinopathy and DME?

In the early stages of diabetic retinopathy, your eye doctor will probably just keep track of how your eyes are doing. Some people with diabetic retinopathy may need a comprehensive dilated eye exam as often as every 2 to 4 months.

In later stages, it's important to start treatment right away — especially if you have changes in your vision. While it won't undo any damage to your vision, treatment can stop your vision from getting worse. It's also important to take steps to control your diabetes, blood pressure, and cholesterol.

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Injections. Medicines called anti-VEGF drugs can slow down or reverse diabetic retinopathy. Other medicines, called corticosteroids, can also help.

Learn more about injections

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Laser treatment. To reduce swelling in your retina, eye doctors can use lasers to make the blood vessels shrink and stop leaking.

Learn more about laser treatment for diabetic retinopathy

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Eye surgery. If your retina is bleeding a lot or you have a lot of scars in your eye, your eye doctor may recommend a type of surgery called a vitrectomy.

Learn more about vitrectomy

What is the latest research on diabetic retinopathy and DME?

Scientists are studying better ways to find, treat, and prevent vision loss in people with diabetes. One NIH-funded research team is studying whether a cholesterol medicine called fenofibrate can stop diabetic retinopathy from getting worse.