DIABETES AND THE EYE: AN OVERVIEW

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INTRODUCTION: Diabetes mellitus is major health concern globally, affecting both developed and developing countries. Currently, over 240 million people have been affected worldwide, and this number is expected to reach 370 million by 2030.[1,2] This problem is further complexed by the fact that diabetes is a progressive disease and if not treated, can adversely affect healthy functioning of the body.[3] Just like diabetes, its complications are also progressive and occur because of chronic exposure to hyperglycemia.[4] Diabetes can cause both macrovascular and microvascular complications. Microvascular complications are often seen in the eye, especially in case of uncontrolled type 1 or type 2 diabetes.[5] Therefore, routine eye examinations are warranted in individuals with diabetes. Those with type 1 diabetes should have an initial comprehensive eye exam within 3–5 years of disease onset. However, in type 2 diabetes, most often, the onset of disease and duration are not known, and therefore these patients should have a complete examination immediately after diagnosis, and regularly followed up annually.[6] Sadly, only 50% of individuals with diabetes comply with these recommendations.[7] Those who have uncontrolled diabetes, and do not follow recommendations are at a higher risk of developing more severe complications.[5] Diabetes can lead to various ocular complications of which diabetic retinopathy (DR) is the most important and common. Others include cataract, glaucoma, dry eyes, keratopathy, refractive changes, occulomotor nerve palsy, and chronic inflammation of the lids.[8] in the current review, we discuss four important ocular complications of diabetes: DR, cataract, glaucoma and dry eye syndrome.

DIABETIC RETINOPATHY: Diabetic retinopathy is a serious complication of diabetes and an important cause of blindness among adults in the working-age group. Vision impairment caused by DR is a major health concern globally. However, the progression of this complication of diabetes can be prevented by tight glycemic control, early detection and management of DR.[9]

Diabetic retinopathy is more common and more severe in subjects with type 1 than type 2 diabetes. About 95% of individuals with type 1 diabetes and 60% of those with type 2 diabetes with disease duration over 20 years, show signs of DR.[10] According to the World Health Organization, there has been a burgeoning increase in type 2 diabetes and DR in India.[11]

The pathogenesis of DR is complex, with many contributing factors. Both type 1 and type 2 diabetes are associated with retinal micro vascular changes.[5] Longstanding hyperglycemia in the retinal blood vessels results in (i) accumulation of advanced glycation end-products (AGEs), (ii) inflammation, (iii) neuronal dysfunction and (iv) oxidative stress.[12] These changes further lead to micro vascular dysfunction causing increased vascular permeability and capillary rarefaction. Subsequently, this dysfunction results in macular edema and neovascularization in the retina.[13]

There are two stages of DR, non-proliferative DR (NPDR) and proliferative DR (PDR), described in figure 1.[5,11]

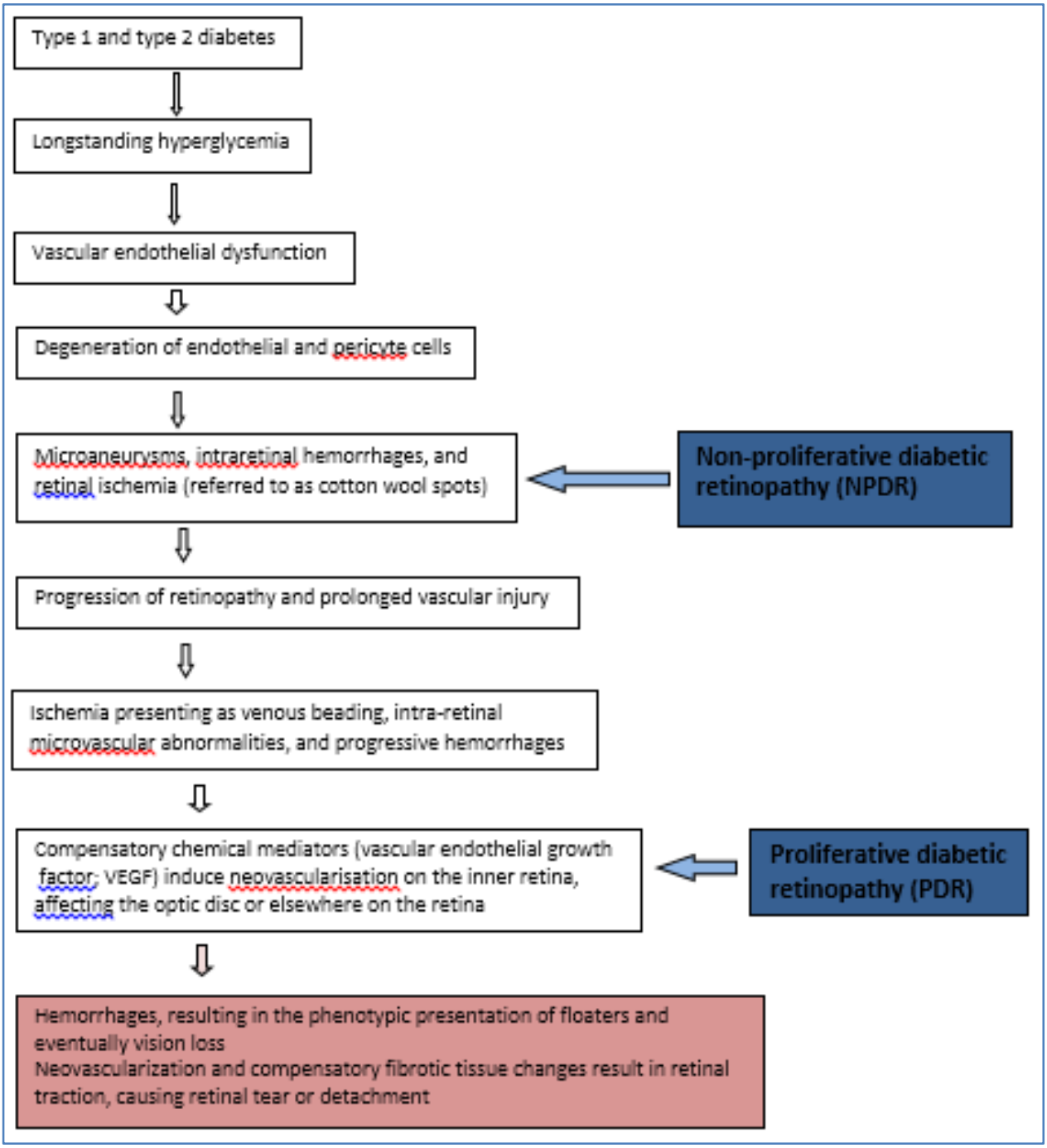

Fig. 1: Progression and Stages of Diabetic Retinopathy

In addition to non-specific retinal changes, the macula can also be specifically affected. Macular edema is often seen in subjects with uncontrolled diabetes and is a leading cause of

preventable vision loss in them, occurring at any stage of DR. The damaged retinal vasculature is permeable and susceptible to plasma and lipid efflux. As a result, there is fluid accumulation in the inner layer of the retina, observed as yellow, hard exudate under direct visual examination. This condition is usually asymptomatic, but may present as blurred vision.[5]

According to the landmark Diabetes Control and Complications Trial (DCCT) conducted in 1993, strict glycemic control was highly effective in primary prevention of retinopathy, reducing the risk of new retinopathy by 76% in the intensive therapy group compared to the conventional therapy group, and the rate of progression of retinopathy in those who had mild-to-moderate NPDR at baseline.[13]

Management of DR includes increased metabolic control, laser treatment, intra vitreal medication, and surgery. Metabolic control includes mainly management of hyperglycemia and hyperlipidemia. Laser treatment is currently considered a promising management option for PDR as well as macular edema, and has been shown to prevent vision loss in these patients, but does not focus on regaining visual acuity. Laser therapy is usually performed over a period of 4-6 weeks; 1.500-2.000 burns, with a size of 500 µm, spacing spots 0.5 burn widths from each other are applied with a duration of 0.1-0.2s.[4]

Currently, various intravitreal agents have been demonstrated to be effective not only in the prevention of visual loss, but also in regaining visual acuity. The two groups of drugs used are steroids and anti-VEGF agents. Intravitreal steroids are preferred in macular edema, due to their anti-inflammatory and anti angiogenic effects that stabilize of the inner blood retina barrier. Intraocular steroid injections are beneficial in PDR by inhibiting production of the VEGF. Intravitreal triamcelone acetate has been extensively studies. However, the effect of this lasts only for about 3 months, and is associated with a higher incidence of glaucoma and cataract. Recently, a novel, biodegradable, slow-release dexamethasone implant has been developed which gradually releases 0.7 mg of dexamethasone in the vitreous cavity, and has the advantage of a lower incidence of cataract and glaucoma than intravitreal triamcelone acetate. Anti-VEGF agents (pegaptanib, bavacizumab, ranibizumab, aflibercept) have shown promising results in the management of macular edema and PDR. In addition, these drugs are useful adjuncts to facilitate effective fibrovascular membrane dissection in eyes with active vascularity components.[4]

Pars plana vitrectomy (PPV) is a surgical option for patients not responding to combined anti-VEGF- laser and/or steroid-laser therapy in macular edema and PDR. Enzymatic vitrectomy performed by the intravitreal injection of autologous plasmin enzyme is a novel therapeutic option, which can be considered as an alternative before other treatments discussed.[4]

GLAUCOMA: Glaucoma is a progressive condition of the eye associated with typical optic disc changes and visual field defects. It may or may not be associated with elevated intraocular pressure. Individuals with diabetes are at risk of developing two major types of glaucoma: primary glaucoma and neo vascular glaucoma (NVG).[14]

Primary Glaucoma

The two common types of primary glaucoma are Open angle glaucoma (OAG) and Angle closure glaucoma (ACG).

OPEN ANGLE GLAUCOMA: Open angle glaucoma is one of the most common causes of vision loss globally,[4] and is characterized by progressive peripheral vision loss, eventually affecting central vision.[6] Diabetes has been considered to be a risk factor for OAG, with the risk being directly proportional to the duration of diabetes.[4,6] Several large epidemiological studies have shown this association.[15,16] However, few studies have not shown any association between these two conditions.[17,18] Additionally, since subjects with diabetes have more regular eye examinations, compared to the general population, the chances of OAG being detected in the earlier stages is higher.[19] Glaucoma occurs more often in subjects with diabetes (5%) than in those without (2%), and the risk of glaucoma is 1.6–4.7 times higher in the former group compared to the latter.[14]

The postulated mechanisms for this increased incidence of glaucoma are: [4,14]

i. Micro vascular damage due to diabetes impairs blood flow to the anterior optic nerve, causing optic nerve damage. Further, diabetes impairs the auto regulation of posterior ciliary circulation, exacerbating the glaucomatous optic neuropathy.
ii. Subjects with diabetes most often have concomitant cardiovascular risk factors which affect vascular perfusion of the optic nerve head.
iii. Subjects with diabetes may be more vulnerable to elevated intraocular pressure, compared to those without, resulting in more severe visual field loss at the same level of intraocular pressure.
iv. Management options are topical intraocular pressure lowering drugs, laser trabeculectomy and surgery like filtering surgery and aqueous drainage devices.

ANGLE CLOSURE GLAUCOMA: Angle closure glaucoma (ACG) is the other common primary glaucoma, characterized by narrow or closed anterior chamber angles, impeding drainage of aqueous humor, resulting in elevated intraocular pressure.15 Studies have shown that diabetes is as a risk factor for developing ACG.[20,21] Subjects with ACG are more likely to have abnormal glucose tolerance than those with OAG or without glaucoma.[22] Angle closure glaucoma can occur more often in subjects with diabetes because of systemic autonomic dysfunction, increased lens thickness owing to sorbitol overload and shallower anterior chambers.[20] Patients with ACG may present with an acute attack, characterized by severe ocular pain, headache, nausea, and substantially elevated intraocular pressure. This is an emergent condition, requiring immediate referral and treatment.[15] Management of ACG includes use of topical, oral, and intravenous pharmacological agents, but the definitive therapy is laser iridotomy.[4]

NEOVASCULAR GLAUCOMA: Neo vascular glaucoma is a severe and intractable type of glaucoma.[4] A consistent association between diabetes and NVG has been observed, with PDR being the leading cause of this type of glaucoma. About 32-43% of NVG cases are caused by PDR.[14] Sometimes, NVG can also occur in cases with no retinal or optic disc neovascularization. Neo vascularisation of the iris is a major precursor of NVG.[14] The incidence of NVG is directly proportional to the duration of diabetes and glycemic control in these patients.[23]

The underlying mechanism of PDR and NVG are similar (see Fig. 1).[6] Neovascularization of the iris is an early precursor of neo vascular glaucoma. Hypoxia in the retina and other ocular tissue result in an increased expression of VEGF, which in turn stimulates neovascularisation in the iris or in the anterior chamber angle.[14] This leads to a physical impedance of natural aqueous outflow, causing acute ACG.[24] This is a medical emergency, and if not immediately detected and treated, can cause permanent loss of vision.[4,6] It requires immediate medical therapy followed by surgery (Trabeculectomy with antimetabolites and valve implantation).[4,14] Panretinal photocoagulation is the treatment of choice for prevention of NVG in PDR,[25] and can cause regression of neovascularisation if done early in the progression of disease.[14]

CATARACT: Cataract is the loss of the normal transparency of the crystalline lens due to an opacity and is one of the leading causes of blindness globally.[26,27] Diabetes is a major risk factor for development of cataract.[27,28] Additionally, the incidence of cataract is 20 years earlier in those with diabetes compared to those without.[6] The incidence of cataract was estimated to be 3.31 per 1000 person-years of type 2 diabetes subjects during a follow-up of 3.6 years,[29] and 20% of all cataract procedures are performed for these subjects.[30] A recent meta-analysis involving 20837 subjects suggests that type 2 diabetes is a risk factor for cataract, especially cortical cataract (CC) or posterior subcapsular (PSC).[31] Furthermore, mixed cataract is more common than mono type cataract (42% vs. 19%, respectively).[32] A combination of CC, PSC and nuclear cataract (NC) was the most common form of mixed type.[32] Among the monotype cataracts, CC was the commonest, followed by NC and PSC. The incidence of cataract in subjects with type 1 diabetes varies from 1-27%.[33]

Three molecular mechanisms may be involved in the development of diabetic cataract: (i) non enzymatic glycation of eye lens proteins, (ii) oxidative stress, and (iii) activated polyol pathway in glucose disposition.[34] Furthermore, three single-nucleotide polymorphisms (SNPs) in chromosome 3p14.1-3p14.2 relating to functions of voltage-dependent anion-selective channel protein, long myosin light chain kinase, adenylyl cyclase-associated protein, and retinoic acid receptor differed significantly in type 2 diabetes subjects with cataracts and those without cataracts.[35]

Adequate glycemic control is the main goal of prevention of cataract. Currently, surgery is the mainstay therapy for the diabetic cataract. Phacoemulsification is associated with improved visual results, decreased intraocular inflammation and lesser capsular opacification compared to extracapsular surgery. Femtosecond assisted cataract surgery is another promising option. Post-surgery, topical anti-inflammatory drugs such as steroids and non-steroidal anti-inflammatory drops have to be used to control inflammation and macular edema. There is a risk of exacerbation of DR and macular edema after cataract surgery, and therefore, these patients should be closely followed up.[4]

DRY EYE DISEASE: The last ocular manifestation of diabetes that we discuss in this paper is Dry Eye Disease (DED). This is one of the most common presentations to the ophthalmologist.[5] It is a complex disease of tear film and anterior surface of the cornea.[4] The symptoms of DED include red eyes, burning, foreign body sensation, irritation, gritty sensation, blurred vision,

excessive tearing and photophobia.[4,5] Although dry eye symptoms can present as a natural course of aging, diabetes is a significant risk factor for this condition.[36,37] Furthermore, there is a 37% decrease in tear production as measured by the Schirmer test in patients with type 1 diabetes compared to those without diabetes.[37] In the Schirmer test, normally, the filter paper gets wet 10 mm for 5 min. A result yielding less than 5 mm shows aqueous tear deficiency. Studies have shown that at least 50% of subjects with diabetes have either symptomatic or asymptomatic DED.[4]

Both DED and diabetes increase the risk of corneal infections and scarring, and in advanced stages, because corneal perforation and irreversible tissue damages.[38] Subjects with DED also suffer from serious corneal complications such as, superficial punctuate keratitis, neurotrophic keratopathy, and persistent epithelial defect.[39]

Dry eye disease occurs in diabetes because of prolonged hyperglycemia resulting in corneal neuropathy. The downstream effects of corneal neuropathy lead to destabilization of the tear film and cause ocular metaplasia. Corneal sensitivity, which is a manifestation of corneal neuropathy, and tear function are significantly decreased in subjects with diabetes compared to those without. Conjunctival goblet cells produce mucin, which helps to stabilize the tear film and minimize evaporation of the tears. There is a decrease in these cells in people with diabetes, resulting in tear film instability and rapid tear break up time (TBUT). Goblet cell loss is also a good indicator of squamous cell metaplasia, which is associated with keratinization of the conjunctival epithelial cells leading to symptoms of DED.[4,5]

The complications of DED like loss of vision, scarring, perforation, and corneal infection can be prevented if the condition is treated early. Topical tear supplements and anti-inflammatory agents are the main therapeutic options.[4] Tear supplements or "artificial tears" contain surfactants, various viscosity agents, and electrolytes.[40] they produce temporary relief of symptoms. However, these agents do not have any direct anti-inflammatory effects.[41,42] Therefore, currently anti-inflammatory agents are widely used for the treatment of DED. The most common drugs are topical corticosteroids, NSAIDs, and cyclosporine A.[41,43] Corticosteroids, although beneficial initially, on long-term use, can produce severe adverse effects like increasing the liekelihood of infections, and glaucoma. Therefore, NSAIDs are preferred over corticosteroids. Topical cyclosporine A has been used to increase tear production and the number of goblet cells.[44]

SUMMARY AND CONCLUSION: Diabetes is major public health problem, and currently India is considered the global capital of diabetes. Uncontrolled diabetes is associated with several complications. Ocular complications are a significant concern currently, with diabetes causing varied detrimental effects on the eye. Diabetic retinopathy is one of the leading causes of blindness. The other chief concerns are glaucoma, cataract, and dry eye disease. Therefore, there is a need for early diagnosis of diabetes, strict glycemic control and regular follow-up to detect complications and adequately manage them, to improve the prognosis and treatment outcomes.

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