EYE AND DIABETES

Awareness on ocular complications of Diabetes

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PINK PETALS PUBLICATIONS

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Dedicated to my

DAUGHTER

EMAAN MARYAM

Motivating Source of light

Preface

Diabetes mellitus is a major disabling disease with numerous ocular complications which are rapidly becoming a significant cause of ocular morbidity affecting the day to day life of an individual. Diabetes related ocular complications have become a general public health problem, so my purpose in this book has been to put emphasis on the frequencies, pathogenesis and management of these ocular complications. In the preparation of this book, Eye and diabetes I have precisely demarcated all the important points and tried to keep errors to the minimum.

I pay my salutations to Allah for always being generous and leading me.

I express my sincere gratitude to my mentor Prof (Dr) Imtiyaz Ahmed lone for being a guiding force and giving constructive suggestions for the completion of this book. Furthermore, I am highly grateful to my respected teachers Prof (Dr) Sheikh Sajjad, Dr Wasim Rashid, Dr Nusrat Shaheen for supervision, critical guidance and constant encouragement.I would also like to thank my family; my husband, my parents and my daughter for their continuous prayers, love, concern and support.

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Chapter 1
INTRODUCTION

Diabetes mellitus is a major disabling disease that gives rise to various systemic complications. The number of persons affected by diabetes has been increasing worldwide, and approximately 300 million people are expected to be affected by the year 2025. Although type II diabetes has a strong familial tendency, it has almost reached epidemic proportions in developing countries; this is probably a reflection of changes in socioeconomic status, lifestyle and diet. Type I diabetes, thought to be primarily autoimmune in nature, is also increasing in prevalence for unknown reasons. Diabetic patients are required (due to the disposition of their condition) to have sufficient knowledge regarding their illness so as to exhibit a positive attitude to health care. Though there is increased tendency of blindness in diabetic patients, studies have shown that most diabetic patients do not seek the recommended ocular examinations (such as regular dilated fundus examination) aimed at preventing visual impairment and blindness. It is therefore very essential that patients' knowledge on the ocular manifestations of diabetes be ascertained, to determine if this is the barrier to seeking recommended eye examination among the diabetic population in our country. Diabetic patients suffer many systemic complications including ocular disorders due to which people living with diabetes are about 25 times more likely of becoming blind compared to the normal population. The incidence of vision loss or blindness due to ocular complications of diabetes raises sufficient public health concern, with diabetic retinopathy alone responsible for 12,000 to 24,000 new cases of blindness yearly in the United States.

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia and disturbances in carbohydrate, protein and fat metabolism associated with absolute or relative deficiencies in insulin secretion or it's action. The metabolic dysregulation associated with diabetes mellitus causes secondary

pathophysiological changes in multiple organ systems that cause a tremendous burden on the individual diabetes.

Diabetes' detrimental effects on multiple organ systems like eye, renal system, heart and nervous system results in diabetic retinopathy, nephropathy and neuropathy by microangiopathy. Its a microangiopathy affecting precapillary arterioles, capillaries and venules and presents itself either as non-proliferative diabetic retinopathy, maculopathy or proliferative diabetic retinopathy. The fact that the onset of moderate and severe visual lossresulting from diabetic retinopathy can be delayed and often kept controlled by good glycemic control, timely intervention in arresting the advancement of retinopathy, early treatment and regular follow-up has been extensively studied and documented. Effective control of risk factors including hyperglycemia, elevated blood pressure and hyperlipidemia delays progression of microangiopathy.

The ocular complications of diabetes mellitus are also numerous and include retinopathy, cataract, ocular surface disorders, uveitis, glaucoma and neuro-ophthalmic disorders. A review of the current literature shows that the emphasis has changed from the laser and surgical management of pre-existent retinopathy to the development of cohesive multidisciplinary screening and education programs and to a better understanding of the biochemical mechanisms at cellular level that underlie the disease. The role of associated and likely modifiable systemic factors is also now recognized. Early intervention with systemic and local therapies may soon provide hope for the better management of diabetic eye disease.

Some of the main ocular complications of diabetes are described in the upcoming chapters.

1. Retinopathy in diabetes
2. Ocular surface disorders in diabetes
3. Cataract in diabetes
4. Uveitis in diabetes
5. Nerve palsies in diabetes
6. Glaucoma in diabetes

CHAPTER 2
RETINOPATHY IN DIABETES

Diabetic retinopathy is the major blinding ocular complication of diabetes, the overall prevalence of diabetic retinopathy varies in different populations, the highest prevalence being 54%. Diabetic retinopathy includes non-proliferative and proliferative retinopathy and the late sequelae of vitreous haemorrhage and tractional detachment. In developed countries, rates of blindness due to retinopathy range from 7.9% in diabetic patients younger than 65 years of age to 14.4% in those 65 to 74 years of age. The need for early identification and intervention is highlighted by the success of such programs as the Early Treatment Diabetic Retinopathy Study trials and the Diabetes Control and Complications Trial, which has asserted the need for tight glucose control.

Risk factors that modify the rate of onset and progression of retinopathy or the development of visual loss due to retinopathy have been studied, among these are duration of diabetes and blood glucose control. Increased duration of diabetes, increased fasting glucose levels, elevated systolic blood pressure, urinary albumin excretion, and decreased body mass index are independently associated with an increased risk for retinopathy.

Diabetic retinopathy is often accompanied by microvascular and macrovascular changes in other systems. Increased glucose levels are correlated with nephropathy, neuropathy, and cardiovascular complications.

We cannot overemphasize the need for early detection, good metabolic control, and early intervention in diabetes. Numerous studies have shown improved visual outcome and prevention of blindness with appropriate and timely intervention. To adequately inform the patients of the need for tight diabetic control is incumbent on physicians and other health care practitioners. Despite this, studies have shown that patient

information is poorly disseminated and that most patients are unaware of the importance of good metabolic control.

HISTORY:

- 1856 –V on Jager -first described diabetic retinopathy
- 1890 –Hirschberg -first classified & elaborated retinopathy
- 1943 - Ballantyne - Lowenstein -clinical and histological confirmation of diabetic retinopathy
- 1949-Gerd Meyer - Schwickerath -first recognised therapeutic effect of light on retina 1950- Jonas Friedenwald -histopathological characterisation of DRJ1
- 1953 –Aarseth - hereditary factors in diabetic retinopathy 1962 - Patz, Moumenee -micro aneurysms in a diabetic dog
- 1965- Engerman, - BloodworthMolitor -retinal changes in dogs rendered diabetic 1966-Gay, Rosenbaum -asymmetrical retinopathy in carotid insufficiency
- 1976-DiabeticRetinopathy - Study -preliminary report on effects of photocoagulation therapy
- 1984-Wisconsin - Epidemiologic Study-prevalence of diabetic retinopathy on Diabetic Retinopathy
- 1985-Early Treatment - Diabetic Retinopathy Study -effect of photocoagulation on diabetic macular edema
- 1985-DiabeticRetinopathy - Vitrectomy Study -effect of early vitrectomy for severe vitreous haemorrhage
- 1988-United Kingdom - Prospective Diabetic Retinopathy Study -effect of blood pressure and blood glucose on diabetic retinopathy
- 1993-Diabetes Control & - Complications Trial -effect of intensive control of blood glucose on retinopathy
- 1998-Klein -risk factors and progression of DR
- 2002-Marbidis, Duker -intravitreal triamcinolone for refractory diabetic macular edema.

RISK FACTORS

1. Level of glycaemic control
2. Serum lipids
3. Blood pressure
4. Duration of diabetes
5. Pregnancy
6. Renal disease and Coronary Artery disease

1. Level of glycemia

Hyperglycemia is a strong factor in the development and progression of diabetic retinopathy. Benefits of better control continue to manifest even after nonproliferative and proliferative diabetic retinopathy has developed. Elevated glycosylated hemoglobin (HbA1c) is a strong factor for the progression to high risk PDR. There is a 35% decrease in the risk of retinopathy progression for every 10% reduction in the presenting HbA1c level. The higher the level of HbA1c, the higher the risk of developing complications related to diabetes.

2. Serum lipids

Elevated levels of serum cholesterol are associated with increased severity of hard exudates. Elevated serum triglyceride levels are associated with an increased risk of developing high risk PDR and decreased visual acuity.

3. Blood Pressure

Intensive control of blood pressure slows down the progression of retinopathy and reduces the risk of other microvascular and macrovascular complications of diabetes mellitus. Abnormal systolic and diastolic blood pressures are associated with the severity of retinopathy in both type I and type II disease. In type I, both are important and in type II, only systolic BP is related to the progression of the retinopathy.

4. Duration of diabetes

Duration of diabetes is an important risk factor for the development of diabetic retinopathy After 20 years of diabetes, all the type I and > 60% of type II patients have some degree of retinopathy.

When age at diagnosis is <30 years

- <5 years of diabetes - retinopathy uncommon
- <10 years of diabetes: 1.2% have PDR
- >15 years of diabetes: 95% have some degree of retinopathy.
- >35 years of diabetes -67.2% have PDR

When age at diagnosis is >30 years

- <5 years of diabetes: 40% taking insulin have retinopathy
- >15 years of diabetes: 25% taking OHA have retinopathy 2% have PDR
- >25 years of diabetes: 53% taking OHA have retinopathy 25% have PDR

5. Pregnancy

Retinopathy progresses during pregnancy because of pregnancy itself or the changes in the metabolic control.

6. Renal disease and Coronary artery disease

Both are associated with increased incidence of proliferative retinopathy.

Sex Incidence

Male sex is associated with more severe retinopathy. The male : female ratio is 3:2.

Genetic Factors

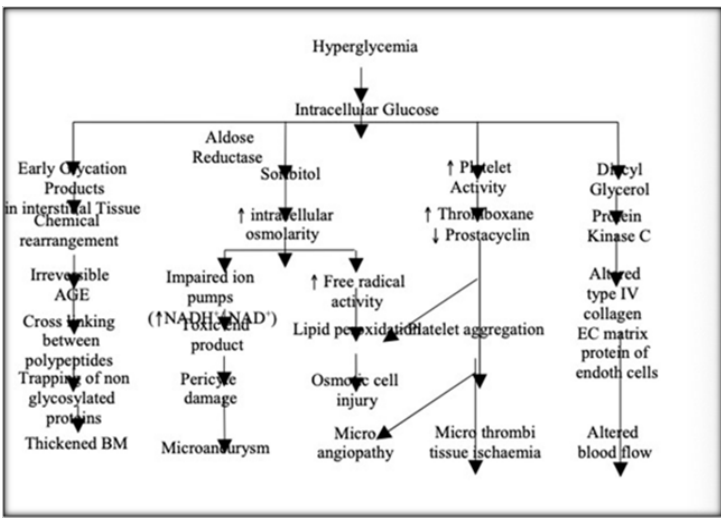
Relationship between HLA antigens expressed on the cell surface and the presence of retinopathy has already been documented. HLA – DR phenotypes 4/0, 3/0, and XX expressionis associated with increased proliferative retinopathy. Other HLA phenotypes conferring such increased risk include HLA B8, HLA B15 and HLA DR4.

Ocular Factors

Myopia reduces the prevalence and severity of diabetic retinopathy. Retinochoroidal scarring from trauma or inflammatory disease, reduces the prevalence of retinopathy by decreasing the retinal metabolism and thereby decreasing the need for oxygen and the release of vasoproliferative factors.

Pathogenesis

There is a complicate interplay of various factors in the pathogenesis of diabetic retinopathy.



I. BIOCHEMICAL MECHANISMS

1. Prolonged hyperglycemia

It is the major risk factor in the micro vascular complications of diabetes mellitus. Three mechanisms seem valid for diabetic retinopathy

i. Alteration in the expression of one or more genes resulting in increased amounts of altered gene products causing altered cell function.

ii. Non enzymatic glycation of proteins leading to cross linking and altered protein function. These products have very long cellular lifetime.

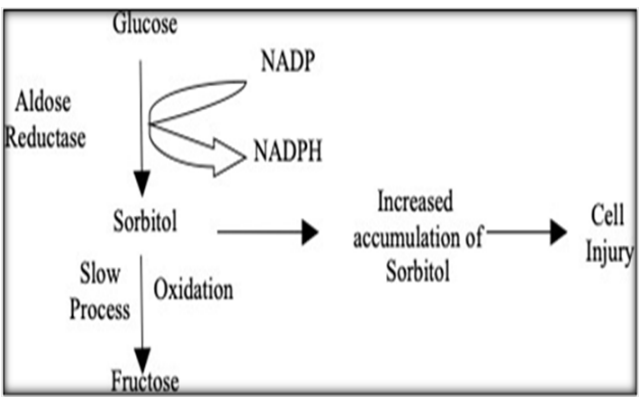
iii. Chronic hyperglycemia causes accelerated oxidative stress in cells resulting in toxic end products. Also increased activity of polyol pathway increases the

NADH/NAD+ ratio resulting in increased toxic end product, by a mechanism called hyperglycemic pseudo hypoxia.

2. Sorbitol Pathway

Aldose sugars are converted to their respective alcohol by the enzyme aldose reductase and again to their key to sugars by dehydrogenase.

Glucose is a relatively poor substrate for aldose reductase with high Km (binding constant). Under normal conditions, glucose is acted on by hexokinase to proceed on the glycolytic cycle.



In uncontrolled hyperglycemia, the hexokinase pathway gets saturated and glucose is acted upon by aldose reductase using NADP as cofactor, resulting in formation of excess sorbitol.

Further oxidation of sorbitol to fructose is a slow process resulting in building up of intracellular sorbitol leading on to cell damage and microvascular complications.

3. Diacyl glycerol and protein kinase C

Hyperglycemia causes an increase in diacyl glycerol which in turn activates protein kinase C which causes alteration in expression of type IV collagen and extra cellular matrix proteins of endothelial cells.

II. Rheological Mechanisms

- Abnormality of Platelets

Increased platelet adhesion, increased aggregation, increased factor VIII – Von Willebrand factor and decreased lifespan of platelets also play a role in retinopathy development.

- Abnormalities of Red Blood Corpuscles (RBC)

In diabetic individuals, there is increased rouleaux formation and reduced deformability of RBC. This is presumed to be due to altered α2 macroglobulin, haptoglobulin and increased fibrinogen.

4. Vascular endothelial growth factor (VEGF)

VEGF is associated with proliferative retinopathy and maculopathy. Hypoxia stimulates the release of VEGF from the retinal and optic nerve glial cells of diabetics.

Pathology

1. Capillary basement membrane thickening

Quantitative electron microscopic immunocytochemical studies show increased thickening of capillary basement membrane

with an increase in type IV collagen. Studies show along with thickened basement membrane, there is Swiss Cheese vacuolisation and fibrillar collagendeposition. Certain functions served by basement membrane are deranged in diabetes. They are:

- Structural rigidity to the blood vessels
- Filtration barrier for various molecules
- Barrier for vasoproliferation.

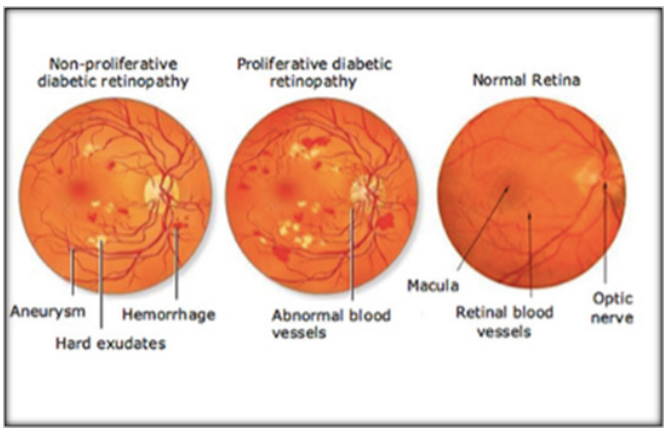


Image: showing different stages of retinopathy.

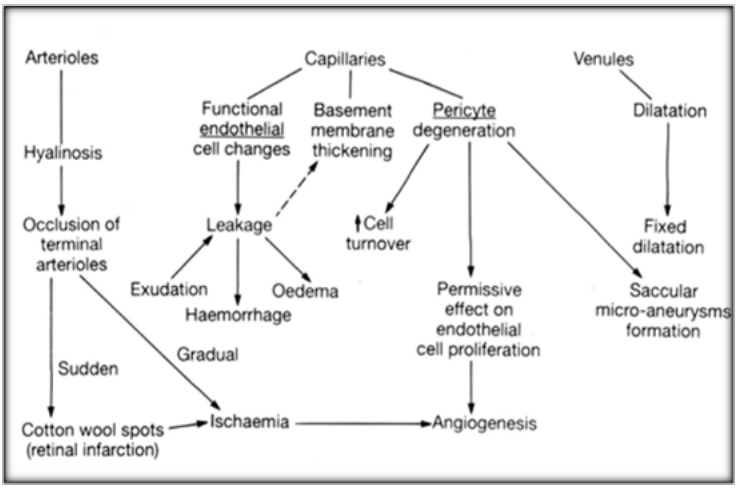
2. Loss of microvascular intramural pericytes

The capillary wall has pericytes surrounding the endothelial cells. Of these, pericytes have aldose reductase rather than endothelial cells. Hence more sorbitol gests accumulated in pericytes causing damage to them. The drop out of pericytes is recognized as empty, balloon– like space bulging from the capillary wall. Normal pericyte to endothelial cell ratio is 1:1. In diabetic retinopathy this ratio gets altered.

3. Microaneurysms

On trypsin digested retinal mounts, microaneurysms appear as hypercellular saccular outpouchings of capillary wall.

Microaneurysms may hyalinize and get occluded with PAS-positive material.



4. Capillary acellularity

Complete loss of all cellular elements from retinal microvessels.

5. Breakdown of blood-retinal barrier

Breakdown of blood-retinal barrier occurs due to:

- Opening of tight junctions (Zonulae occludentes) between adjacent microvascular endothelial processes.
- Fenestration of endothelial cell cytoplasm. Increase in transport by endocytic vesicles.

6. Exudates

Hard exudates: 14 Hard, yellow, waxy lesions

7. Neovascularisation

The growth of new vessels in retina either on disc or elsewhere.
Stage 1 : The stage of naked vessels.

Fine, new vessels without supporting connective tissue arising

from capillaries, grows in the plane of retina or invades vitreous.

Stage 2: The stage of condensation of connective tissue There is laying of connective tissue around the naked vessels which starts condensing.

Stage 3: The stage of cicatrisation

Gradual reduction in number and size of new vessels is associated with an increase in the connective tissue density. This on contraction forms sheets and bands on the retina.

Classification

Diabetic retinopathy is classified by Hirschberg as early as 1890. Later it was further classified by Ballantyne and Michaelson (1947 – 1962), Scott (1951), Alaerts and Slosse (1957) and Lee (1966). Duke Elder classified diabetic retinopathy as

1. Pre-retinopathy Stage

Decreased activity in ERG and EOG

2. Simple Diabetic Retinopathy

Appearance of microaneurysms, superficial and deep retinal haemorrhages, hard and soft exudates and vascular anomalies.

3. Proliferative Stage:Neovascularisation over the disc or elsewhere, vitreous haemorrhage and complications like retinal detachment can occur in this stage.

Early treatment diabetic retinopathy study (ETDRS) classifies nonproliferative diabetic retinopathy (NPDR) as follows

- Mild: at least one microaneurysm, microaneurysms or haemorrhages< standard photograph 2A
- Moderate:microaneurysms&haemorrhages> standard photograph 2A, soft exudates, venous beading and intraretinal microvascular anomalies (IRMA)
- Severe: any one of the following (4:2:1 rule) microaneurysms / haemorrhages in 4 quadrants or venous beading in >2 quadrants or IRMA in one quadrant.

- Very severe: any two or more of the above mentioned.

ETDRS classifies clinically significant macular edema as

1. Thickening of retina at / within 500 micron from center of the macula or
2. Hard exudates at / within 500 micron from center of the macula with adjacent retinal thickening or
3. zone of retinal thickening of one disc area or larger, a part of it is within, one disc diameter of the center of macula

Diabetic Retinopathy Study classifies proliferative diabetic retinopathy (PDR) as

- Early: New vessels on the disc / elsewhere
- High risk: New vessels over disc >1/3–1/4 disc area or New vessels over disc and preretinal or vitreous haemorrhage or New vessels elsewhere >1/2 disc area and preretinal or vitreous haemorrhage.

Studies on Diabetic Retinopathy

Early treatment diabetic retinopathy study (ETDRS)

This is a randomised clinical trial to ascertain the effect of laser in diabetic retinopathy. Results:

- Aspirin did not alter the progression of diabetic retinopathy or increase vitreous haemorrhage.
- Early PRP is not indicated in eyes with mild - moderate retinopathy.
- Early PRP resulted in reduction in the risk of severe visual loss.
- Focal photocoagulation for diabetic macular edema reduced the risk of moderate visual loss and increased moderate visual gain.

Diabetic Retinopathy Study (DRS)

This clinical trial evaluated the effect of PRP in diabetic retinopathy. Results :

- Xenon arc photocoagulation caused a > 50% reduction in the rates of severe visual loss (SVL).
- Treated eyes with high risk PDR achieved the greatest benefit.

United Kingdom Prospected Diabetic retinopathy Study (UKPDS)

This is a randomised control trial which was conducted to evaluate the effectiveness of intense control of blood pressure and blood glucose in type II diabetic patients.

Results: Intense control of blood pressure and blood glucose slowed the progression of retinopathy and reduced the risk of microvascular complications.

Diabetes Control and Complications Trial (DCCT)

This study was conducted with the aim to evaluate the effectiveness of intense control of blood glucose in type I diabetes.

Results:

- Intensive control of blood glucose reduced the risk of developing retinopathy by 76% and slowed the progression by 54%.
- It reduced the risk of neuropathy by 60% and nephropathy by 54%.

Diabetic Retinopathy Vitrectomy Study (DRVS)

This randomised prospective clinical trial investigated the role of vitrectomy in diabetic retinopathy.

Results: Early vitrectomy in type I diabetics had clear benefit

over deferral group, especially severe PDR benefited more.

Wisconsin Epidemiologic Study on Diabetic Retinopathy (WESDR)

This study depicted the prevalence and risk factors associated with diabetic retinopathy.

Clinical Features

I. Non proliferative diabetic retinopathy

The pathological processes in NPDR include retinal capillary micro aneurysm, increased vascular permeability and eventual capillary closure.

1. Microaneurysm

Meckanzie and Nettleship were the first to note microaneurysms. They appear as deep red dots varying from 15micron to 60 micron in diameter. It is most common in posterior pole and appears & disappears with time. Weakness of capillary wall, loss of pericytes, release of vasoproliferative factor, abnormalities of adjacent retina and increased intra luminal pressure play a role in its development.

2. Hard exudates

With progressing retinopathy, vascular permeability of retinal capillaries increases resulting in leakage of serum and lipids resulting in hard exudates and macular edema. Hard exudates are yellow - white intra retinal lipid deposits located at the border of edematous and nonedematous retina. They present as clusters, plaque and circinate / ring patterns.

3. Intra retinal haemorrhages

Superficial haemorrhages: Flame shaped due to the accumulation of blood in the superficial retinal layers parallel to the coursing nerve fibres.

Deep haemorrhages: Dot and blot in the inner nuclear and outer plexiform layers and its breaks through the confines of Muller cell processes.

4. Capillary closure

Capillary closure results in patchy areas of nonperfused retina with clusters of microaneurysms, cotton wool spots, IRMA, haemorrhages and venous beading.

Cotton wool spots: White patches with fraying borders merging into the retina, present in areas of microvascular occlusion and nonperfusion.

IRMA: Intra retinal vascular shunts and they do not leak on fluorescein angiography.

II. MACULOPATHY

It is one of the major causes of visual loss in diabetic retinopathy. It is more commonly associated with NIDDM and older patients. Maculopathy presents either as macular edema ormacular ischaemia. Macular edema can present as focal or diffuse edema which may be clinically significant.

Focal macular edema:

- **areas of leakage from micro aneurysm and IRMA.**
- **associated with rings of hard exudates and microaneurysms**

Diffuse macular edema:

- **has diffuse retinal thickening**
- **wide spread retinal capillary abnormality with diffuse leakage due to extensive breakdown of blood retinal barrier.**
- **associated often with cystoid macular edema.**

Macular Ischaemia: capillary nonperfusion

- microaneurysm clusters at the margins of nonperfusion

- more visual loss with clinically normal appearing macula
- enlargement of foveal avascular zone
- if >1000 micron in diameter, severe visual loss ensues.

Clinically significant macular edema (CSME):

The CSME was defined by ETDRS which helps in its management. 10% of diabetics have macular edema and in 40% of these, the center of the macular is involved and have significant visual loss.

III. Proliferative Diabetic Retinopathy (PDR)

The appearance of new vessels over disc or elsewhere in the retina is considered as PDR. The most plausible explanation for endothelial proliferation is ischaemia of inner retinal layers secondary to closure of parts of retinal capillary bed. Based on the location the new vessels can be grouped as

- New vessels involving the retina but sparing the disc
- New vessels involving the disc
- New vessels in the anterior chamber angle

STAGES OF PDR

Stage of proliferation

- Fine new vessels at the disc margin of size one eighth to one fourth that of major retinal vein.
- New vessels more frequently occur along supero-temporal vein and grow along retinal plane or invade vitreous either radially or irregularly.
- Deposition of fibrous tissue around blood vessels.

Stage of regression

Decrease in the calibre and the number of vessels occurs and it is followed by replacement of them with fibrous tissue.

SEQUELAE

1. Contraction of vitreous

- Thickened posterior vitreous adjacent to the site of new vessels with fibrous tissue along its posterior surface.
- Vitreous contraction with the vector pulling the posterior vitreous forward.
- Eventual posterior vitreous detachment commonly occurs along superotemporal vessels, temporal to macula and above/ below the disc. The traction on new vessels can lead to vitreous haemorrhage.

2. Tractional retinal detachment

The occurrence and severity of retinal detachment is influenced by the timing and degree of vitreous shrinkage and vitreoretinal adhesions. With contraction of fibrovascular proliferation, distortion and displacement of macula occurs. Macula is usually dragged nasally and vertically.

3. Involutional diabetic retinopathy

With complete vitreous contraction and detachment, marked reduction in the calibre of retinal vessels is characteristic. There is severe retinal ischaemia, resulting in marked visual **loss.**

Clinical Evaluation

Visual Acuity

The evaluation of retinopathy patients starts with assessing visual acuity. Refraction is to be done in all cases of diabetic retinopathy and best corrected visual acuity must be documented.

Colour vision

In diabetes, the sensitivity of blue cones is depressed and the common defect observed is in the blue-yellow range. It is best detected by fransworthmunsell hundred hue test.

Fields

Examination of fields by perimetry shows areas of scotoma which represent the corresponding abnormal areas of retina.

Intraocular pressure

IOP is measured in diabetics to rule out secondary glaucoma.

Ophthalmoscopy

By direct ophthalmoscopy, detailed fundus examination is carried out. Even though the area visualized is smaller, it provides a good magnification for the details to be seen clearly. Indirect Ophthalmoscopy is carried out to visualize the entire retina including peripheral retina.

Slit Lamp Examination

Using slit lamp biomicroscope, the retinal examination and angle study are done with Goldmann 3 mirror lens, +78D and 90D lens.

Macular Function Tests

The assessment of macula is recommended in all cases of maculopathy. The following tests can be performed:

1. 2 point discrimination
2. Photo stress Test
3. Amsler grid test
4. Blue field entoptoscope

Flourescein angiography indications in diabetic retinopathy:

- to define the focal and diffuse leaks in diabetic maculopathy
- to delineate the extent of ischaemic zone in maculopathy
- to locate areas of capillary nonperfusion and leakage from new vessels in proliferative stage

- to identify the persistence, progression or resolution of macular edema following laser photocoagulation.
- to detect small microaneurysms <20 microns

The property of fluorescein to absorb higher energy, shorter wavelength blue light and to emit lesser energy, longer wavelength, green light, with this change occurring over a brief period of time (<10-8) is called fluorescence. This property is used in fluorescein angiography

Features

Microaneurysms: well-definedhyperfluorescence against dark choroidal background Retinal haemorrhages: well defined areas of hypoflourscence.

- Superficial: blocked retinal & choroidal fluorescence.
- Deep: blocked choroidal fluorescence alone Hard exudates: areas of blocked fluorescence Cotton wool spots: areas of blocked fluorescence.

Capillary nonperfusion: well defined areas of hypoflourescence between retinal vessels. Non visibility of capillaries

NVD/NVE: increasing intense hyperfluorescence due to leakage.

Focal macular edema: focal leaks from microaneurysms with blocked fluorescence from hard exudates and haemorrhages.

Diffuse macular edema: dilatation of capillaries and diffuse leaks in early venous phase. Floral pattern in cystoid macular odema.

Ischaemic maculopathy: enlarged and irregular foveal avascular zone , capillary dropouts in perifoveal area.

Management

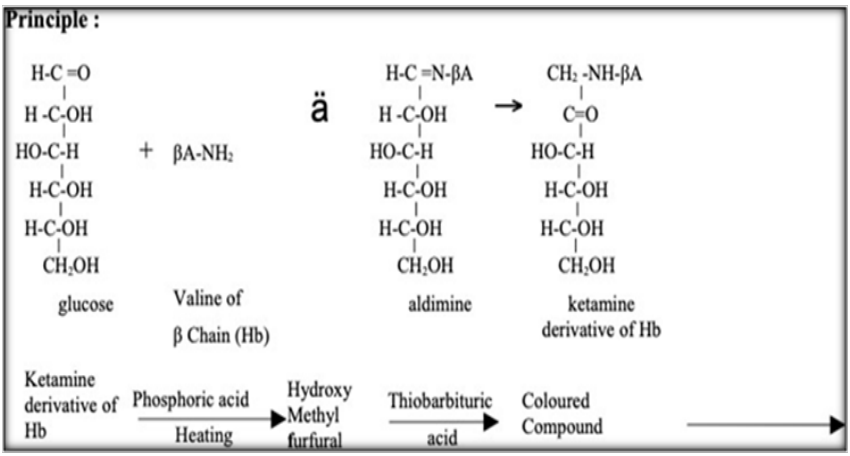
Evaluation biochemical parameters

1. Estimation of Fasting Blood Glucose

This is done by orthotoludine method.

2. Glycosylated heamoglobin (HbA1c)

Estimation of HbA1c is done using high pressure liquid chromatography.



This coloured compound is then measured.

3. Total Cholesterol (Modified Salkowski's Method– Wybenga Method)

The principle of this reaction is that cholesterol reacts with ferric chloride ions in acetic acid followed by sulphuric acid. This method is modified by Wybenga and this is used to estimate total cholesterol.

4. HDL Cholesterol (Loper and Virella)

In this procedure, the VLDL, chylomicrons and LDL are separated by phosphotungstate in the presence of Mg+ ions and HDL cholesterol is estimated from the supernatant.

5. Triglycerides (Foster and Dunn) Hantzsch Reaction

Triglycerides are extracted by heptane isopropanol from phospholipids and are saponified by potassium hydroxide.

The liberated glycerol is oxidised to formaldehyde which then combines with acetyl acetone and ammonia to give a dihydrobutidine derivative. It is then measured.

Treatment

The treatment depends on the type and severity of retinopathy.

Non-proliferative retinopathy

For mild and moderate NPDR, strict adherence to normal levels of glycemia, blood pressure and lipid status is the mainstay of the treatment. Scatter laser photocoagulation is generally not recommended.

The Early Treatment Diabetic Retinopathy Study and the Diabetic Retinopathy Study recommend photocoagulation as the treatment of choice for severe and progressive form of retinopathy and clinically significant macular edema.

Severe NPDR

For severe NPDR, scatter laser treatment is appropriate when disease process is progressing rapidly.

Close follow-up unlikely.

Macular edema

ETDRS demonstrated that retinal laser therapy applied to macula reduces the risk of substantial worsening of vision by 50%.

a) Focal macular edema:

Direct laser using green or yellow wavelength applied over microaneurysms that are between 500-3000µm from the center of the macula. Parameters for focal treatment are:

Spot size: 50-100µm

Duration: ≤0.1s

Power: sufficient to cause blanching of microaneurysm / RPE

b) Diffuse macular edema:

A light intensity grid pattern using green or yellow wavelength to all areas of diffuse leakage

>500µm from the centre of macula and 500µm from the temporal margin of the optic disc. Parameters for grid pattern.

Spot size: 50-100µm Duration: ≤0.1s

Power: sufficient to cause blanching of RPE

Spots are placed at least one burn width apart. CSME is more benefited from laser.

c) Ischaemic maculopathy:

As the macula has capillary non perfusion, focal or grid laser is not recommended.

Image: showing Grid laser done on a patient.

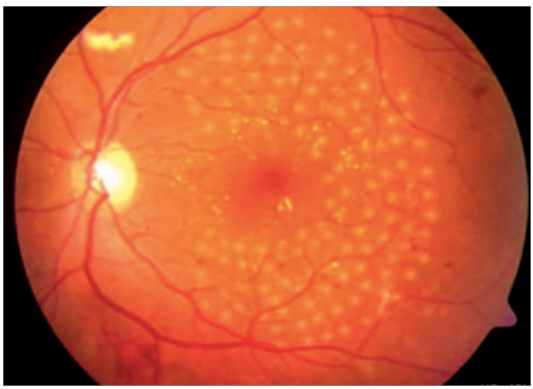
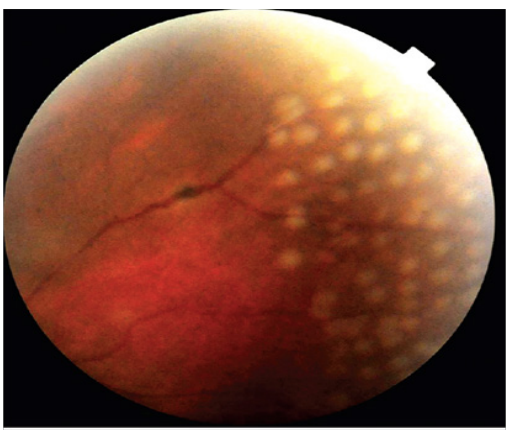


Image: showing Sectoral laser done on a patient



Proliferative Diabetic Retinopathy

Medical management:

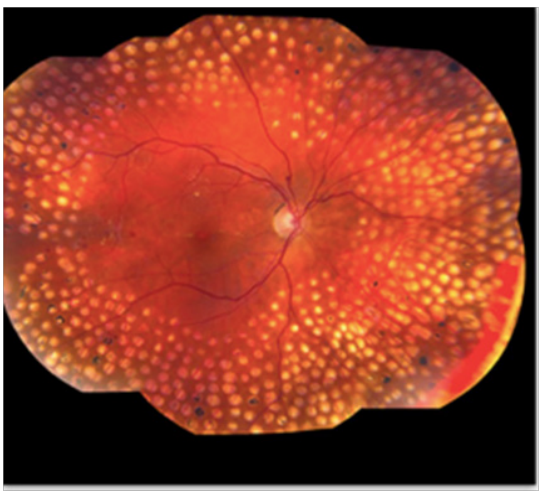
The principal goal is controlling both systemic and local factors that influence the progression from NPDR to PDR. This includes good glycemic control, control of hypertension, renal disease and coronary artery disease.

DCCT and UKPDS have documented that intensive glycemic control is associated with a reduced risk of newly diagnosed retinopathy and a reduced progression of existing retinopathy.

Panretinal photocoagulation (PRP):

PRP is done to cause regression of existing new vessels to prevent progressive neovascularisation.

Image: Showing pan retinal photocoagulation done in a patient having diabetic retinopathy



ETDRS and DRS study model, the parameters are Number of burns: ≥1200

Spot size: 500µm

Duration: 0.1.

Spots are placed at least 1⁄2 burn width apart and the number of sessions are more than two. The rate of severe visual loss is reduced from 16% in untreated eyes over two years to 6% in treated eyes, documenting a reduction of 57%.

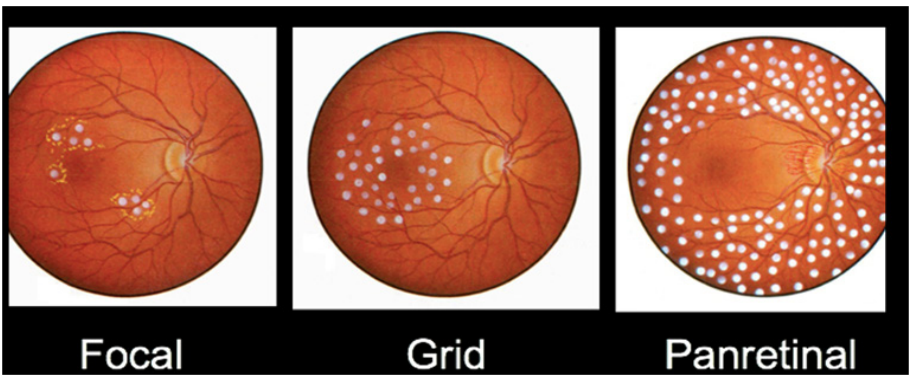
Surgical management

The mainstay of contemporary management for vitreous haemorrhage and tractional retinal detachment is surgery.

Indications for pars plana vitrectomy:

- Dense non clearing vitreous haemorrhage
- Tractional retinal detachment threatening macula
- Combined tractional and reghmatogenous detachment
- Diffuse macular edema with post hyaloid traction
- Recurrent vitreous haemorrhage

Image: Showing different lasers done for diabetic retinopathy



Recent Advances

In patients with refractory CSME, intravitreal administration of corticosteroids or anti VEGFS has proven to be useful. Currently, several drug delivery modalities are in clinical trials to investigate their efficacy.

ETDRS Recommended Ocular Examination Schedule

Age at Onset	Time Recommended	Routine Minimal
≤ 30 yearly	5 years of diabetes	yearly
> 30 yearly	At the time of diagnosis	yearly
Pregnancy	Before conception/ first trimester	3 monthly

Recommended Follow-up Schedule in Diabetic Retinopathy Patients

Dr Erum KhateebRetinal Abnormality	**Suggested Followup**
Normal or rare micro aneurysms	Annually
Mild NPDR	Every 9 months
Moderate NPDR	Every 6 months
Severe NPDR	Every 4 months
CSME	Every 2-4 months
PDR	Every 2-3 months

Levels of Prveventionof Diabetic Retinopathy

The visual loss due to diabetes can be prevented by doing intervention at various stages of the disease.

Primary prevention

Once the diagnosis of diabetes is made, strict control of glycemic status by diet, exercise and drugs should be done.Periodic ophthalmic examination must be carried out. Referral of the diabetic individuals to ophthalmologists regularly or as soon as signs of micro angiopathy like microalbuminuria sets in should be done.

Secondary prevention

In NPDR patients by the modification of the risk factors blindness can be prevented. Fundus fluorescein angiography is

done to find out the type of maculopathy at initial stages. Laser photocoagulation is done for maculopathy and PDR to prevent visual loss.

Tertiary prevention

When the patient is in advanced proliferative stage, relevant surgical treatment is given. Further visual rehabilitation is given by low vision aids.

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CHAPTER 3:
CATARACT IN DIABETES

DM can affect all ocular structures, with cataract being the most common ocular complication. Cataract is the leading cause of blindness worldwide. There is an increased incidence of cataract formation in the diabetic population due to several mechanisms. Now cataract surgery is a common and safe procedure due to advancement in surgical technology. However, the diabetic population is still at risk of vision-threatening complications, such as diabetic macular edema (ME), postoperative ME, diabetic retinopathy progression, and posterior capsular opacification.

Cataract is one of the major causes of visual impairment in diabetic patients. Patients with DM are reported to be up to five times more likely to develop cataract, in particular at an early age. Due to the increasing prevalence of DM, the incidence of diabetic cataracts has also increased. Cataract extraction is one of the most common surgical procedures among the general population and the number of cataract surgeries each year also continues to increase. Recent technological advancements in cataract surgery have improved surgical outcomes. In diabetic individuals,however, the scale of improvement is still a matter of debate, and many studies have revealed both the results and complications of cataract surgery in diabetic patients.

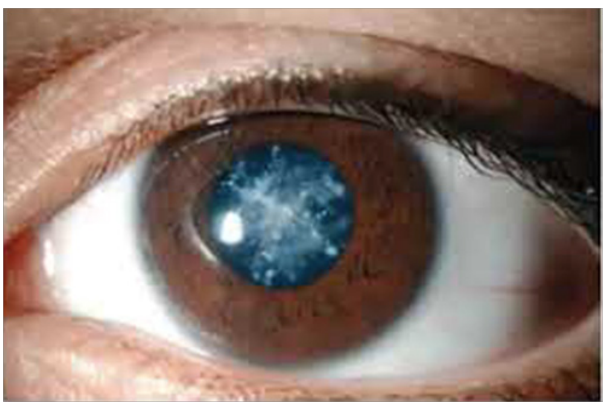

Image: showing SNOWFLAKE diabetic cataract

Biochemical Mechanisms for Cataract in Diabetes

Different types of mechanisms have been proposed for the pathogenesis of cataract in cases of DM.

Polyol pathway:

It has been suggested that the polyol pathway-via which the enzyme aldose reductase (AR) catalyzes the reduction of glucose into sorbitol-is a central part of the mechanism of cataract development. Multiple studies have been conducted to explain the AR pathway's role in this process. The increased intracellular accumulation of sorbitol leads to a hyperosmotic effect, resulting in hydropic lens fibres that degenerate and form cataract. The production of sorbitol in diabetic patients (as compared to nondiabetic patients) takes place more quickly than it can be converted into fructose by the enzyme sorbitol dehydrogenase. Intracellular removal ofsorbitol through diffusion is also prevented because of its polar character. A hyperosmotic effect is created when an accumulation of sorbitol results in an infusion of fluid. Finally, animal studies have shown that the intracellular accumulation of polyols causes liquefaction of lens fibres resulting in the formation of lens opacities.

Osmotic and oxidative stress:

Osmotic stress as a result of extensive swelling of the cortical lens fibres is another compounding mechanism in the rapid development of cataracts, especially in young patients with type 1 DM. Osmotic stress resulting from the accumulation of sorbitol induces stress in the endoplasmic reticulum (ER), the main site of protein synthesis, resulting in the formation of free radicals. Stress in the ER can also be caused by fluctuation of glucose levels that initiate an unfolded protein response producing reactive oxygen species and cause oxidative stress damage to lens fibres. Moreover, increased glucose levels in the aqueous humour may lead to glycation of lens proteins, a process that results in the formation of advanced glycation end products. Fenton reactions

resulting from elevated levels of hydrogen peroxide (H2O2) in the aqueous humour of diabetics also induces the generation of hydroxyl radicals (OH–) after entering the lens. Another factor that is elevated in the lens and aqueous humour of diabetic patients is free radical nitric oxide (NO•), which may cause an increase in peroxynitrite formation, which contributes to cell damage due to oxidizing properties.

However, diabetic lenses have increased susceptibility to oxidative stress due to their impaired antioxidant capacity. Superoxide dismutase (SOD) is the most predominant antioxidant enzyme in the lens that degrades superoxide radicals (O2-) into H2O2 and oxygen. Several in vitro and in vivo animal studies have shown that SOD has protective properties against cataract development in the presence of DM.

Some studies have shown that osmotic stress in the lens resulting from sorbitol accumulation causes apoptosis in lens epithelial cells and leads to cataract formation. Rapid glycemic control can also increase these effects in the lens by creating a hypoxic environment that reduces protective enzymes and increases oxidative radicals. High AR expression could constitute a risk factor that predisposes the lens to distortions in signalling through the extracellular signal-regulated kinase and c-Jun N-terminal kinase pathways-involved in cell growth and apoptosis, respectively-thereby altering the balance required for lenshomoeostasis. These findings show that impairments in osmoregulation may render the lens susceptible to even the smallest increase in AR-mediated osmotic stress, potentially leading to progressive cataract formation.

Autoimmunity:

Another recently proposed mechanism is autoimmune hypothesis in acute bilateral type 1 diabetic cataracts. The authors reported that insulin autoantibodies became positive within three months of beginning insulin treatment, and that this period coincided with cataract formation. Their suggestion that there could be an autoimmune process behind acute bilateral cataract in DM warrants further investigation.

The type of cataract seen in diabetic patients has also been investigated. The most common is the senile type. However, snowflake cataracts, which are characteristic for DM, are very common in type 1 diabetics. Posterior subcapsular cataracts have also been shown to be significantly associated with diabetes. Increased levels of glycated haemoglobin were demonstrably associated with an increased risk of nuclear and cortical cataracts. Further analysis revealed that diabetic patients were prone to developing cortical cataracts and that this process was associated with the duration of diabetes.

Finally, the initiating mechanism in diabetic cataract formation is the generation of polyols from glucose by AR. However, osmotic stress, apoptosis of the lens epithelial cells, and the autoimmune theories may be confounding mechanisms in the development of the cataract formation in DM.

Cataract incidence in diabetic patients:

Several clinical studies have reported that cataract formation occurs more frequently and at an earlier age in diabetic patients than in nondiabetic patients. Some studies also report that cataracts are three to four times more prevalent in patients with diabetes under the age of 65. In patients over 65 having diabetes, cataracts are twice as prevalent. Longer duration of diabetes and poor metabolic control being the main risk factors. Although older patientssuffer from irreversible cataract formation, good metabolic control may reverse cataract in young diabetics.

Several important studies have investigated cataract incidence in diabetic patients. The Wisconsin Epidemiologic Study of Diabetic Retinopathy investigated the incidence of cataract and factors associated with a higher risk of cataract surgery. They found 8.3% of patients suffering from type 1 diabetes and 24.9% of those with type 2 diabetes had a 10-year cumulative incidence of cataract surgery. For type 1 diabetics, they found some risk factors, including age, severity of diabetic retinopathy (DR), and proteinuria; for Type 2 diabetics, risk factors included age and use of insulin.

The Beaver Dam Eye Study also reported an association between DM and cataract formation. The study took place over five years and consisted of 3684 participants aged 43 and older. It showed an increased incidence and progression of cortical and posterior subcapsular cataracts for DM patients. It also found an increased risk of nuclear and cortical cataracts with increased levels of glycated haemoglobin. Further analysis of the study showed that diabetics had a higher rate of cortical lens opacities and previous cataract surgery than nondiabetics. A longer duration of diabetes was also associated with increased frequency of both cortical cataracts and cataract surgery.

The Blue Mountains Eye Study aimed to examine the relationship between nuclear, cortical, and posterior subcapsular cataract. The study supported the findings of previous research, but also found an association between posterior subcapsular cataracts and DM. In contrast to the Beaver Dam Eye Study, nuclear cataracts showed a weak association with DM.

The Barbados Eye Study evaluated the relationship between diabetes and lens opacities among 4314 black participants. The authors found that a history of DM (18% prevalence) was related to all lens changes, especially at younger ages. Another study by Srinivasan et al found that for diabetics the cumulative incidence of cataracts is much higher than that of progression. Moreover, they indicated that the main risk factor for cumulative incidence and progression of most types of cataract is age, with higher rates of both in older patients.

Timing of surgery:

Approaches to the timing of cataract surgery in diabetic patients seem to be changing worldwide. Earlier a more conservative approach was applied but now there is a growing tendency toward early surgery. Some studies reported that the main cause of poor visual outcomes is macular edema (ME). Due to which, they do not recommend cataract extraction for eyes with DR until visual acuity has deteriorated to 20/100–20/200.

The growing tendency toward earlier cataract surgery in patients with diabetes has contributed to improved visual outcomes. This

approach facilitates panretinal photocoagulation (PRP) and also allows for the identification and adequate treatment of diabetic macular edema (DME) before cataract surgery. In addition, if surgery is undertaken before lens opacities make it more difficult to detect retinal thickening using macular assessment, then risk of ME decreases and visual outcomes may be considerably improved.

Preoperative evaluation:

Preoperative counselling is crucial for diabetic patients. Before surgery, patients should have good glycemic control and no evidence of ocular or periocular infection. Transient refractive changes related to morphologic and functional changes in the crystalline lens have to be observed during periods of unstable blood sugar. Hyperglycemia induces myopia and, when intensive medical therapy is applied, patients tend to become more hyperopic as opposed to hyperglycemia. Changes in corneal topographic parameters during periods of glycemic changes can be a potential source of error in keratorefractive and biometric calculations as well.

A thorough and comprehensive ophthalmologic examination-including an assessment of best corrected visual acuity (BCVA) and relative afferent pupillary defect; using slit lamp biomicroscopy to assess the corneal health, ocular adnexa and neovascularization of the iris (NVI); and using tonometry, dilated fundoscopy, and gonioscopy for the evaluation of neovascularization at the angle is mandatory. In select cases, advanced diagnostic evaluations such as fluorescein angiography, optical coherence tomography (OCT), and B-scan ultrasonography may be helpful.

Consultation with vitreoretinal subspecialists is recommended by some studies, especially in complicated cases. PRP is recommended preoperatively in patients with pre-existing proliferative diabetic retinopathy (PDR), because it can rapidly progress after cataract surgery. In situations where lens opacity precludes PRP, it can be performed after surgery.

Another approach is preoperative pan-retinal cryopexy or combined cataract surgery with vitrectomy and endo-laser

photocoagulation, particularly in cases with posterior pole tractional retinal detachment (TRD). ME should be efficiently treated preoperatively, since pre-existing maculopathy usually worsens postoperatively and is strongly associated with a poor visual outcome.

Treatment options for ME are laser photocoagulation, pharmacotherapy with intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents, or steroids. Because pre-existing DME can increase the risk of ME progression by 20%–50%, intravitreal anti- VEGF agents are recommended perioperatively . Steroids have been shown to be effective for persistent or refractory DME. Dexamethasone implants and fluocinolone implants resulted in significant improvement in clinically significant ME and visual outcomes. It has also been shown that dexamethasone has a potentially lower risk of intraocular pressure elevation and cataract formation compared to fluocinolone acetonide and triamcinolone acetate. Recently, preoperative use of nonsteroidal anti-inflammatory drugs, such as diclofenac and nepafenac, has been examined. Most studies suggested that they did not reduce the chances of postoperative ME in patients with DR but the post operative use of these drugs is recommended as it does prevent post op ME associated with diabetes.

Patients with NVI also need prompt treatment, including PRP. In patients who develop neovascular glaucoma (NVG), medical therapy is the first line of defence, however, it is usually ineffective. Eyes with active NVI are at greater risk for intraoperative and postoperative complications. Anti-VEGF agents such as bevacizumab showed dramatic short- term responses in terms of intraocular pressure reduction and regression of neovascularization in the treatment of NVG. Cataract surgery after administering anti-VEGF agents should be done with or without vitrectomy as early as possible to enable treatment of the posterior segment. When NVG is a problem, a combination of trabeculectomy with phacoemulsification may also be considered after regression of NVI by anti-VEGFs. Despite all these options, the visual outcomes following phacoemulsification in eyes with

NVG are generally poor.

Cataract surgery in diabetic patients:

Cataract surgery in diabetic patients yields better results since the introduction of phacoemulsification, when compared to extracapsular or intracapsular cataract surgery. Different options are available during surgery that can lead to better surgical results and improved postoperative retinopathy evaluation. As anterior capsular phimosis is more common in diabetic eyes, capsulorhexis size should be larger than normal but smaller than the intraocular lens (IOL) optic diameter, in order to prevent anterior IOL displacement and posterior capsular opacification (PCO). However, a large diameter optic is also important for the postoperative diagnosis and treatment of peripheral retinal pathology.

Progression of retinopathy after cataract surgery is another problem in diabetic patients. The duration and complexity of cataract surgery are the main risk factors for progression of retinopathy; it is therefore important to reduce the time and complexity of the surgery. Poor pupillary dilatation can be seen in diabetic patients as the result of damage to pupillary parasympathetic supply and elevated prostaglandin levels. This means that pupil dilation is also a problem for these patients. As such, iris hooks, malyugin rings, or other iris expanders should be considered for intraoperative use. In cases with NVI, bleeding in the anterior chamber during or after surgery should also be kept in mind. Photic retinopathy during cataract surgery, especially surgeries of a longer duration, was also more prevalent in diabetic patients than nondiabetics.

While the presence of DM does not increase complications such as posterior capsular rupture, zonular dehiscence, or vitreous loss, the effect of DM on the entire eye can result in other problems. The effects of DM on the ocular surface include neurogenic effects and impaired corneal stem cell and epithelial cell division, which can result in kerato-epitheliopathy and lead to corneal epithelial defects/abrasions, which may heal slowly. It has also been shown that corneal endothelial cell loss is higher in people with

diabetes than in nondiabetics; this means that routine evaluation of diabetic patients using specular microscopy is recommended. Moreover, surgeons should take greater care in order to reduce endothelial stress during surgery.

Intraocular lens choice:

The most common problem for diabetic patients is DR. For this reason, optimal visualization and treatment of the retina should be kept in mind during cataract surgery. As the diameter of the lens increases, it will provide a larger optical area difference that may be crucial for optimal management of DR.

PCO is another concern following cataract extraction. It has been reported in some studies that the development and severity of PCO is increased in DM patients as compared to non- diabetic patients. Various studies have also shown a relationship between the development of PCO and lens material type, and that the shape of the lens. A square edge design seems to inhibit lens epithelial cell proliferation and may therefore prevent PCO formation.

Several studies have evaluated the biocompatibility of three common materials used to manufacture foldable IOLs with diabetic patients. One performed a comparison between hydrophobic acrylic and plate-haptic silicone IOLs in diabetic patients; although PCO developed less frequently with hydrophobic acrylic IOLs, it was demonstrated that this material was associated with a higher risk of anterior chamber flare in the early postoperative period. In addition, hydrophobic acrylic lenses have the lowest propensity for silicone oil adhesion, meaning that they may be the IOL of choice for diabetic patients. Because diabetic patients may need vitreoretinal surgery during the course of managing their disease, silicone IOLs that develop condensation during pars plana vitrectomy may be relatively contraindicated in such individuals. Hydrophilic acrylic IOLs are prone to opacification, particularly in patients with PDR, since elevated levels of phosphorus in the serum combined with the aqueous humour of diabetic patients may lead to opacification. Several reports have proved progressive calcific opacification of

hydrophilic acrylic IOLs in diabetic patients.

Rodríguez-Galietero et al evaluated contrast sensitivity and colour discrimination in diabetic patients and suggested that blue-light filtering IOLs do not cause chromatic discrimination defects, but that they may even improve colour vision in the blue-yellow chromatic axis. The use of multifocal and accommodative IOLs in people with diabetes are controversial as the postoperative laser treatment and fundus visualization during vitrectomy are difficult because of the optics of these types of lenses. Additionally, the design of multifocal IOLs reduces contrast sensitivity and could be a cause of visual dissatisfaction for patients with pre-existing maculopathy.

The implantation site in diabetic patients is also important. For DM patients, the ideal site is the capsular bag, as usual. The use of anterior chamber angle-fixated lenses and sulcus fixated posterior chamber IOLs in diabetic patients is controversial. It is suggested that iris claw lenses be avoided in patients with DM, due to the increased risk of iris neovascularization. The theoretical risk of cystoid ME, ovalization of the pupil, and poor mydriasis are other risk factors for diabetic patients after iris claw IOL implantation.

Postoperative management and indicators of poor visual outcomes:

Carefully performed cataract surgery in diabetic patients should yield optimal postoperative results. Patient follow-up should also be done carefully. Preoperatively, patients diagnosed with NPDR who have adequate retinal view should undergo detailed retinal examination within three months of cataract extraction. Patients with PDR or those with inadequate retinal view prior to cataract extraction should be examined closely after surgery in order to evaluate their DR status.

Endophthalmitis is the most serious complication of cataract surgery. The risk of postoperative endophthalmitis in diabetic patients has increased and is associated with a poor visual prognosis.

As a patient's age and duration of diabetes increases, there is greater prevalence of corneal epithelial defects and persistent erosions due to impaired corneal innervation. Corneal endothelial cell damage and persistent corneal edema in diabetic patients following cataract surgery have also increased. Specular microscopy should therefore be used to evaluate DM patients and all the necessary precautions should be taken intraoperatively. Also more frequently observed in diabetic patients are severe iritis, posterior synechiae, pupillary block, and pigmented precipitates on the IOL.

The Early Treatment Diabetic Retinopathy Study (ETDRS) outlines the prognostic factors after cataract surgery. The presence of clinically significant macular edema (CSME) at the time of surgery was found to be a predictor of poor final BCVA in cases of uncomplicated phacoemulsification. Another determinant of poor postoperative BCVA was the severity of

DR at the time of surgery. As the severity of retinopathy increased, the risk of macular ischemia or edema also increased. More severe retinopathy also correlated with a reduced tendency for spontaneous resolution of postoperative ME, which is itself associated with poor postoperative BCVA. PDR without any treatment prior to cataract surgery is another factor- one which comes with an increased risk of vitreous haemorrhage and TRD following surgery.

Complications:

Despite the advancement in phacoemulsification technology, poor visual acuity following cataract extraction is still common in patients with DM. PCO, postoperative cystoid macular edema (CME), DME, and worsening of the DR are the main complications seen in diabetic patients.

PCO formation:

PCO is one of the most common causes of decreased vision after cataract extraction. Modifications in surgical technique and improvements in IOL technology have although reduced the incidence of PCO but it is still a problem for these

patients. Proliferation of lens epithelial cells and the degree of postoperative inflammation are associated with development of PCO. PCO formation is affected by several factors, including optic edge design, optic- haptic junction, and IOL material. However, surgical trauma and contact with the IOL can induce inflammation and cause epithelial cells to produce cytokines, which induce collagen production and fibrous metaplasia.

While some studies revealed a higher incidence of PCO in diabetic patients, others showed fewer cases of PCO in diabetic eyes, regardless of the retinopathy stage, over the course of two years. In a study by Hyashi et al, the development of PCO was significantly higher in diabetic patients 18 months after surgery, even though it was similar to the control group for the first 12 months. According to some studies , severity of retinopathy did not have an impact on the development of PCO, according to some studies.

Macular odema:

Other frequent causes of postoperative vision deterioration among the general population are development of DME, pseudophakic macular edema (PCME), CME, or Irvine-Gass syndrome Altered concentrations of angiogenic factors after cataract surgery may aggravate maculopathy. OCT imaging has also revealed increased retinal thickness following an uneventful cataract surgery in diabetic eyes without retinopathy as compared to non-diabetic eyes. Chu et al reviewed 81,984 eyes and reported that, even in the absence of retinopathy, diabetic patients' eyes had an increased relative risk of ME after surgery. In addition, patients with pre-existing DR had a higher relative risk of ME, with this risk being proportional to the increasing severity of retinopathy.

The incidence of CME varied between 0.2% and 20% in older studies. However, recent studies report lower rates of CME, ranging from less than 1% to 2%-3%. The methods of detection used in these studies have a significant effect on the rate of CME detection.

Fluorescein angiography and OCT are more sensitive tools for reporting higher rates of CME than clinical detection. It is also important to differentiate DME from PCME (Irvine-Gass syndrome), since the pathogenesis, treatment, natural course, and outcomes for both are very different. While the underlying presence of DR, exudates, and ME point toward DME, if there is minimal or no DR and there are no exudates in the posterior pole, this suggests PCME. When in doubt, fluorescein angiography can help to distinguish; if the angiography shows a petaloid pattern associated with hyper-fluorescence of optic disc and there is no retinopathy or microaneurysms, edema may be considered as a result of Irvine-Gass syndrome. Therefore, the prevention of CME in diabetic patients is very important. Recently, both prophylactic and therapeutic usage of both topical steroidal and non-steroidal anti- inflammatory eye drops (NSAIDs) has become central to perioperative management of CME in diabetic patients. Especially NSAIDs have been shown to decrease the incidence of CME in the general population. In addition to facing a higher risk of CME, diabetic patients with pre-existing DME are at an increased risk of worsening edema following cataract surgery.

The development of postoperative CSME may be the result of the natural progression of the disease rather than a direct effect of surgery on many patients. It is possible that severe ME after cataract surgery represents a postoperative deterioration of pre-existing ME that was previously untreated because of lens opacity. Attempts to stabilize and resolve DME will help improve outcomes, if DME is present prior to cataract surgery. Many strategies for thepreoperative medical management of DME are available. Postoperative laser photocoagulation for diabetic ME is controversial. The ETDRS established the utility of focal/grid laser photocoagulation for the treatment of ME. Focal/grid laser treatment (as described in the ETDRS) was considered as first line treatment for CSME, prior to the use of anti-VEGF agents for central involved DME. It remains an alternative treatment in cases in which anti-VEGFs are not applicable or the centre of the macula is not involved On the other hand, Pollack et al and Dowler et al showed that ME resolves spontaneously if it

arises postoperatively but not when it is present preoperatively. They suggested that early laser treatment is unnecessary for all cases of postoperative DME. Generally, experts do not perform argon laser treatment until six months after cataract surgery. The advent of anti- VEGF injections has shifted the paradigm in the treatment of DME. Many studies performed on anti-VEGF agents in diabetic patients have shown their effectiveness at preventing and treating CSME. Current opinion supports that anti-VEGF agents are first-line therapy in preoperative treatments, perioperative stabilization of DME, and postoperative management and that they show great success in anatomic recovery and visual function. Focal laser treatment and steroid injections still provide significant additional support.

Progression of retinopathy:

Numerous studies have evaluated the effect of cataract surgery on the progression of DR. The progression of DR after intracapsular (ICCE) and extracapsular (ECCE) cataract extraction has been extensively studied. Sebestyen et al and Alpar et al demonstrated the progression of retinopathy after ICCE and ECCE, with ICCE showing worse results than ECCE. However, the effect of phacoemulsification is controversial. Modern phacoemulsification procedures are considered faster, safer, and more cost-effective than ICCE and ECCE. Even with the advances in modern phacoemulsification techniques, some studies have demonstrated a similar trend of DR progression after phacoemulsification surgery; others have reported no significant change. The risk factors for DR progression have also been investigated. Dowler et al reported that a smaller incision size and shorter surgical duration for phacoemulsification decreased inflammation and may induce less breakdown of the blood– ocular barrier, meaning that uncomplicated phacoemulsification cataract surgery does not accelerate DR progression. Additionally, recent studies suggest that anti-VEGF injections may also affect the incidence of DR progression. If not used prophylactically, atleast the use of anti-VEGFs in patients with more advanced NPDR or PDR and DME should beconsidered. Other ocular co-morbidities such as vitreous

haemorrhage, epiretinal membranes, or TRD may benefit from a combined pars plana vitrectomy and cataract surgery As the number of people with DM is estimated to continue to increase, cataract surgery will remain important for diabetic patients. Patients with diabetes have multiple issues to be evaluated preoperatively, perioperatively, and in the postoperative period. With the advent of modern surgical and pharmacologic therapies, these patients can, like other cataract patients without diabetes, recover excellent vision. Postoperative monitoring and management of surgical complications will also help to alleviate the risk of vision loss in these patients.

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CHAPTER 4:
OCULAR SURFACE DISORDERS IN DIABETES

1. DRY EYE IN DIABETES

Diabetes is a leading cause of ocular morbidity which is progressive and preventable with early diagnosis and treatment. In both the developed and developing countries It is a major cause of avoidable blindness. Ocular complications of diabetes mellitus include diabetic retinopathy, cataract, glaucoma, and ocular surface disease among others. Duration of diabetes, glycemic control, coexisting hypertension, hyperlipidemia, nephropathy and anaemia have proven to a play role in the progression of diabetes and its complications.

Recently ocular surface problems especially dry eye has drawn attention in diabetic patients. Diabetes and dry eye appear to have a significant impact on the quality of life of patients in several studies.

Dry eye was earlier termed a complex disorder of the tear film and ocular surface as a result of tear deficiency or excessive tear evaporation. Damage to interpalpebral ocular surface occurs, with a variety of symptoms such as ocular discomfort and visual disturbance among others . Dry eye syndrome (DES), is a multifactorial disorder due to inflammation of the ocular surface and lacrimal gland, neurotrophic deficiency and meibomian gland dysfunction. Grittiness, burning sensation, foreign body sensation, photophobia, redness and blurred vision are some of the symptoms of patients with dry eye. The micro vasculopathy and autonomic neuropathy in long term diabetics can lead to absence of these symptoms but presents with clinical signs of dry eye. According to Tear film ocular society (TFOS) dry eye workshop 2 Patients with dry eye can have serious corneal complications such as, superficial punctuate keratitis, neurotrophic keratopathy and persistent epithelial defect.

According to DEWS conducted in the year 2017, dry eye was defined as a multifactorial disease of ocular surface characterized

by a loss of homeostasis of the tear film, accompanied by ocular symptoms, in which tear film instability, hyperosmolarity, ocular surface inflammation and neurosensory abnormalities play a major role in etiology. Dry eye can beclassified into 2 types as tear-deficient and evaporative. Similarly, in diabetes, dry eye may be tear deficient or evaporative.

The tear film consists of 3 layers, outer lipid layer (secreted by meibomian glands), middle aqueous layer (secreted by the lacrimal gland) and inner mucin layer (secreted by goblet cells of conjunctiva). The ocular surface comprises of the cornea, conjunctiva and also includes the lacrimal gland, meibomian gland, lids, with the sensory and motor nerves that connect them.

Quantitative and qualitative abnormalities in tear secretion, alteration of epithelial barrier leading to poor adhesion of regenerating epithelial cells, autonomic neuropathy causing decreased corneal sensitivity lead to tear film and ocular surface changes in diabetes causes dry eye which can affects the quality of life of an individual. There is no gold standard diagnostic test for dry eye disease hence a combination of signs and symptoms is commonly used as the basis for diagnosis. Several studies have been conducted to study dry eye, its risk factors, tear film parameters, ocular surface irregularities, prevalence and the various methods to diagnose dry eye. Examination of diabetic patients for dry eye should be an integral part of assessment of diabetic eye disease along with evaluation of diabetic retinopathy.

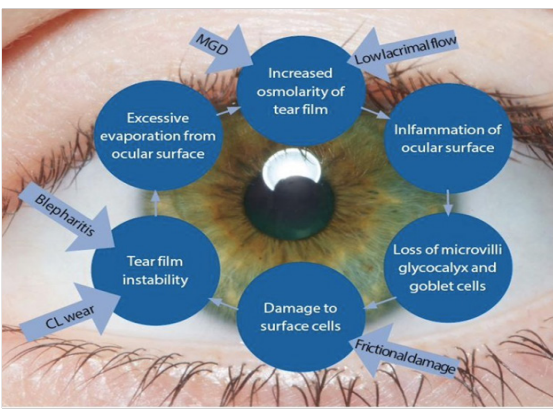

Image: Vicious cycle of tear film and ocular surface disorder

Pathophysiology of dry eye:

DM can lead to DES (DRY EYE SYNDROME) through a variety of mechanisms, but the association between DM and DES is unclear. Extensive hyperglycemia is the most possible mechanism responsible for dry eye in DM which causes corneal neuropathy. Corneal neuropathy inturn leads to tear film instability and lower tear film break up time (TBUT) values due to conjunctival goblet cell loss. Mucin, which forms the mucin layer of the tear film covers the villus surface of the corneal epithelium and reduces evaporative tear loss is produced by conjunctival goblet cells. The other suggested mechanisms for disruption ofcorneal integrity include AGE accumulation and polyol pathway bi-product accumulation within the corneal layers. It is believed that DM affects tear production and quality by compromising the functional integrity of the lacrimal gland as well. Corneal sensitivity is also reduced in DM, which affects the stimulation of basal tear production. Both lacrimal gland integrity and corneal sensitivity are shown to be affected by diabetic neuropathy. These proposed mechanisms imply that DM affects both tear production and corneal integrity, suggesting disruption to one or both may cause and lead to the exacerbation of DES.

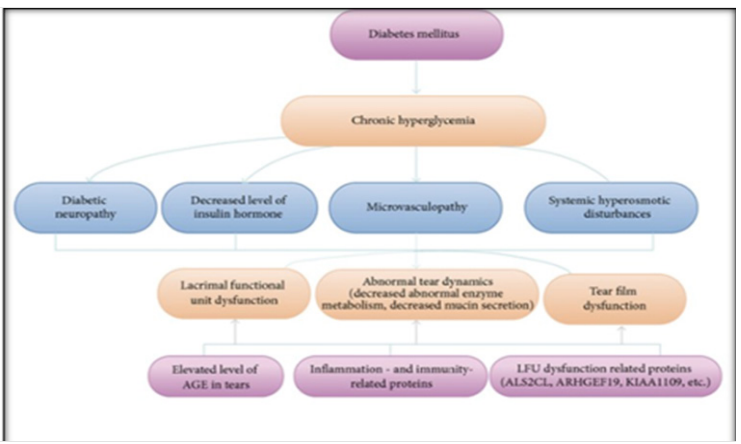

Image: showing pathophysiology of dry eye.

Tests to evaluate dry eye:

1. Ocular symptoms:

- Grittiness
- Foreign body sensation
- Burning
- Irritation
- Stinging
- Watering
- Photophobia
- Diminution of vision
- Blurring of vision
- Redness
- Dryness

Presence of symptoms is graded as follows

- Less than 2 symptoms: normal
- More than 2 symptoms: abnormal

2. Schirmer test without anaesthesia:

Whatman filter paper no 41 is used to perform the Schirmer test. The patient is asked to look up and the strip is placed in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd. The patient is asked to sit with eyes gently closed for 5 minutes and the distance of the strip wetted is measured in millimetre and reading of 10 or lesser is considered abnormal. A scoring was given to each patient based on the millimetre of Schirmer strip wetting as follows

- 0 to 5 mm – Grade 1, abnormal
- 6 to 10 mm – Grade 2, abnormal
- 11 to 15 mm – Grade 3, normal

- More than 15 mm – Grade 4, normal

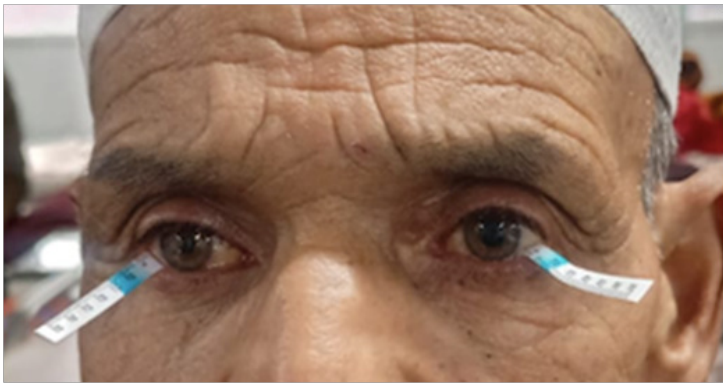

Image: showing schirmer test being done

3. Tear meniscus height (TMH):

1% fluorescein dye strip is used to stain the tear film and to measure the tear film meniscus height. Precorneal tear film is stained by placing the strip in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd. The patient is placed in front of the slit lamp and using the cobalt blue filter, height of the fluorescent stained meniscus is measured with a scale in millimetre. Graded as follows:

- Less than 1mm–abnormal
- More than 1mm-normal

4. TBUT – tear film breakup time:

With the dye stained pre corneal tear film, the patient is asked to blink few times then seated on a slit lamp and viewed under cobalt blue filter. The time taken to visualize the first dry spot on the cornea is noted with a stopwatch. Reading of 10 or lesser seconds is abnormal.

Graded as follows:

- Less than 10 seconds – abnormal

- More than 10 seconds – normal

5. Corneal staining with fluorescein

It is scored using the Oxford system of grading for cornea and conjunctiva which is adapted from corneal and conjunctival staining clinical education, multimedia from American academy of Ophthalmology.

It is graded as follows:

0- absent

1- Minimal

2- Mild

3- Moderate

4- Severe

5- Very Severe

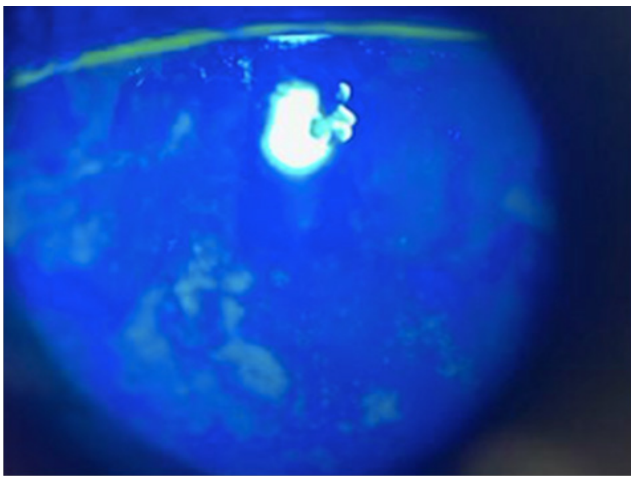

Image: showing corneal fluorescein staining positive in a dry eye patient

Score of 3 or more is abnormal as was considered as corneal staining positive.

- Corneal stain positive – abnormal

- Corneal stain negative – normal

PANEL	GRADE	CRITERIA
A 	0	Equal to or less than panel A
B 	I	Equal to or less than panel B, greater than A
C 	II	Equal to or less than panel C, greater than B
D 	III	Equal to or less than panel D, greater than C
E 	IV	Equal to or less than panel E, greater than D
>E	V	Greater than panel E

Image: showing grades of corneal staining in dry eye (ref AAO)

6. Conjunctival staining:

Lissamine green is used to stain the conjunctiva to look for dead and degenerated cells. Conjunctiva is stained with the strip after 5 minutes of the previous fluorescein staining and done by placing the lissamine green strip in the lower fornix at the junction of medial 2/3rd and lateral 1/3rd. Patient is placed in front of the slit lamp and using the red free filter, the extent of conjunctival staining both temporal and nasal conjunctiva was graded using the Oxford system of grading for cornea and conjunctiva.

0- absent.

1- minimal.

2- mild.

3- moderate.

4- marked.

5- severe.

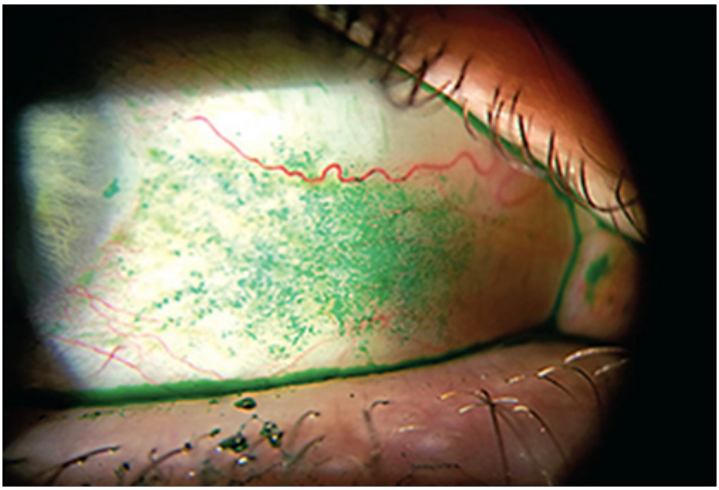

Image: showing conjunctival stain positive with lissamine green stain.

Score of 3 or more is abnormal.

- Conjunctival stain positive – abnormal
- Conjunctival stain negative - normal

7. Presence of strands / filaments:

Presence of strands / filaments is noted as positive or negative by viewing with the slit lamp after fluorescein staining.

- Strands/ filaments present – abnormal
- Strands/ filaments absent – normal More than 3 positive tests : dry eye disease

Duration of diabetes also plays a major role in development of dry eye disease, so patients having diabetes for longer durations

have more chance of having dry eye than recently diagnosed patients. Besides duration status of retinopathy also plays a role in dry eye.

Patients with diabetic retinopathy usually have worse scores on tear film tests and ocular surface analysis compared to patients without retinopathy which suggests poor glycemic control is also an important factor in causing dry eye.

The first and very important step in the diagnosis of dry eye is symptom assessment, dry eye is believed to be a 'symptom based' disease. So the first test in dry eye is evaluating the ocular symptoms of the patient. proper history taking thus takes a very important role is guiding us towards dry eye diagnosis.

1. Therapy:

DES may cause loss of vision, scarring, perforation, and corneal infection among other complications. If patients with dry eye are treated in time, it will prevent complications ofDES. The patients of DES are treated with tear supplements called "artificial tears" which contains surfactants, different viscosity agents and electrolytes.

Dry eye disease is the outcome of various factors resulting in inflammation of the cornea and conjunctiva. Artificial tears can reduce blurred vision, and the symptoms of dry eye, temporarily. These agents do not contain the cytokines and growth factors which are comprised in normal tears and do not have direct anti-inflammatory effect so Anti- inflammatory drugs are also widely used for the treatment of DES. The most widely used anti-inflammatory agents are topical corticosteroids, NSAID, and cyclosporine.

Correlation of dry eye with other modalities of evaluation of tear film and ocular surface such as tear osmolarity and conjunctival impression cytology have proven to be better markers in studies. Thus the progression of dry eye is multifactorial. If untreated it causes serious ocular complications and much distress to the patient. Thereby early identification of symptoms, signs and timely evaluation by the treating Ophthalmologist, must be

given priority in the analysis for dry eye in diabetic patients.

2. Diabetic keratopathy:

DM can trigger acceleration of ocular surface abnormalities which have been termed diabetic keratopathy. Patients with diabetes in contrast to healthy persons, have corneal epithelial erosions that may recur and be associated with unresponsiveness to conventional treatment regimens. This clinical condition is known as diabetic keratopathy. Diabetic keratopathy includes various symptomatic corneal conditions, such as, punctate keratopathy and persistent corneal epithelial defect.

Diabetic keratopathy is a common complication of patients with evidence of DR. A study reported that several symptomatic corneal epithelial lesions usually occur in diabetic patients at the rate of 47% to 64%. Other study showed that the incidence of diabetic keratopathy in diabetic patients with DR was 2 times greater than that of patients without DR. Several studies reported that the incidence of diabetic keratopathy increased following pars planavitrectomy, penetrating keratoplasty, laser iridectomy, and refractive surgery in diabetic patients.

Pathogenesis:

Several pathophysiological abnormalities have been shown in diabetic keratopathy which are an abnormally thickened and discontinuous basement membrane, abnormal adhesion between the stroma and basement membrane, increased epithelial fragility, decreased epithelial healing rates, increased sorbitol concentrations, decreased oxygen consumption and up-take, increase in the polyol metabolism, decreased or alter epithelial hemidesmosomes, and increased glycosyl transferase activity.

Recently, studies have demonstrated that there is a relationship between AGE and development of diabetic keratopathy as well. Increased AGE in the laminin of the corneal epithelial basement membrane causes abnormaly weak attachment between the basal cells and basement membrane of the cornea in diabetics. Also, the loss of the corneal sensation and neural stimulus have been regarded as the reason of the development of diabetic

keratopathy. Axonal degeneration of corneal unmyelinated nerves occurs under chronic hyperglycemic conditions.

Clinical evaluation:

Diabetic keratopathy is a condition that should be closely monitored because it can result in blindness . Early diagnosis and treatment of diabetic keratopathy, particularly, before corneal complications occur, is very essential. If the diagnosis is late, patients will become resistant to the routine treatment of corneal defects. Nonhealing corneal epithelial erosion may also occur after pars plana vitrectomy for advanced PDR. If corneal epithelium is removed manually for clarity by surgeons, this conditions may accelerate dramatically. So, when diabetic patients are examined after vitrectomy their corneas should be examined carefully.

Therapy:

Keratopathy is generally treated with artificial tears, and antibiotics. Additionally, bandage contact lens, and tarsorrhaphy have been used for re-epithelialization. In selected cases newtreatments modalities will be used such as, topical administration of naltrexone, nicergoline, aldose reductase inhibitor and some growth hormones to accelerate re-epithelialization. All of these drugs were associated with a high corneal epithelial wound healing rate.

Recently, new topical drugs such as substance P and IGF-1 were tested on diabetic animals to accelerate re-epithelialization. Successful outcomes were obtained with these new drugs.

Corneal epithelial barrier function was improved by topical aldose reductase inhibitors, but superficial punctate keratopathy could not be prevented by these topical drugs.

Aminoguanidine had beneficial effects in corneal epithelial defects, by improving attachment between the epithelial cells and basement membrane of the cornea. The in vivo beneficial effect of amino-guanidine were unknown. In additional to these new drugs, amniotic membrane transplantation is used to treat persistent corneal epithelial defects and can provide relief to the

patient.

Conclusion:

DM and its ocular complications remain a major cause of blindness despite increased understanding of these ocular conditions and identification of successful treatments because early diagnosis is not done. Timely diagnoses and therapy can prevent all the complications of diabetes. Therefore, periodic eye examinations are required for the reduction of diabetes- related vision loss. Good blood glucose control and other systemic risk factors such as hypertension, and hyperlipidemia are main goal to prevention of ocular complications of DM.

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CHAPTER 5

GLAUCOMA in diabetes

Glaucoma is a progressive optic disease that is mainly caused by high pressure in the eyes and is characterized by gradual death of retinal ganglion cells (RGC). Glaucoma, which is a leading cause of irreversible blindness worldwide, has generated a major public health problem. Primary open angle glaucoma (POAG) is the most common type of glaucoma in diabetic individuals, with nearly 70 million affected worldwide. Therefore, potential risk factors for POAG need to be identified so that interventions to reduce its incidence can be developed.

The pathogenesis of POAG is still not well understood, so far. Some researches suggested damage to the microvasculature network and/or reduced nutritional supply to the RGC axons due to interference of blood regulation in the optic nerve head area. This nutritional deficiency can lead to degeneration of RGCs and initiate glaucomatous impairment.

Therefore, any vascular-related systemic disease, such as diabetes, which directly or indirectly disrupts nutritional supply to RGCs, may result in development of POAG.

Diabetes has been deemed as a risk factor for POAG by some reports, however, epidemiologic studies of the relationship between diabetes and POAG are still controversial.

Some studies have revealed that the incidence of glaucoma markedly increased by 36% in patients with diabetes compared with individuals with no diabetes Several hypotheses on biological links between diabetes mellitus and glaucoma have been proposed by various authors. Firstly, it was postulated that diabetes would lead to impairment of micrangium and vascular autoregulation. These vascular injuries would reduce blood flow to the retina and optic nerve, resulting in reduced nutrient and oxygen supply to the RGC axons and increased expression of hypoxia-inducible factor-1 in the retinal cells in response to

elevated IOP. Ultimately these changes were likely to induce the degeneration of the RGCs and initiation of glaucomatous impairment. Secondly, there was a large amount of evidence that the hyperglycemia and lipid anomalies induced by diabetes could increase the risk of neuronal injury indicating that the RGCs were more likely to be destroyed in the patients with diabetes.

Third, the hyperglycemia of aqueous humour in the eyes of diabetes patients would stimulate the synthesis and accumulation of fibronectin in the trabecular meshwork to promote depletion of trabecular meshwork cells, which could impair the outflow system of the aqueous humour and finally result in POAG.

Both diabetes and glaucoma seem to share some common risk factors and pathophysiologic similarities with studies also reporting that the presence of diabetes and elevated fasting glucose levels in an individual are associated with elevated intraocular pressure – which is the primary risk factor for glaucomatous optic neuropathy.

The burden of diabetes on the health care system has manifested in many different ways. Diabetic patients require more outpatient visits, chronic medications, and are at risk for a number of systemic microvascular complications that result in end organ damage and associated complications: renal disease, cardiovascular disease, amputations, vision loss, and premature death. Vision loss from diabetic retinopathy (DR),in particular,represents one of the most devastating complications on quality of life and is the leading cause of blindness in todays working age.

Mechanical stress from elevated IOP is thought to occur primarily at the level of the lamina cribrosa – the point at which the optic nerve fibres penetrate the posterior sclera. The optic nerve fibres arise form the axons of the RGCs, but IOP-induced mechanical stress causes posterior bowing and thinning of the lamina, which disrupts axonal transport. As a result, the RGCs undergo apoptotic cell death in conjunction with loss of neuroretinal rim tissue of the optic disc and corresponding enlargement of the optic cup.

Glaucoma Risk Factors and Correlation with Diabetes

Common Pathophysiologic Mechanisms in Glaucoma and Diabetes:

Several common mechanisms have been postulated to contribute to the possible link between glaucoma and diabetic retinopathy. Diabetes and hyperglycemia is associated with glycation of lipids and abnormalities of lipid metabolism which may increase oxidative stress and promote cellular apoptosis – the same mechanism by which RGC loss occurs in glaucoma.

Vascular dysregulation has been described in both diabetic eye disease and glaucoma, and upregulation of nitric oxide, a potent vasodilator, has been reported in both conditions. Nitric oxide is a known regulator of not only vascular tone, but also apoptosis. In addition, reactive nitrogen species have been shown to contribute to inflammatory responses via oxidative stress and optic nerve degeneration as well. The contributory role of PKC in the pathophysiology of diabetic retinopathy has also been established and there is evidence to suggest that elevated PKC may also be associated with abnormalities of matrix metalloprotease in the trabecular meshwork causing impaired aqueous outflow and elevated IOP. Also, overexpression of matrix metallprotease-9 has been associated with structural optic nerve head changes in diabetic patients, thus providing another potential link between diabetes and glaucoma.

Other pathways by which scientists have linked diabetes and glaucoma include glial cell dysfunction and impairment of retrograde axonal transport. Glial cells, such as astrocytes, are non-neuronal cells that support and protect neurons in the central nervous system, including the retina and optic nerve. Dysfunction of these cells has been demonstrated in animal models of diabetes and glaucoma and is believed to contribute to neuroinflammatory pathways of apoptosis . In addition, it has been postulated that alterations in connective tissue remodelling due to diabetes may affect both the lamina cribrosa and the trabecular meshwork, thereby potentially increasing susceptibility to glaucoma through biomechanical changes at

the optic nerve and impairment of aqueous humour outflow affecting IOP homeostasis.

Diminished neurotrophic factor delivery secondary to abnormalities in axonal transport has been demonstrated in both diabetic peripheral neuropathy and the optic nerve in glaucoma. Alterations in neurotrophic factor expression, such as insulin-like growth factor and neurotrophin-3, are also seen in the presence of elevated intraocular pressure, which is the primary risk factor for glaucomatous optic neuropathy. In particular, insulin-like growth factor is necessary for proper glucose metabolism in the central nervous system and resistance to insulin may be a contributor to neurodegenerative processes. With regard to the eye and glaucoma, insulin and insulin-like growth factor have been shown to play a role in RGC survival. Also, insulin has been reported to affect IOP with lower IOP being associated with insulin-induced hypoglycemia while increased IOP has been associated with insulin resistance. Clinically, a large retrospective cohort of diabetic patients with open angle glaucoma reported that metformin, a first-line agent used to treat insulin-resistance in type 2diabetes, is associated with a decreased risk of developing open angle glaucoma even after accounting for variations in glycemic control. In addition, genetic polymorphisms related to pancreatic beta-cell function in type 2 diabetes mellitus were associated with increased risk of POAG and provide further support for these findings.

Neurodegeneration and Ganglion Cell Apoptosis:

RGC apoptosis and retinal nerve fibre layer (RNFL) thinning are characteristic structural findings seen in glaucoma that have also been described in diabetic retinopathy. In conjunction with RNFL loss, excavation or cupping at the level of the optic nerve head is the pathognomonic finding that is most commonly associated with glaucoma. However, a similar appearance of the optic nerve head may also be seen in the presence of anterior ischemic optic neuropathy, which occurs more frequently in diabetic patients in some studies, or after laser photocoagulation treatment for proliferative diabetic retinopathy. Structural optic nerve abnormalities have also been reported in an experimental

rat model of diabetes, which also showed corresponding RGC dysfunction as measured by electroretinogram. Such similarities can present challenges in distinguishing glaucomatous from non-glaucomatous optic neuropathy, especially in the presence of both conditions.

Though diabetic retinopathy is generally considered primarily a microvascular complication of diabetes, it is now known that neurodegeneration is also a significant component in its pathophysiology and may even precede the microvascular changes that are typically seen in diabetic eye disease. In a recent study by Sohn and colleagues, progressive loss of both the nerve fibre layer and RGC/inner plexiform layer was observed using optical coherence tomography (OCT) in 45 patients with no or minimal diabetic retinopathy. In the same study, they also demonstrated progressive inner retinal thinning and RGC loss in a streptozotocin- induced mouse model of type 1 diabetes on both OCT and immunohistochemistry. These findings are consistent with earlier work from the same investigators, who reported selective thinning limited to the inner retina in type 1 diabetic patients. Cross-sectional human studies from other groups comparing RNFL thickness in healthy subjects and patients with preclinical diabetic retinopathy have also demonstrated mean and superior quadrant RNFL thickness to be reduced in diabetic patients when measured by OCT. As a result, neurodegeneration in diabetic eye disease appears to occur in the same location of the neural retina as glaucomatous optic neuropathy.

Also, neurodegeneration in both glaucoma and diabetic eye disease is believed to be relatively nonselective, affecting all RGC types. In general, RGCs can be classified based on their functional features and projections from the optic nerve head to layers of the lateral geniculate nucleus. Studies in experimental primate models of glaucoma have shown that RGC loss of all types occurs by apoptosis with greater loss occurring as a direct function of IOP. Specifically, loss of neurons in the magnocellular and parvocellular pathways has been demonstrated in glaucoma, which has also been reported in a histologic study of human retinas with diabetic retinopathy by Meyer-Rusenberg and

colleagues as well.

Functional Abnormalities in Glaucoma and Diabetes:

From a functional standpoint, it is well-established that RGC loss in glaucoma is associated with visual field deterioration and loss. Several animal and human electrophysiologic studies have reported a variety of abnormalities in the presence of both diabetic retinopathy and glaucoma compared to normal eyes. A recent study of visual field profiles for POAG from the Nurses' Health Study found that early peripheral, as opposed to paracentral, visual field loss was more common in POAG patients with diabetes mellitus. While the diagnosis of diabetes in this study was based on patient self-report and did not exclude diabetic patients with retinal laser photocoagulation (which can also produce peripheral visual field loss), chart review in a subset of these subjects demonstrated that self-report was a valid method for accurate classification of diabetes among health professionals. Nevertheless, these findings suggest that there may be important phenotypic differences in glaucoma patients depending on diabetes status.

Metabolic Syndrome and Insulin Resistance in Glaucoma and Diabetes:

Metabolic syndrome is a cluster of clinical risk factors, including hypertension and dyslipidemia, which is a significant predictor of diabetes. Insulin resistance is thought to be involved in the pathophysiology of metabolic syndrome and as a result, the components of metabolic syndrome are comprised of significant systemic risk factors for either elevated IOP or glaucoma.In a study examining individual components of metabolic syndrome, Newman- Casey and colleagues found that hyperlipidemia alone in the absence of diabetes or glaucoma was not a risk factor for open angle glaucoma. However, both diabetes mellitus and systemichypertension, either alone or in combination, were associated with an increased hazard of open angle glaucoma.

With regard to insulin resistance, a recent study comparing IOP changes in diabetic and non- diabetic individuals found reported that hyperglycemia during oral glucose tolerance testing has a

positive correlation with IOP. Similarly, data from the Korean National Health and Nutrition Examination Survey also reported higher mean IOP to be positively correlated with estimated insulin resistance in addition to the presence of diabetes mellitus, hypertension, metabolic syndrome, and lipid abnormalities. In a study of normal tension glaucoma patients and components of metabolic syndrome, Kim and colleagues found hypertension and impaired glucose tolerance were associated with a significantly higher prevalence of normal tension glaucoma. However, a slightly lower prevalence of glaucoma was seen among participants with metabolic syndrome in the Singapore Malay Eye Study and neither pre- diabetes or metabolic syndrome were consistently associated with glaucoma in a cross- sectional study of subjects from the 2005–2008 National Health and Nutrition Examination Survey . Recently, a study using healthcare claims data reported a dose-dependent reduction in POAG risk among diabetic persons using metformin, the first-line medication used to treat patients with type 2 diabetes mellitus and improve insulin sensitivity. In addition, those subjects with a higher HBA1c had an increased risk of glaucoma, suggesting that glycemic control and insulin sensitivity may contribute to glaucoma risk. Many of the risk factors associated with diabetes may also be contributory to glaucoma as well, when considered together,Both diabetes and glaucoma are major ophthalmological issues in the aging population. Several epidemiologic studies suggest that diabetic individuals are at increased risk for the development of glaucoma and there may be pathophysiologic similarities to support an association between these two conditions as discussed above. Given the potential to utilize early detection and treatment efforts to significantly reduce vision loss from both glaucoma and diabetic retinopathy in at-risk individuals, the possible role of routine glaucoma evaluation in diabetic persons demands further consideration as we continue to learn more about the association between these two blinding conditions.

Since glaucoma is now considered as a major diabetes side effect and a leading cause of blindness, diabetes doctors and ophthalmologists advise an eye examination periodically based upon the risk of a person to get glaucoma.

While glaucoma is generally suspected in a normal eye examination, certain diagnostic tests are prescribed in order to confirm the diagnosis of glaucoma. These tests include:

Diagnostic tests for glaucoma

- Tonometry – This test is done to determine the intraocular pressure
- Ophthalmoscopy – This test is done to examine (damage to) the optic nerve
- Gonioscopy- This test measures whether the angle where the iris meets the cornea is wide, open, or narrow
- Pachymetry – This test is done to measure the corneal thickness
- Perimetry- This test is done to measure the field of vision
- Slit-lamp examination
- Optical coherence tomography
- Dilated fundus examination with 78D/90D
- Laser scan of the retina (Laser tomography)

Based upon the results of these tests, the treatment options for glaucoma is evaluated and the appropriate treatment is given by the ophthalmologist in conjunction with a diabetes doctor.

Treatment

The main goal for glaucoma treatment is slowing the disease progression and preservation of quality of life. Reduction of intraocular pressure to desired target pressure is the only proven method to treat glaucoma. The target intraocular pressure should be achieved with the fewest medications and minimum adverse effects. Several different classes of pressure-lowering medications are available:

Class of Medication	Example	Usual Dosages	Mechanism of Action
Prostaglandin analogues (prostamide)	Latanoprost, travoprost, tafluprost, unoprostone, bimatoprost	1/d At night	Increase in uveoscleral outflow of aqueous humor
β-Adrenergic blockers	Timolol, levobunolol, carteolol, metipranolol, betaxolol	1/d In the morning	Reduction of aqueous humor production
α-Adrenergic agonists	Brimonidine, apraclonidine	3/d (Sometimes 2/d)	Initial reduction of aqueous humor production with subsequent effect of increase in outflow
Carbonic anhydrase inhibitors	Dorzolamide, brinzolamide, acetazolamide (oral)	3/d (Sometimes 2/d)	Reduction of aqueous humor production
Cholinergic agonists	Pilocarpine, carbachol	Usually 4/d, but may vary	Increase in aqueous humor outflow

Image: showing various topical anti-glaucoma medications with their mechanism of action.

When medical treatment does not achieve adequate intraocular pressure reduction with acceptable adverse effects, laser or surgeries are indicated.

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CHAPTER 5:
UVEITIS IN DIABETES

UVEITIS:defined as the inflammation of uveal tissue of the eye.

Types of uveitis: There are several types of uveitis:

a) Based on the site of inflammation:

Anterior uveitis– It isthe most common form, occurs in very young to middle-aged people. It occurs when the iris and the ciliary body become inflamed, and has been linked to patients suffering from rheumatologic, skin, gastrointestinal, lung and infectious diseases. This type is usually seen in diabetes.

Intermediate uveitis– occurs mostly in children, teenagers and young adults. It occurs when the area behind the ciliary body i.e vitreous becomes inflamed and has been associated with patients suffering from inflammatory bowel disease, sarcoidosis and multiple sclerosis usually.

Posterior– the least common type, occurs when the choroid and the retina at the back of the eye become inflamed.

Panuveitis– when all three major parts of the eye are affected by inflammation.

b) Based on pathology:

Granulomatous uveitis: Granulomatous uveitis is an inflammation of the uveal tract characterized by the formation of granulomas due to infectious or non-infectious causes. It may be associated with a systemic disease and can involve any part of the uveal tract. The systemic diseases can include debilitating and life-threatening conditions for which ocular manifestations may be the first presentation.

Non-granulomatous uveitis: Non-granulomatous uveitis is a type of uveitis that is characterized by acute onset, severe pain, and intense sensitivity to light. The causes of non- granulomatous uveitis include seronegative arthropathy, trauma, Behcet's

syndrome, leptospirosis, sarcoidosis, tuberculosis, and syphilis. Non-granulomatous uveitis typically has an acute onset and shows fine KP (keratic precipitates). Though there are many causes for non-granulomatous uveitis, it is more likely to be idiopathic.

c) **Based on eitiology:**

Traumatic

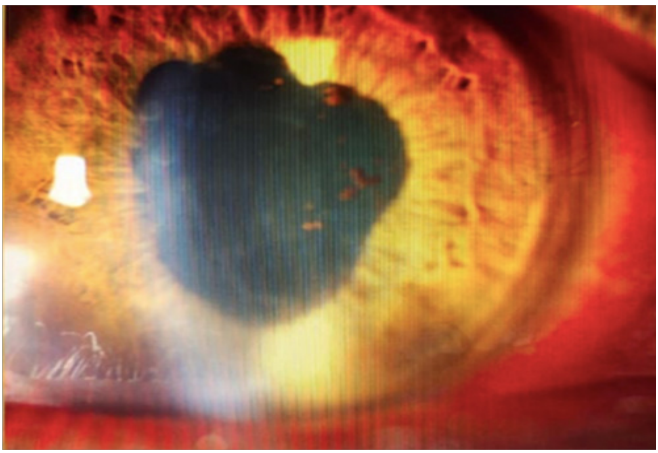
Immunologic

Infectious

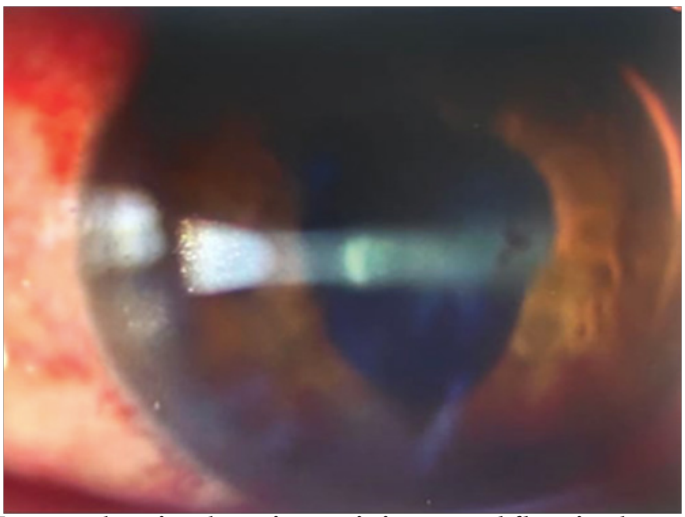
Masquerade

Association of uveitis with diabetes:

Diabetic eye problems are generally caused due to blood vessel and nerve damage that occur due to high sugar levels. Poor diabetes control is known to be a major cause for many diabetic eye diseases including conditions of the iris. Diabetic eye problems of the iris include iritis (anterior uveitis), iris transluminance, and rubeosisiridis. These conditions arise due to uncontrolled diabetes and chronic high blood sugar levels. A variety of conditions cause uveitis which can be a potentially blinding condition. While many cases are idiopathic, it is associated with a number of systemic diseases and infectious agents. It is the fifth commonest cause of blindness in the developed world. The incidence of diabetes mellitus (DM) is increasing rapidly in developed nations. link between diabetic autonomic neuropathy and uveitis has been suggested, and others have found a definite association between DM and uveitis.



a) Image: showing acute anterior uveitis in a diabetic patient



b) Image: showing keratic precipitates and flare in the same patient

Pathology:

A proposed mechanism for the relationship between DM and uveitis is the disruption of the blood-ocular barrier in diabetic patients in both the anterior segment as well as in the posterior segment leading to a higher degree of inflammation,

hence leading to an increased risk of developing acute anterior uveitis(AAU) in anterior segment. Several studies haveshowed that poor glycaemic control can result in a more severe ocular inflammation than good control in diabetic patients. Aqueous flare intensity has also been shown to be significantly elevated in patients with proliferative diabetic retinopathy compared with that in control or patients with non-proliferative retinopathy. Some studies have suggested that poor glycaemic control may be a trigger for recurrence of uveitis of all types as well.

Examination of iris specimens from eyes of patients with diabetes who have undergone iridectomy during cataract surgery has revealed the formation of gaps between the endothelial cells of the iris vessels. These findings suggest that severe disruption of the blood–ocular barrier occurs in conditions of more severe hyperglycaemia, which in turn likely promotes infiltration of inflammatory cells and leakage of protein from the iris vessels.

Interestingly It has also been found that diabetes treatment drugs suppress inflammation in endotoxin-induced uveitis. Kemmochi and colleagues have suggested that diabetes might be one of the contributing factors to the better inflammatory control of uveitis because drugs for diabetes improved carbohydrate metabolism and also decreased ocular inflammation.

Furthermore, Some studies have proposed that several antidiabetic drugs used in clinical practice for patients with diabetes exert anti-inflammatory effects partly as a result of reducing high blood glucose levels. Thus, it is possible that glucose-lowering therapy might also contribute to the reduction of ocular inflammation with anterior uveitis.Thus, it would be reasonable to consider good glycaemic control as an important factor in the prevention of recurrent inflammation. It has been found that uveitis cases associated with decompensated diabetes mellitus were always anterior and had a much worse inflammation compared with diabetes mellitus associated uveitis (DMAU) in patients with well-controlled diabetes.

Patients with DMAU with poorly regulated DM presented a more intense anterior chamber reaction, presence of hypopyon,

fibrin and posterior synechiae, and a worse diabetic retinopathy than patients with DMAU with well-controlled DM. Although all patients in the DMAU with poorly controlled DM usually respond well to topical or periocular steroids within weeks.

Whether the hyperglycemia by itself initiates the inflammation process by inducing ischemia, a break- down of the blood-ocular barrier or modifying the immune response, or makes a different underlying inflammation process worse, is difficult to assess. It is hypothesized that the uncontrolled diabetes by itself can drive inflammation through a seriesof mechanisms that induce a severe anterior chamber inflammation, and thus may be an independent cause of uveitis.

Blood ocular disruption is the main proposed mechanism in association of diabetes and uveitis, but several other hypotheses have been put forward as well. Rothova et al proposed an inflammatory process as they found the absence of retinopathy in more than half of the diabetic patients with uveitis, recurrent episodes, and a good response to local steroids.

Castagna et al found a significant increase in the CD8+ subset, with CD4 + T cells within normal limits, and a decrease in the CD4+/CD8 ratio in all patients with anterior uveitis and type 1 DM, which could be an expression of the unstable lymphocyte equilibrium. Along the same line, Guy et al found an association between iritis and severe symptomatic autonomic neuropathy, suggesting a common pathogenic mechanism where insulin antibodies may cross-react with nerve growth factor, which can accumulate in the iris upon sensory or sympathetic denervation. Finally, the blood-ocular barrier breakdown and/or ocular ischemia from pre-existing DM could be an additional pathogenic pathway.

Diagnosis of uveitis:

Iritis or anterior uveitis occurs more in people with type 1 diabetes and people with other diabetes complications like diabetic neuropathy and diabetic nephropathy. Anterior uveitis or iritis is a condition that causes inflammation of the iris. Though this condition is caused due to infectious diseases, it occurs more in

people with type 1 diabetes due to nonspecific causes.

In order to diagnose iritis or anterior uveitis, it is important to consider the clinical presentation of the patient. Tests to diagnose anterior uveitis include:

- Slit-lamp examination
- B-scan ultrasonography
- Fluorescein angiography
- Optical coherence tomography
- Ultrasound biomicroscopy

Treatment of uveitis:

If the uveitis is infectious, whether viral, bacterial or fungal, we treat with the appropriate antiviral, antibacterial or antifungal medication

Management of anterior uveitis:

Anterior uveitis can generally be managed by medical therapy and requires surgical intervention only if structural complications supervene and those can be either secondary glaucoma or secondary cataract. The general goals of medical management are:

- Relief of pain and photophobia
- Elimination of inflammation
- Prevention of structural complications such as synechiae, secondary cataract and glaucoma
- Preservation or restoration of good visual function.

However, one needs to remember the potential side-effects and long-term iatrogenic complications secondary to the use of steroid therapy. The risk-benefit ratio should be analyzed on a case-to-case basis.

Noninfectious anterior uveitis is treated using the following drugs:

A) Corticosteroids

Corticosteroids are the drug of choice in the treatment of uveitis. Steroids act by modifying and decreasing the inflammatory response in the eye. They act on both cycloxygenase pathways of inflammatory response and inhibit them. Various routes of administration are:topical,periocular and systemic.

Topical drops are the commonest and easiest method with the least side-effects , some topical corticosteroids are :

- Prednisolone acetate 0.125% and 1%
- Betamethasone 1%
- Dexamethasone sodium phosphate 0.1% (also available in 0.05% ointment form)
- Fluorometholone 0.1% and 0.25% (also available in 0.1% ointment form)
- Loteprednol

The choice of topical steroid should be based on the severity of uveitis; in cases with severe AC reaction topical steroid with strong potency such as prednisolone acetate should be preferred whereas in cases with mild anterior uveitis weak topical steroid such as betamethasone or dexamethasone can be applied. In steroid responders one should try and avoid steroid as far as possible and can use topical non-steroidal anti-inflammatory drugs (NSAIDs) like flurbiprofen.

Periocular injection is indicated where maximum concentration of the drug is required for a longer time with minimal side-effects. The drugs which can be considered for periocular injections are dexamethasone or triamcinolone acetonide. Posterior sub-tenon's injection is recommended in intermediate and posterior uveitis.

Systemic corticosteroids are indicated when the anterior uveitis is not responding to topical drugs alone or if the disease is recurrent and bilateral or if there is posterior segment involvement. The guidelines for oral corticosteroids therapy are:

- Use enough, soon enough, often enough, and long enough to secure the desired results.
- Start with high dose and taper according to the clinical response.
- Suppress inflammation till the pathogenic effect ends.
- The dose of steroid should be planned but in accordance to the response of the disease.

B) Mydriatics/cycloplegics:

These are given as supportive measures. They cause paresis of the iris and ciliary muscle and keep the pupils mobile thus preventing the formation of synechiae. These cycloplegic agents are cholinergic antagonists which work by blocking neurotransmission at the receptor site ofthe iris sphincter and ciliary muscle. They serve three purposes in the treatment of anterior uveitis:

- They relieve pain by immobilizing the iris
- They prevent adhesion of the iris to the anterior lens capsule (posterior synechia), which can lead to iris bombe and elevated IOP
- They stabilize the blood-aqueous barrier and help prevent further protein leakage (flare).

Cycloplegic agents useful in treating anterior uveitis are:

- Atropine, 0.5%, 1%, 2%
- Homatropine, 2%, 5%
- Cyclopentolate, 0.5%, 1%, 2%.

Phenylephrine, 2.5%. phenylephrine has neither a cycloplegic nor anti-inflammatory effect and may cause a release of pigment cells into the AC and it is generally not recommended as an initial part of the therapeutic regimen. Although it helps in breaking recalcitrant posterior synechia.

C) Non-steroidal anti-inflammatory drugs

These work by inhibition of arachidonic acid metabolism and include drugs such as indomethacin, flurbiprofen and diclofenac sodium. When used alone,however, their efficacy in treating acute intraocular inflammation has not been established.

D) Immunosuppressive agents

These are used mainly in corticosteroid-resistant cases or as steroid-sparing agents. The immunosuppressives commonly used are methotrexate or azathioprine. One needs to start immunosuppressive in conjunction with the internist.

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CHAPTER 6
NERVE PALSIES IN DIABETES

Neuro-ophthalmological manifestations are very common ocular pathologies in diabetics. The severity of these affections is variable, but they can lead to important visual function impairment. Oculomotor nerve palsy (ONP) raises less interest in literature than diabetic retinopathy which has become a public health problem in our country. The cause of neuropathy can be explained by metabolic alterations, inflammation or vascular occlusion producing the ischemic degeneration of the nerve, infarction or haemorrhage in the nucleus or in the path of the cranial nerve from its emergence to the orbit. ONP affects 0.4% to 14% of diabetics; it is seven to eight times commoner in people having diabetes than in non-diabetic ones. Other conditions such as blood hypertension, coronary artery disease, left ventricular hypertrophy, high hematocrit, are thought to promote ONP.

The VIth cranial nerve is also commonly involved. The IVth cranial nerve palsy is not common with an incidence of about six to 15%, despite its limited number of nervous fibres compared to the other oculomotor nerves (making it more susceptible to micro-vascular lesions).

Pathology:

ONP in diabetes is due to micro-angiopathy that results in nerves lesions by the mean of vasa nervosum occlusion and leads to mesenchymal and interstitial tissues necrosis particularly in the intra-cavernous portion. Anatomy and pathophysiology explain the rarity of multiple and bilateral forms. In fact, the three oculomotor nerves had a common blood supply at the cavernous sinus by internal carotid artery branches. Some authors explained the simultaneous nerve lesions by one of these branches occlusion; another physio-pathological hypothesis is ischemia of the posterior fossa.The bilateral involvement especially of the same nerve is even rarer . The possibility of two vasa nervosum infarction at the same time remains relatively

low. It is even rarer for ischemia to involve the identical vasa nervosum on both sides at the same time. An ischemic injury of the oculomotor nerves nuclei might be another explanation, in the absence of histological evidence. The diabetic origins of bilateral palsies remain an exclusion diagnosis, neurological exploration and MRI are compulsory and other differential diagnosis must be eliminated in these cases, such as: tuberculous or fungalmeningitis, syphilis, botulism, thyroid ophthalmopathy, multiple sclerosis, arteritis, insufficiency of the basilar artery, Wernicke encephalopathy or rarely a tumour.

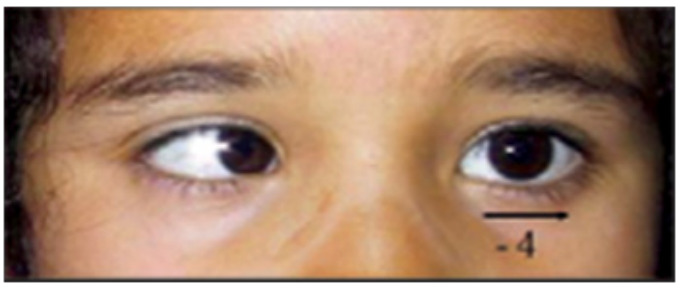

Image : showing left lateral rectus palsy

Image: showing oculomotor nerve palsy

Diagnosis:

Clinically, binocular diplopia is the main symptom; however, it can be unrecognized when the palsy is minimal. That is why, any headache in diabetics must evoke a sub-clinical occulomotor palsy suspicion, especially in the presence of unexplained visual disturbances.

Evaluation of light reflex may be contributory to diagnosis. In fact, pupillary involvement in diabetes-associated oculomotor nerve palsy occurs in about 1/4th of all cases. Certain characteristics help us to differentiate an ischemic insult from an aneurysmal injury to the IIIrd nerve such as an incomplete involvement and anisocoria < 2 mm. Patients with pupillary involvement usually have no diabetic retinopathy changes or less severe grades of diabetic retinopathy. Besides, ophthalmoplegia resolves much earlier than anisocoria in diabetic oculomotor nerve palsies.

Pupillary conditions that arise out of diabetes are mainly caused due to diabetic neuropathy of the autonomic nerves. This leads to diabetic autonomic neuropathy. Damage to the nerves and blood vessels of the eyes lead to disorders of the oculomotor nerves and lead to conditions like small pupil sizes and diabetic ophthalmoplegia.

When it comes to the diagnosis of pupillary conditions, the patient's past medical history, existing medical conditions, and a physical examination of the eyes are usually conducted. While the presence of smaller pupil sizes is clearly seen in a physical examination of the eyes, the responses of the pupil to light and darkness is tested by other tests including:

- Swinging Flashlight test
- Pupil dilation test
- Slit-lamp examination
- Pharmacologic pupil dilation/constriction test

By determining the size of the pupils, pupillary responses, and their dilation and constriction, pupillary conditions are evaluated and diagnosed.

Diagnosis of Diabetic Ophthalmoplegia

Diabetic ophthalmoplegia is a condition that arises when the oculomotor nerves are affected by diabetic autonomic neuropathy,which leads to weakness and paralysis of the eye muscles. This condition is also called as diabetic third nerve paralysis. Apart from conducting nerve function tests and

other pupil tests, the diagnosis of diabetic ophthalmoplegia is differential.

Tests include:

- Pupil dilation/constriction test
- Slit-lamp test
- Swinging flashlight test

Management:

Brain imaging is required to eliminate a tumoral, a vascular or an inflammatory cause. MRI is the mainstay of investigation.

ONP regresses spontaneously after three months in average. According to statistics seventy- three percent of patients cure within 6 months following the acute episode. A complete resolution might be obtained in 86% to 100% of cases.

ONP in diabetics are alternating and recurrent. The relapse does not obscure the prognosis and the average time of evolution is shorter than the first episode.

Mostly in these conditions spontaneous resolution occurs, so the clinical monitoring and an equilibrium of diabetes is the rule. The patient can be advised with an alternating occlusion or prism wearing, to control diplopia. Botulinum toxin has also been used successfully in some diabetics. The surgery is indicated from nine to 12 months of evolution in the absence of diplopia regression.

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