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.

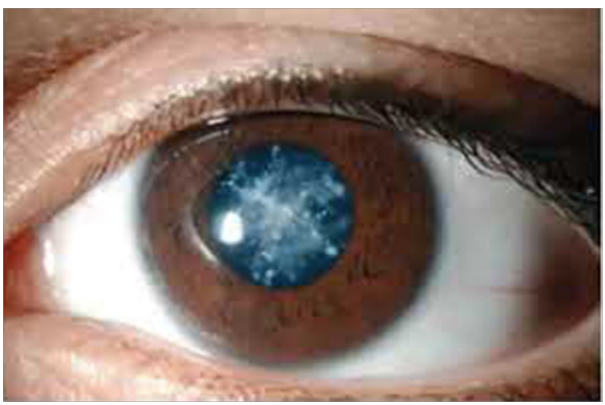

Image: showing SNOWFLAKE diabetic cataract

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