DRY EYE IN DIABETES

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DRY EYE SYNDROME - Recognised as a lacrimal function unit (LFU) dysfunction disease by the international dry eye workshop in 2007. LFU comprises of- cornea, conjunctiva, lacrimal gland, meibomian glands, lids and the neuronal connection between them. Diabetes mellitus has known ocular complications e.g diabetic retinopathy and cataract, but dry eye syndrome is also common in them.

DEWS [DRY EYE WORKSHOP] 2007 defined Dry Eyes as -

Dry eye is a multifactorial disease of the tears and ocular surface that results in symptoms of discomfort,visual disturbance,tear film instability with potential damage to ocular surface. It is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface.

MAGNITUDE OF PROBLEM

Diabetes is a global academic. According to international diabetes federation in 2016 the magnitude of problem is as follows

China – largest no. 98.4 million

India - 2nd no. -65.1 million

USA - 3rd no.- 24.4 million

Relationship in diabetes and dry eye is not yet established, but DES is known to occur more in diabetes than in non-diabetic, that too more in uncontrolled ones than in controlled ones. Prevalence of DES is 54% [both symptomatic and asymptomatic] in DM[1]. Incidence of DES is correlated with the level of HBA1C, higher the HBA1C-higher the incidence of DES[2]. Beaver Dam Eye Study revealed that approximately 20% of dry eyes occurred in individuals with Type 2 diabetes. Hom and De Land reported that 53% with diabetes or borderline diabetes had self-reported, clinically relevant dry eyes[3]. A hospital based study revealed significant associations between DR and DES[4]. Out of the patients of DMDES (Diabetes Mellitus Dry Eye Syndrome) - 17.1% had mild NPDR, 17.1% had moderate NPDR, 11.1% had severe NPDR and 25.1% had PDR. DR has been shown to be more prevalent in individuals with DR ±CSME group as compared to non-DR group[5].

ETIOLOGY OF DMDES

Hyperglycemia can affect any component of LFU, which in turn is reflected on entire lacrimal due to the neuronal connections – hence causing DE by various pathways[6]. Some of which are-

1. LFU dysfunction
2. Abnormal tear dynamics
   - Abnormal enzyme metabolism
   - Decreased mucin secretion
3. Diabetic neuropathy
4. Tear film dysfunction

LFU DYSFUNCTION – DM is a risk factor for corneal epithelial abnormalities. It causes epithelial barrier dysfunction which can result in superficial punctate keratitis, trophic ulcers, persistent epithelial defects and recurrent corneal erosions. Diabetes with HbA1C are more predisposed to impaired barrier function in corneal epithelium[7].

ABNORMAL ENZYME METABOLISM – High glucose levels in cells of lacrimal gland triggers the polyol pathway, causing activation of aldose reductase which in turn leads to accumulation of sorbitol within cells. It

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Hence resulting in decreased tear secretion

DECREASED MUCIN SECRETION – Corneal and conjunctival epithelial damage by the above mechanism leads to reduction of number of goblet cells, causing decrease in mucus production. Hence the hydrophillicity of the ocular surface is lost , and the tear film becomes unstable[8]

In humans mucosal and ocular surface are covered and protected by a high molecular weight,heavilyglycosyalted protein, which is secreted by goblet cells and exogenous glands. About 20 basic type of mucins have been identified throughout the human body, atleast 7-8 types are present in ocular surface

Tear mucin is secreted by conjunctival goblets cells and corneal epithelial cells and contributes to the mucous layer. It serves two purpose 1.protective function 2. Forms the glycocalyx that contributes to cell adhesion molds the tear film hydrophilic.

DIABETIC NEUROPATHY – hypoglycemia causes corneal epithelium barrier dysfunction and corneal neuropathy,hence the trophic changes are seen[9]. DES is common in patients with type 2 diabetes mellitus complicated with polyneuropathy. Impaired corneal neurons and reduced corneal sensitivity have been reported in diabetic patients with polyneuropathy. MyelinatedA delta and unmyelinated c fibres are the main neural components of human cornea.

TEAR FILM DYSFUNCTION

Tear lipid thickness [especially the lipid layer of the tear film],stability,corneal sensitivity and tear quantity were significantly decreased in patients with diabetes. Tear film stability was inversely associated with the total neuropathy score

PATHOGENESIS

1. Insulin is critical for proliferation of acinar lacrimal gland and cornea epithelial cells
2. High glucose level in diabetic patients leads to increased expression level of advanced glycolated end products modified proteins which may be used as biomarkers
3. Hyperglycemia initiates an inflammatory cascade that generates innate and adaptive immune response of LFU
4. Hyperglycemia causes tear film hyperosmolarity inducing hyperosmolarity of the ocular surface epithelial cells-stimulating a cascade of events that involve MAP-Kinase and NFKB signaling pathways
5. The expression of apoptosis related proteins has been reported to be increased

CLINICAL FEATURES

They are essentially the same as non-diabetic DES. Grittiness being the most common symptom, soreness, difficulty in vision, photophobia, itching and tearing are the other common symptoms. Signs e.g. decrease in Schirmer and TBUT values, decrease in corneal sensitivity, decrease in tear meniscus height, staining of the ocular surface etc.

WHY EARLY DIAGNOSIS IS CRUCIAL

1. Severe DMDES leads to ulcer- secondary bacterial infections- corneal scarring- visual impairment.
2. DM has a synergistic effect on keratitis.
3. It not only leads to occurrence of dry eye but simultaneously aggravates the ocular surface- causing a persistent epithelial defect.

METHODS OF DIAGNOSIS

These objective tests lack sufficient sensitivity and specificity, so they are not adequately reproducible. SYMPTOMS AND SIGNS ARE NOT ALWAYS DIRECTLY PROPORTIONAL TO THE RESULTS OF THESE TESTS. There is battery of investigations available for evaluating different aspects of tear function. We

diagnosis.

OSDI QUESTIONNAIRE-

It has a Likert design. It assesses frequency of ocular subjective symptoms [soreness, blurred vision], difficulty with vision related function [TV,visual display unit, driving,reading] and discomfort due to environmental triggers [low humidity, high wind].The patient answers 12 questions with higher scores representing greater disability .Score range: 0-12 no disability, 13-22 light dry eye, 23-32 moderate dry eye and 33-100 severe dry eye.

SCHIRMER TEST

It is invasive and indirect test. It measures changes in volume of tears in the tear reservoir. Schirmer 1 measures the total secretion whereas Schirmer 2 measures the basal secretion.Strip is folded at notch and placed at junction of middle and lateral third of eyelids and allowed there for 5 minutes with normal blinking. Values of less than 5 mm is abnormal, 6-10 mm is borderline whereas more than 10 mm is normal.

TFBUT

It assesses tear film stability. No anaesthesia is required. Apply a flourescein strip after moistening it with a drop of normal saline to the lower tarsal conjunctiva. The time lapse between the last blink to the appearance of the first random dry spot was taken.Less than 5 seconds is considered severe dry eye, whereas 6-10 seconds is moderate dry eye. More than 10 seconds is considered to be normal.

TEAR OSMOLARITY MEASUREMENT

It is assessed by freezing point depression technique, and has been proposed as the gold standard test for the diagnosis of DES. However it is technically difficult, costly, time consuming; and requires tear volume much higher than those collectable in several forms of DES. It can also induce excessive reflex tearing during tear sampling. Sample size of 0.1 µL is required.

TEAR MENISCUS HEIGHT MEASUREMENT (MENISCOMETRY)

It is used to diagnose aqueous tear deficiency. A rotatable projection system with a target comprising black and white stripes is projected onto the lower central tear film meniscus. Images are recorded and transferred to computer in order to calculate the radius of curvature. Several alternative methods have been proposed to achieve the same e.g. using a video slit lamp biomicroscope, measurement after instillation of fluorescein etc. Cut off is 0.18 mm (Farell et al 2003).

OTHER FACTORS WHICH MAY EFFECT THE RESULTS are social context, environmental conditions, race, ethnicity and season. Time of day, temperature, humidity, air speed and illumination are assumed to influence the results. So they should be kept constant at all follow ups.

PREVENTION AND TREATMENT

Tear film dysfunction increases the incidence of dry eye and also aggravates the ocular surface, which induces a corneal defect. Treatment protocol of dry eye whether diabetic or non-diabetic is essentially the same. Artificial tears are drug of choice for symptomatic relief of dry eye.

Anti-inflammatory drugs are required to stabilize the ocular vsurface and block the inflammatory cascade e.g corticosteroids, non steroidal anti- inflammatory drugs, cyclosporine A, tacrolimus, autologous blood serum etc. Lower concentration of milder steroids are recommended for shorter duration (1-2 weeks). It suppresses the cellular infiltration and increased synthesis of lipocortin[10]. But it also predisposes to infectious keratitis. Hence cautious use is advised.

Non – steroidal anti-inflammatory drugs are safer alternative e.g bromfenac. Immunomodulator e.g cyclosporine eye drops and tacrolimus ointment are also used. They increase tear production, suppress immune response and reduce damage to goblet cells by inflammation but they reduce the corneal sensitivity so usage in DMDES should be with precaution

Autologous blood serum eye drops containing immunoglobins, vitamin A, fibronectin, growth factors and anti-

inflammatory cytokines which are essential components present in natural tears[11]. 50% of autologous serum is very helpful in severe dry eye and persistent corneal epithelial defect. However it is non-preserved, so carry potential risk of infection.

Secretogogese: Rebamipide [quinolone derivative mucin secretogoge] and others are undergoing clinical trials. Gene therapies are undergoing research.

CONCLUSION

In addition to DR, increasing prevalence of DMDES, is of real concern. It predisposes to keratitis,persistent epithelial defects and also reduces the quality of vision in normal cornea. Hence ocular surface examination must be a compulsory part of diabetic ocular examination-whether he/she is symptomatic or not. Preservative free artificial tear and anti-inflammatory drugs are recommended to improve the hyperosmolar state of tear and decrease the local inflammatory reaction.

KEYWORDS

DR: Diabetic retinopathy

DES: Dry eye syndrome

DMDES: Diabetes mellitus associated dry eye syndrome

DM: Diabetes mellitus

LFU: Lacrimal function unit

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