

A Comprehensive Review about Risks of Type-II Diabetes on Ocular Tear Film

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Abstract:- Millions of people worldwide suffer from diabetes mellitus (DM), which can lead to systemic issues in a number of organs. Ocular problems, such as dry eye syndrome (DES), are among its less well-known side effects. This review delves into the interactions between diabetes and the composition of tear films, emphasizing alterations in the mucin, aqueous and lipid layer. Dry eye symptoms are exacerbated by induced changes in the components of the tear film in diabetes DM, which lead in decrement in tear production, increment in tear evaporation and tear film instability. Lipid layer is a lubricant, that reduces friction between the ocular surface and the eyelids which promotes high-quality, smooth refractive surface. The lacrimal function unit shields the tear film, preserves the normal function of the ocular surface. The mucin layer is secreted by the conjunctival goblet cells, in hyperglycemia the functionality of the cells are reduced thus, the mucin secretion is also altered which causes instability of the tear film. Diabetic patients can have their tear film integrity assessed with the help of diagnostic methods like Schirmer's Test and Tear Break-Up Time (TBUT). In order to relieve symptoms and maintain ocular health, there should be a complete management of diabetes and the induced tear film disorders.

Keywords:- Diabetes Mellitus (DM), Dry Eye Syndrome (DES), Dry Eye (DE) Tear Film (TF), Meibomian Gland Dysfunction (MGD), Lacrimal Function Unit (LFU).

I. INTRODUCTION TO DIABETES AND TEAR FILM COMPOSITION

About 100 million people worldwide (about 6% of the population) suffer with Diabetes Mellitus (DM), the most common endocrine disorder. It is caused by the pancreas' insufficiency produce enough insulin, which causes variations in blood glucose levels. It has been documented to cause damage to a number of biological systems, including the blood vessels, eyes, kidneys, heart, and nerves.[1] Diabetes mellitus can manifest in two different forms: Type I insulin-dependent diabetes (IDDM) and Type II non-insulin-dependent diabetes (NIDDM). Peripheral insulin intolerance and impaired insulin-secreting cells are the hallmarks of Type II diabetes, whereas

the autoimmune disease Type I diabetes results in an inflammatory response centered in and around islets, eventually preceded by the particular destruction of insulin-secreting cells.[2] Retinopathy and cataracts are two conditions of the eye that frequently coincide with diabetes and are among the leading causes of blindness in adults between the ages of 20 and 70. But lately, focus has been correlated to problem with the surface of the eyes, particularly dry eye in diabetics. Tear production can vary both quantitatively and qualitatively in diabetic keratoepitheliopathy, which can result in impaired corneal sensitivity and inadequate adhesion of regenerated epithelial cells. Most occurrences of dry eyes linked with diabetes are caused by inadequate tear production as a result of "autonomic neuropathy," which damages neurons controlling the lacrimal gland, as found in researches. [3] Several sources on the ocular surface, including the lacrimal gland, meibomian glands, accessory lacrimal glands, and goblet cells, release a complex mixture of constituents known as the tear film. The lipid, aqueous, and mucin layers are its three constituent layers. For the tear film to continue functioning unaffected, each layer is crucial. [4]

Several studies reported that individuals with diabetic mellitus, functioning and integrity of the ocular tear film are severely affected. The values of schirmers 1 and BUT with the correlation of severe symptoms of dry eye in type 2 diabetes. [5] Severe dry eye symptoms were associated with increase in diabetes duration and age.[6] The occurrence of Dry Eye Syndrome (DES) in diabetics over 65 years ranges from 15 to 33% and 50% females are more likely to develop DES than males.[7]

This review aims to study the ocular tear film changes association with type-II diabetes mellitus with duration and uncontrolled diabetes.

II. DIABETES INDUCED CHANGES IN TEAR FILM COMPONENT

A condition of the ocular tear film, dry eye damages the interpapillary ocular surface and is accompanied by a range of symptoms that indicate discomfort in the eyes. It arises from either insufficient or excessive tear evaporation.

Keratoconjunctivitis sicca (KCS) another name for dry eye syndrome is a frequent condition characterized by inflammation of the lacrimal glands and the ocular surface. [8] Andleeb A et al, conducted cross sectional study at Lahore which state that the individuals with diabetic mellitus (DM) have a major probability of dry eye disease, since their vulnerability of injuries and infections to corneal epithelial is greater. International Diabetic Federation states that more than half of individuals with diabetes suffer from dry eye. It may be caused by metabolic inefficiency, neuropathy or malfunctioning of tear glands. Diabetic patients are at high risk of developing corneal diseases. [9]

A. Lipid Layer Changes

The outermost lipid layer is composed of two layers: the outside non-polar lipid layer that interconnects with air and an inner polar lipid layer that forms a connection with the aqueous layer. The lipid layer of the tear film is secreted by meibomian glands which release meibum to form the lipid layer. It serves as a lubricant between the eyelid and the ocular surface to reduce friction and facilitates in the formation of a high-quality, smooth refractive surface. [10] The main function of this layer is to enhance the stability and to reduce the evaporation rate of the tears. [11] the most frequent cause of evaporative dry eye is MGD, which may also play a role in aqueous-deficient dry eye. The immortalized human meibomian gland epithelial cells (HMGECS) are stimulated by insulin, whereas elevated glucose levels were found to be toxic for HMGECS. Insulin resistance/deficiency and hyperglycemia which are toxic HMGECS, this states that DM may have association with MGD. [12]

B. Aqueous Layer Changes

Diabetes can cause damage to the lacrimal glands, which generate the aqueous component of tears, which can result in decreased tear production. Dry eyes may result from this decrease in tear production, which could be uncomfortable, causes redness in the eyes and appear grittiness [13] the cornea, conjunctiva, meibomian gland, lacrimal gland, and the neuronal network that joins to make up lacrimal function unit (LFU). It preserves the normal function of the ocular surface and shields three layers of the ocular TF. Blink irregularities, altered tear film composition, and decreased tear production could result from injury to any part of the LFU. Long-term hyperglycemia increases the probability of LFU malfunction in those who are affected. [14]

C. Mucin Layer

This layer is mainly composed of mucoglycoproteins.[15] In chronic hyperglycemia, the functionality and density of conjunctival goblet cells is decreased which secretes mucin.[16] The changes in mucin compositions and reduced secretion of mucin causes tear film

instability in diabetic patients.[17] Mucins, particularly membrane-associated mucins (such as MUC1, MUC4, and MUC16), create a glycocalyx on the corneal epithelial cells, which is essential for the adherence of the middle (aqueous layer), of the TF. A stable tear film is maintained by this and prevents desiccation of the cornea. [18]

III. MEIBOMIAN GLAND DYSFUNCTION

Yu T et al, states that the comparison of controlled and uncontrolled group of DM, laser scanning confocal microscopy (LSCM) demonstrated that the meibomian glands (MGs) had cytological alterations, which increased MG acinar unit enlargement and decreased MG acinar unit density.[19] Several surface alterations in the eyes are predisposed by type II diabetes. Sawy N et al conducted a prospective observational study in Egypt, in which patients with type 2 diabetes have more severe meibomian gland dysfunction (MGD) than people without the disease. To avoid more serious eye issues, it should be detected early and treated appropriately. As a result, the ocular surface needs to be closely observed, particularly in cases with long-term diabetes mellitus. [20]

IV. DIAGNOSTIC TECHNIQUES FOR ASSESSING TEAR FILM IN DIABETES

Here are some of the diagnostic tests for quantitative and qualitative analysis of the TF with dry eye in Type II DM patients.

A. Tear Break-Up Time (TBUT)

The fluorescein strips were used for TBUT assessment. Patient was instructed to look in down gaze; the strip was gently touched to the superior conjunctiva. The patients was instructed to blink first and after that keep the eyes open. The time calculated between the first and last dark spots appearance of pre-cornea tear film in seconds. The same procedure is repeated in another eye. The approximate value for dry eye is <10s. [21]

B. Sc

Schirmer's Test

The test is performed to assess the tear production in suspected cases of Keratoconjunctivitis sicca. It is used to diagnose the amount of tears in the eyes. The test is performed without anesthesia using schirmer stripes for basal and reflex tear secretion placed temporally at the lower lid edge for 5 minutes. Schirmer test by removal of the stimulus that initiate reflex tearing analyze basal tear secretions alone. During the test the patient can blink regularly. After five minutes the wetted schirmer strip was measured via millimeter scale. Schirmer strips or filter paper (Whatman Filter paper). [22]

Table 1. Shows Different Studies Association of Type-II Diabetes Mellitus on Ocular Tear Film.

S. No.	Studies	Result	Conclusion
1.	Naik K et al,[23]	OSDI Score 57 ± 19.22 TFMH $0.2 \pm 1.38\text{mm}$ ($P < 0.0001$) TBUT $8.92 \pm 1.32\text{s}$ ($P < 0.001$)	The incidence of dry eye was found to be higher in patients with uncontrolled Diabetes Mellitus for a longer duration
2.	Wu H et al, [24]	The DM group had a higher STI 54.14 ± 2.12 ($P < 0.001$) BUT $4.80 \pm 0.83\text{P}$ < 0.001	Meibomian gland dysfunction are early signs in type II diabetes mellitus for dry eye and are associated with HbA1c levels and duration of diabetes
3.	Abusharha A et al,[25]	The tear osmolality between the control and uncontrolled groups of diabetes mellitus difference was found to be not significant ($P = 0.06$). The OSDI score in diabetic group was higher (11.75 ± 5.98). There was no significant correlation between osmolality an OSDI score.	Changes in tear film characteristics in people with diabetes mellitus may be more closely linked to the duration of diabetes than its severity.
4.	Viswanathann et al,[26]	In the group with diabetic retinopathy, the mean Schirmer value was 10.84 ± 4.785 , the mean TBUT value was 7.73 ± 2.908 , and the mean KES value was 1.34 ± 0.745 . In the non-DR group, the mean Schirmer value was 12.84 ± 2.947 , the mean TBUT value was 10.43 ± 2.035 , and the mean KES value was 0.73 ± 0.726 .The Diabetic Retinopathy group had significantly worse Schirmers ($p=0.009$), TBUT ($p=0.001$), and KES ($p=0.001$).	There is a strong correlation between the grading of diabetic retinopathy and the signs and symptoms of dry eye, which have been reported to increase with the severity of the condition.
5.	Aggarwal M et al,[27]	Based on the Ocular Surface Disease Index, it was determined that 36% of diabetics had dry eye disease. 16%, 16%, and 4% of patients had mild, moderate, or severe dry eyes, respectively. TBUT had the highest diagnostic accuracy and extremely good agreement. There was good and moderate agreement between the Schirmers and Fluorescein tests, respectively.	Utilizing the Ocular Surface Disease Index, it was determined that 36% of diabetics had dry eye disease. In terms of dry eyes, 16% mild, 16% moderate, and 4% severe dry eye patients were found. Highest diagnostic accuracy and excellent agreement were demonstrated by TBUT. The agreement between the Schirmers and Fluorescein tests was good to moderate.

V. MANAGEMENT STRATEGIES FOR DIABETES-RELATED TEAR FILM COMPLICATIONS

Dry eye leads to several ocular symptoms and if left untreated may cause damage to the ocular surface. Hence it is very important to get a regular ocular examination for early detection of dry eye disease to avoid further ocular complications.[28] Tight blood glucose management is the first line of defense in controlling all forms of diabetes; in fact, hyperglycemia is the primary determinant of diabetic microvascular diseases.[29] Artificial tear lubricants keep the ocular surface hydrated and reduce dryness.[30] The pathophysiology of dry eye illness is significantly influenced by inflammation, particularly in those with diabetes. Corticosteroids and cyclosporine are examples of topical anti-inflammatory drugs that can help reduce inflammation and relieve discomfort.[31] Environmental pollution also contributes in symptoms of dry eye disease.[32] The environmental risk factors for type II diabetes are social environment, chemicals, air pollution, climate, nutrition, physical activity, smoking, alcohol, psychological health.[33] Dry eye symptoms may be reduced and ocular health may be supported by specific dietary changes and nutritional supplements. Fish oil supplements contain omega-3 fatty acids, which have anti-inflammatory characteristics and can help to those with dry -eyes. [34]

VI. CONCLUSION

In diabetes mellitus, particularly Type II, significantly impacts the ocular tear film, contributing to dry eye disease (DED). This condition, exacerbated by prolonged hyperglycemia and insulin resistance, alters the aqueous, lipid and mucin layers of the TF, leading to symptoms like discomfort, redness, and corneal sensitivity. Studies show a strong association with the duration of diabetes, severity in diabetic retinopathy, and the incidence of DE, with a higher prevalence in older patients and women. Early detection and management, including tight blood glucose control, use of artificial tears, anti-inflammatory treatments, and lifestyle modifications, are essential to mitigate the effects of DED and prevent further ocular complications in diabetic patients. Regular ocular examinations are crucial for early intervention and maintaining eye health in individuals with diabetes. The previous research has shown that diabetes affects the probity of the ocular surface and is associated with dry eye disease. Furthermore, diabetes has been linked to lower levels of circulating sex hormone in postmenopausal diabetic females, which may increase this condition. So further studies can be conducted regarding this for accurate findings.

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