**REVIEW ARTICLE**

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# Diabetes-Associated Dry Eye Syndrome: Clinical Features, Underlying Mechanisms and Treatment Options

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**Abstract**

Over the past 15 years, significant advancements have been made in understanding the ocular surface system and the lacrimal functional unit. Keratoconjunctivitis sicca, commonly known as dry eye syndrome (DES), is one of the most frequently observed ocular conditions, with diabetes mellitus recognized as a major contributing factor. Poor glycemic control adversely impacts both the anterior and posterior segments of the eye, and the prevalence of diabetes-associated DES (DMDES) has been on the rise in recent years. However, the exact pathogenesis and defining characteristics of DMDES remain unclear, and current interventions are largely adapted from general DES management. This review discusses the pathogenesis, clinical presentation, and available preventive and therapeutic approaches for diabetes-related DES.

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## Introduction

The International Diabetes Federation (IDF) reports that the global diabetes epidemic continues to rise. As per the IDF's 2013 data, China has the highest number of diabetics (98.4 million), surpassing India (65.1 million) and the USA (24.4 million) (1).

Although diabetic retinopathy (DR) and diabetic cataracts are well-recognized complications, dry eye syndrome (DES), also known as keratoconjunctivitis sicca, is equally prevalent among individuals with diabetes. Research indicates that 54% of diabetic patients experience both symptomatic and asymptomatic DES (2). Despite this high prevalence, the link between diabetes and DES remains poorly understood. This review focuses on the prevalence, underlying causes, and treatment options for diabetes-associated DES, highlighting the critical need for early diagnosis and timely interventions.

The Tear Film & Ocular Surface Society defines dry eye disease (DED) as a multifactorial condition caused by a loss of tear film homeostasis, with inflammation and neurosensory abnormalities potentially playing a role in its pathogenesis (3). Previous research has demonstrated abnormal tear dynamics in individuals

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with diabetes mellitus (DM), both in vitro and in vivo, with changes in tear osmolarity (4, 5). Alterations in enzyme metabolism and reduced mucin secretion are also believed to contribute to DM-related DED (6). Additionally, dysfunction of the lacrimal gland and lacrimal functional unit, often linked to diabetic neuropathy, plays a significant role in DM-associated DED (7). Combined with Meibomian gland dysfunction (8), these abnormalities lead to tear film instability due to decreased tear lipid quantity and quality, ultimately resulting in DED.

Diabetes-related ocular complications often necessitate surgical interventions. Chronic hyperglycemia has been associated with cataract formation (9), requiring cataract surgery for vision improvement. Diabetic retinopathy (DR) may also demand various treatments, including pan-retinal photocoagulation (PRP) (10), intravitreal injections (IVI) of anti-vascular endothelial growth factor or steroids (11), and trans-pars plana vitrectomy (TPPV) (12). These surgical procedures have been linked to DED, with studies reporting a 9–32% incidence of post-cataract DED (13). Evidence also suggests that IVI worsens ocular surface health (14), while TPPV and PRP contribute to symptoms and signs of DED, including reduced tear break-up time and Schirmer test values (15).

Several studies have explored the prevalence and risk factors of DED in patients with DM, with prevalence rates ranging from 15% to 54.3% (16). Risk factors include advanced age, female sex, smoking, higher glycated hemoglobin (HbA1c) levels, and diabetic retinopathy (17-19). However, findings on the roles of diabetic neuropathy and nephropathy have been inconsistent (20). The impact of antihyperglycemic medications on ocular surface disease remains unclear. This study aims to examine the factors associated with DED in a cohort of patients with DM, with a particular focus on the effects of antihyperglycemic treatments.

## Prevalence

Diabetes mellitus (DM) is recognized as a major systemic risk factor for dry eye syndrome (DES). Among diabetic individuals aged over 65, the prevalence of DES ranges from 15% to 33% and increases with age. Additionally, DES is 50% more prevalent in women compared to men. The incidence of dry eye has been shown to correlate with glycated hemoglobin levels, with higher levels being associated with a greater likelihood of developing dry eye (21, 22).

The Beaver Dam Eye Study found that approximately 20% of individuals with Type 2 diabetes, aged between 43 and 86 years, experienced dry eye. Similarly, Hom and De Land reported that 53% of patients with diabetes or borderline diabetes self-reported clinically significant dry eye symptoms (23). Furthermore, a hospital-based study revealed that 54% of individuals with diabetes had DES, with a significant correlation between the presence of DES and the duration of diabetes. These findings underscore the importance of including dry eye assessments as a routine component of ocular examinations in diabetic patients (2).

## Etiology

Diabetes mellitus-associated dry eye syndrome (DMDES) is caused by a complex interplay of systemic and local factors that disrupt the ocular surface and tear film homeostasis. One key mechanism is tear film instability, which arises from hyperosmolarity caused by diabetes, leading to increased evaporation and instability (24). Reduced tear production, often due to lacrimal gland dysfunction caused by diabetic neuropathy, further exacerbates this instability. Additionally, Meibomian gland dysfunction (MGD) impairs lipid secretion, reducing the tear film's stability and promoting evaporation.

Lacrimal functional unit dysfunction also plays a significant role in DMDES. Diabetic neuropathy affects the innervation of the lacrimal gland and other components of this unit, impairing tear production and reflex secretion (25, 26). Chronic low-grade inflammation, commonly associated with diabetes, contributes to damage and reduced function of the lacrimal gland. Another contributing factor is altered mucin secretion, as diabetes affects the goblet cells of the conjunctiva, reducing mucin production, which is vital for maintaining tear film adhesion and ocular surface health (6).

The tear film is a crucial and dynamic component of the lacrimal function unit (LFU), essential for regulating epithelial function and interacting with surrounding tissues (27). Dysfunction of the tear film is strongly linked to dry eye syndrome (DES). In diabetic patients, both chronic tear secretion deficiency and tear film dysfunction have been observed (28). In these patients, there is a significant reduction in tear lipid thickness (particularly the lipid layer), tear stability, corneal sensitivity, and tear production. Additionally, tear film stability has been found to be negatively correlated with the total neuropathy score (29).

## Pathogenesis and clinical characteristics

Diabetes mellitus-associated dry eye syndrome (DMDES) is influenced by factors such as chronic hyperglycemia, diabetic peripheral neuropathy, decreased insulin levels, microvasculopathy, and systemic hyperosmotic disturbances. These contribute to dysfunction of the lacrimal function unit (LFU) and tear film, leading to abnormal tear dynamics. Insulin

plays a vital role in supporting the proliferation of lacrimal gland cells and corneal epithelial cells, with insulin replacement therapy helping to reverse some of the dysfunction caused by diabetes (30). Hyperglycemia causes histological changes in the lacrimal gland and induces oxidative stress, which may worsen dry eye symptoms (31). Elevated glucose levels in diabetic tears increase the expression of advanced glycation end-product (AGE)-modified proteins, which could serve as biomarkers for diagnosing diabetes and diabetic retinopathy (32, 33).

Inflammation is a key factor in the development of DMDES, with hyperglycemia triggering an inflammatory cascade. This cascade involves immune responses and several immune-inflammatory regulators, including matrix metalloproteinase-9 (MMP-9), CD4+ T-helper cells, and various cytokines such as interleukin-1 and tumor necrosis factor-α (24, 34). Additionally, proteins involved in LFU dysfunction, such as ALS2CL and ARHGEF19, have been identified in diabetic patients, suggesting that further investigation into their roles is needed (35, 36).

Clinically, DMDES presents with symptoms like gritty sensation, sore eyes, decreased visual acuity, photophobia, and abnormal test results (e.g., TUBUT, Schirmer's test, corneal staining). More severe cases may lead to corneal lesions, conjunctivitis, and keratopathy. Symptoms are typically more severe in patients with poorly controlled diabetes (2, 37). Longer diabetes duration may reduce symptom reporting, possibly due to diminished corneal sensitivity from diabetic neuropathy (38). Routine clinical tests like BUT and the Schirmer test are recommended for diagnosis and early intervention to prevent visual impairment.

**Prevention and Treatment Regimens**

Severe diabetic dry eye syndrome (DMDES) can lead to visual impairment, corneal scarring, ulcers, and secondary bacterial infections. The combined effect of corneal infection and diabetes accelerates corneal lesions, which cause irreversible damage to the ocular surface, resulting in visual impairment (39). Tear film dysfunction not only contributes to dry eye but also worsens the condition of the ocular surface, leading to corneal epithelial defects, which are common in diabetics (40).

Early diagnosis and treatment of dry eye are crucial to prevent complications. Current treatments for diabetic and non-diabetic dry eye patients are generally similar, but no universal treatment for dry eye syndrome (DES) exists. Artificial tears, which include surfactants and various viscous agents, are primarily used to alleviate symptoms. While artificial tears provide temporary relief from blurred vision and other symptoms, they lack the active components, such as growth factors, found in natural human tears (41).

The most common anti-inflammatory drugs include corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclosporin A, tacrolimus, autologous blood serum, and several others in clinical trials (42). Patients with DMDES experience corneal epithelial defects and side effects from topical treatments more frequently than those with DES without diabetes, necessitating regular follow-up during treatment. Devices are also being developed to alleviate symptoms (43).

Topical corticosteroids help reduce symptoms and inflammation in dry eyes, preventing corneal epithelial damage. They improve the ocular surface disease index score and dendritic cell density (44). Corticosteroids may work by suppressing cellular infiltration and increasing lipocortin synthesis, which blocks the inflammatory cascade (45). However, side effects such as bacterial and fungal infections, increased intraocular pressure, and cataracts are possible. For patients with DMDES, it is recommended to use lower steroid concentrations for short periods.

To avoid the side effects of corticosteroids, NSAIDs are more commonly used in clinical practice (46). Drugs like pranoprofen, bromfenac sodium hydrate, and RESTASIS® (which contains cyclosporine) increase tear production, suppress immune responses, and reduce inflammation-induced damage to goblet cells. While these drugs relieve symptoms of aqueous-deficient dry eye and promote corneal epithelial recovery, they do not enhance tear production and may reduce corneal sensitivity, leading to potential corneal epithelium damage. Therefore, they should be used cautiously in diabetic patients.

Tacrolimus, which has a stronger anti-inflammatory effect than cyclosporin A, suppresses inflammation by inhibiting the expression of cytokines and chemokines (47). Autologous blood serum eye drops, which contain essential components like immunoglobulins, vitamin A, fibronectin, and growth factors, have been shown to be effective in treating severe dry eye resistant to other treatments (48). These drops are also beneficial for persistent corneal epithelial defects. However, since autologous serum tears lack preservatives, they carry a risk of secondary infections, so caution is needed, particularly for DMDES patients.

Several other drugs are undergoing clinical trials, including chemokine receptor antagonists, tofacitinib, LFA-1 antagonists, rebamipide, and others (49). Gene therapies targeting the lacrimal gland have shown promise in animal models of dry eye, and further research is needed to develop targeted treatments for diabetic dry eye (50).

In clinical practice, regular fundus examinations are

standard for diabetic patients, and it is suggested that ocular surface and tear function assessments become routine for diabetic eye care. Preservative-free artificial tears and anti-inflammatory drugs are recommended to improve the hyperosmolar state of tears and reduce local inflammation. Protecting the cornea and preventing DMDES should be considered in patients with poor glycemic control or islet dysfunction.

In conclusion, DMDES prevalence has risen in recent years, and it is an important complication of diabetes, often overshadowed by diabetic retinopathy. While the pathogenesis of DMDES remains unclear, more research and clinical trials are needed to better understand the condition and assess the effectiveness of current treatments. As biomedical research progresses, new drugs and gene or stem cell therapies with specific targets for treating DMDES in diabetes are likely to emerge.

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