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# Dry eye disease and GLP-1 receptor agonists – current state of knowledge and emerging therapeutic perspectives

**Marzena Jargiło[1], Julia Kucza[2], Ewa Mrukwa-Kominek[3,4]**

[1] Student Research Club, Chair and Clinical Department of Ophthalmology, Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland
[2] Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice, Poland (student)
[3] Chair and Clinical Department of Ophthalmology, Faculty of Medical Sciences, Medical University of Silesia in Katowice, Poland
[4] Department of Adult Ophthalmology, Kornel Gibiński University Clinical Center, Medical University of Silesia in Katowice, Poland

**Summary:** Dry eye disease is a multifactorial disorder of tear-film homeostasis whose prevalence is steadily increasing, particularly among patients with diabetes mellitus. However, the impact of GLP-1 receptor agonists (GLP-1 RAs), widely used in the management of diabetes mellitus, on the ocular surface remains incompletely understood. The aim of this study is to analyze the influence of GLP-1 RA therapy on the development and course of dry eye disease based on the currently available literature. Diabetes mellitus promotes the development of dry eye disease through oxidative stress, inflammation, and neuropathy. The pleiotropic effects of GLP-1 RAs, including anti-inflammatory and antioxidant activity, may potentially improve lacrimal gland function. Current clinical data indicate improvements in tear-film parameters and a protective effect on the ocular surface. GLP-1 RAs may therefore represent a therapeutic option for diabetic patients with coexisting dry eye disease. However, further studies are needed to clarify their mechanisms of action and confirm their clinical efficacy.

**Key words:** dry eye disease (DED), GLP-1 receptor agonists, diabetes mellitus (DM), ocular surface, inflammation, semaglutide, liraglutide, dulaglutide.

## Introduction

Dry eye disease (DED) is an increasingly common ophthalmic condition with a complex pathophysiology. It is characterized by disruption of tear film homeostasis and associated ocular disturbances. Among the numerous risk factors, diabetes mellitus (DM) plays a significant role. Inflammation, oxidative stress, and neuropathy present in patients with diabetes may contribute to the development of DED and to its more severe course. One of the currently used therapeutic approaches in the treatment of DM involves glucagon-like peptide-1 receptor agonists (GLP-1 RAs). In addition to lowering blood glucose levels, these agents exhibit numerous pleiotropic effects, including anti-inflammatory and neuroprotective activity. Although the influence of GLP-1 RAs on DED has been well documented, it remains incompletely understood. Recent reports, however, suggest their protective effect on the ocular surface.

## Dry eye disease

Dry eye disease is a multifactorial disorder resulting from tear-film imbalance [1]. It is one of the most common ophthalmic conditions, affecting an increasing number of patients [2, 3]. Because of its chronic nature, it requires ongoing therapy to maintain ocular-surface homeostasis [4].

Defined by the International Dry Eye Workshop in 2017 and reaffirmed in 2025, DED is characterized as follows: "Dry eye is a multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, and accompanied by ocular symptoms, in which tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiologic roles" [5, 6].

Based on etiology, DED is classified into two types: aqueous-deficient dry eye (ADDE), characterized by reduced tear production, and evaporative dry eye (EDE), caused by increased tear film evaporation [2, 3, 5, 7–9].

Symptoms are identical in both types of DED, with patients reporting mild-to-severe discomfort, irritation, burning, and eye fatigue. Patients may also experience eye pain, grittiness, a foreign body sensation, or itching. Over time, photophobia may develop, along with corneal complications such as keratitis, epitheliopathy, ulceration, or even perforation, which can ultimately lead to vision loss [2, 3, 5, 7, 10].

The diagnosis of DED requires the presence of characteristic clinical symptoms. Initial visual acuity assessment may reveal distorted vision, presenting as continuous or intermittent blurring. Subsequently, the quantity of secreted tear film must be measured using the Schirmer test. Slit-lamp examination enables the visualization of ocular surface damage and, following staining, the determination of tear break-up time (TBUT). In DED, TBUT is shortened to less than 10 seconds. A typical pattern of corneal epithelial defects in the course of DED, visualized after fluorescein staining, is presented in Figure 1. Additional tests, such as LipiView and the Oculus Keratograph, are used to quantitatively evaluate the thickness of the tear film lipid layer [11].

The primary objective of managing and treating DED is to restore tear film homeostasis [11]. Treatment encompasses both pharmacological and non-pharmacological interventions. Pharmacological options include topical preparations, such as lubricating "artificial tears," corticosteroids, anti-inflammatory agents, and immunomodulators (e.g., cyclosporine A). Systemic treatment is also available, including antibiotics (azithromycin, tetracyclines, and their derivatives), as well as supplementation with omega-3 polyunsaturated fatty acids and antioxidants [4, 10, 12]. Non-pharmacological methods involve lifestyle modifications and device-based therapies (such as eyelid hygiene devices, neuro-

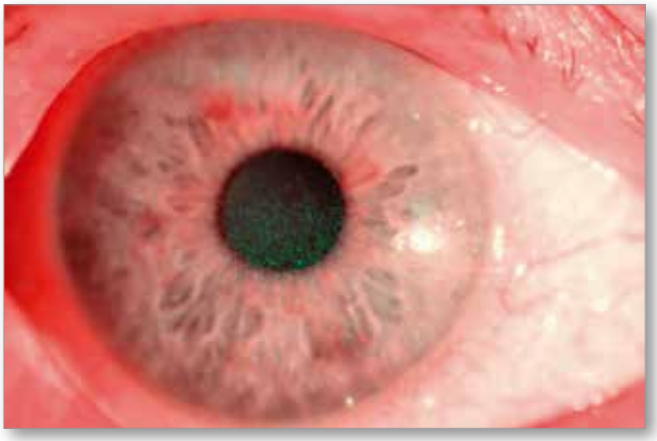

**Fig. 1.** Fluorescein-stained punctate epithelial erosions of the cornea (under cobalt blue illumination), characteristic of dry eye disease.

stimulation, thermal or moisture chamber goggles, and warm compresses), as well as punctal occlusion procedures, thermal pulsation, intense pulsed light (IPL) therapy, and low-level light therapy (LLLT) [6, 11].

While numerous treatments for DED are available, they frequently prove insufficient, driving significant interest in novel therapeutic methods.

## Diabetes mellitus and dry eye disease

Diabetes mellitus is a prevalent chronic metabolic disorder characterized by hyperglycemia resulting from insulin deficiency, impaired insulin action, or both. The classification of DM primarily distinguishes between type 1 diabetes (T1D), which has an autoimmune etiology, and type 2 diabetes (T2D), which is driven by insulin resistance [13]. DM is associated with numerous pathological processes, many of which contribute to the development of DED.

Sustained hyperglycemia in patients with poorly controlled diabetes induces chronic inflammation and increases the expression of pro-inflammatory cytokines. This inflammatory response can damage ocular surface cells, leading to increased tear film osmolarity and reduced mucin secretion [13–15].

Concurrently, oxidative stress further contributes to meibomian gland (MG) dysfunction by disrupting lipid metabolism, increasing tear evaporation, and impairing cell differentiation. These dysfunctions subsequently disrupt tear film homeostasis [15, 16]. Progression of MG dysfunction ultimately leads to gland dropout in both the upper and lower eyelids. The resulting alterations in meibum composition increase its viscosity and induce inflammation, thereby triggering a vicious cycle [17].

Furthermore, patients with T2D exhibit more severe lid margin abnormalities and a higher frequency of gland orifice plugging compared to patients diagnosed with DED who do not have coexisting diabetes [15].

Another DM-related process that contributes to DED is peripheral and autonomic neuropathy. This neurodegeneration results in a decreased blink rate, excessive tear film evaporation, and a reduction in corneal nerve fiber length [13, 18–20]. Patients with diabetic neuropathy demonstrate lower TBUT scores and a significantly higher risk of developing severe forms of DED [13].

Diabetic patients frequently experience other ophthalmic complications, such as cataracts, glaucoma, and diabetic retinopathy, the treatments for which can also contribute to the development of DED. Current research indicates that interventions undertaken to manage these conditions increase the risk of DED and reduce treatment efficacy. Panretinal photocoagulation (PRP), trans pars plana vitrectomy (TPPV), and intravitreal injections (IVIs), as well as the use of associated pharmacological agents, can lead to a deterioration of the ocular surface state, shortened TBUT, and poorer Schirmer test scores [21, 22].

## GLP-1 RAs

Glucagon-like peptide-1 (GLP-1) is a multifunctional insulinotropic hormone produced primarily by enteroendocrine L cells in the epithelium of the distal ileum [23, 24]. It exhibits numerous short- and long-term pleiotropic effects [25].

Peripheral GLP-1 secretion is stimulated by carbohydrates, proteins, amino acids, and lipids present in the lumen of the small intestine. Released in the gut, it acts on receptors within the vagus nerve and, via the activation of preproglucagon neurons, stimulates central GLP-1 release in the brain [23, 26]. Secretion is also stimulated by neurotransmitters such as acetylcholine and GRP, olfactory receptor activation by nonanoic acid, ghrelin, as well as cholinergic and β-adrenergic stimulation. Conversely, atropine and the activation of α-adrenergic receptors by norepinephrine inhibit this process [23].

GLP-1 exerts numerous metabolic activities, including glucose-dependent insulin secretion, inhibition of gastric emptying, cardioprotective and nephroprotective effects, and reduction of inflammation [23].

GLP-1 influences insulin secretion through several molecular pathways, including cyclic adenosine monophosphate (cAMP) production, voltage-gated calcium channels, and proinsulin granule recruitment [27]. Activation of GLP-1 receptors located on pancreatic β-cells leads to the production of cAMP. The resulting increase in cAMP concentration activates protein kinase A (PKA) and exchange protein directly activated by cAMP (Epac). Both cAMP effectors participate in GLP-1-induced insulin secretion by enhancing glucose-dependent insulin release [27–29]. Protein kinase A, through phosphorylation of the SUR1 subunits of K+ATP channels in pancreatic β-cells, causes channel closure and depolarization – the first stage of glucose-induced insulin secretion. Activation of Epac leads to a reduction in ATP concentration, which also results in closure of K+ATP channels [29].

Activation of both PKA and Epac also affects the second phase of insulin secretion – the recruitment and replenishment of insulin-carrying vesicles. They expand the vesicle pool, accelerate the replenishment of the readily releasable vesicle pool, and increase its overall size [29].

Another molecular pathway involved in insulin secretion is the influx of Ca2+ into pancreatic β-cells, leading to depolarization and subsequent initiation of insulin vesicle exocytosis, as well as increased release of calcium ions from the endoplasmic reticulum. An increase in intracellular Ca2+ concentration enhances ATP synthesis, thereby sustaining insulin secretion. Through activation of PKA and Epac, GLP-1R increases the sensitivity of IP3 and ryanodine receptors (RyR), which regulate these processes. GLP-1 acts on L-type calcium channels, thereby increasing the intracellular concentration of calcium ions [29, 30].

Calcium ions are also essential for the preparation of transport vesicles for exocytosis. This process is supported by Epac, which induces their acidification [29].

The effect of GLP-1 on glucose-dependent insulin secretion forms the basis of its pharmacological use in DM management. Currently, glucagon-like peptide-1 receptor agonists, resistant to degradation by DPP-4 and administered predominantly by injection, are used. The principal agents in this class include semaglutide, liraglutide, and dulaglutide [31].

Semaglutide is a novel GLP-1 RA used in the treatment of T2D in both subcutaneous injectable and oral forms. By binding to specific receptors on pancreatic β cells, it enhances postprandial insulin release and inhibits glucagon secretion. It reduces glucose and HbA1c levels and also exhibits numerous pleiotropic effects,

such as reducing inflammation, inducing satiety, and decreasing appetite, thereby contributing to weight loss [32, 33].

Liraglutide is an acylated GLP-1 RA that binds to albumin after administration. The process prolongs its duration of action. In patients with T2D, it increases postprandial insulin secretion during both the first and second phases [34]. In addition to its hypoglycemic effect, it promotes weight loss by stimulating anorexigenic proopiomelanocortin (POMC) neurons, which are responsible for receiving signals from adipotoxic and satiety factors in the circulation, and by inhibiting neuropeptide Y [35–37].

Dulaglutide is a GLP-1 RA approved for use as an adjunct to diet and physical activity in patients with T2D and is administered subcutaneously. It is characterized by a sustained hypoglycemic effect and prevention of cardiovascular events. Its efficacy has been demonstrated both as monotherapy and in combination with oral antidiabetic agents [38].

The described GLP-1 RAs differ in both efficacy and adverse-effect profiles. Semaglutide yields the greatest reduction in HbA1c levels; however, no significant differences have been observed regarding fasting glycemia, body weight, or BMI. The use of dulaglutide is associated with a lower risk of gastrointestinal adverse effects, such as cholelithiasis or cholecystitis. The use of semaglutide, regardless of the route of administration, may be associated with a higher incidence of diarrhea and nausea [32, 38, 39].

## GLP-1 RAs and dry eye disease

### General mechanisms and hypotheses

It is believed that GLP-1 RAs, by lowering glucose levels and exerting anti-inflammatory effects, may protect against the development of DED and the worsening of its symptoms [14]. Drugs such as dulaglutide and semaglutide also exhibit anti-inflammatory properties and modulate tear secretion [40]. Although the relationship between MG dysfunction and GLP-1 RAs has not yet been studied, hypotheses exist suggesting that agonists alleviate this disorder, which in turn is a common risk factor for DED [41].

### Molecular mechanisms and preclinical studies

A novel study published in 2025 demonstrated that lacrimal gland tissue expresses the GLP-1 receptor, shedding new light on the potential for local application of these agents. In a murine model, topical administration of liraglutide eye drops increased tear secretion. Inhibition of lacrimal gland fibrosis and suppression of the DM-induced inflammatory response within the lacrimal gland were also demonstrated. An important aspect of this study was the finding that liraglutide alleviated oxidative damage to the lacrimal gland induced by high glucose concentrations. Local activation of the GLP-1 receptor combined with antioxidant activity increased tear production; this process could not be attributed either to the systemic action of the drug or solely to regulation of blood glucose levels.

In addition, the authors highlighted the role of autophagy, demonstrating reversal of autophagic blockade within the lacrimal gland, suggesting that this drug may restore normal autophagosome degradation and reduce abnormal accumulation of autophagy substrates in the gland responsible for tear production [42].

Furthermore, systemic administration of GLP-1 RAs may produce adverse effects that could potentially be avoided with topical eye-drop formulations [43].

Additionally, a study evaluating MAP kinase phosphorylation using the Western blot technique in a murine model demonstrated that the GLP-1 RA SM102 (a G protein-biased agonist) reduced oxidative stress by decreasing phosphorylation of intermediate pathway products. As a result, tear production increased and TBUT improved. The authors suggested that this agonist represents a strong candidate for the treatment of DM-associated DED [44].

### Clinical evidence and retrospective analyses in patients

Empirical studies have demonstrated a protective effect against DED in patients with DM treated with GLP-1 RAs [45–47].

Analyses of clinical parameters support this association. Use of GLP-1 RAs in patients with T2D was associated with improved ocular surface parameters, including increased tear film stability and enhanced tear production. In these studies, TBUT was significantly prolonged and Schirmer I test values were higher. Compared with studies involving other therapies for T2D, GLP-1 RAs yielded more favorable outcomes. This suggests that GLP-1 RAs may exert a protective effect on the ocular surface through potential anti-inflammatory or neurovascular mechanisms [16, 48].

It is worth noting that these benefits may depend on patient age. This was demonstrated in a retrospective cohort study involving patients with T2D treated with exenatide or liraglutide, which showed a lower incidence of DED and a more pronounced reduction in patients younger than 60 years receiving GLP-1 RAs [45].

### Therapeutic perspectives in comparison with other treatment modalities

Due to its anti-inflammatory properties, semaglutide significantly reduces the incidence of DED, as confirmed by com-

| Author/year | Study type | Key findings | Mechanism of action |
|---|---|---|---|
| Sun et al., 2025 [42] | preclinical | increased tear secretion after topical administration of liraglutide; decrease in lacrimal gland fibrosis | activation of the GLP-1R; restoration of normal autophagy and autophagosome degradation |
| Hao et al., 2022 [44] | preclinical | increased tear production; improved tear film stability (TBUT) | reduction of oxidative stress by inhibiting phosphorylation in the MAP kinase pathway |
| Zuo et al., 2026 [52] | preclinical | restoration of the function and structural integrity of the lacrimal gland | reduction of oxidative stress in aging cells and inhibition of fibroblast-induced fibrosis |
| Fan et al., 2023 [45] | clinical | decrease in the incidence of DED; effect is particularly significant in patients under 60 years of age. | ocular surface protection dependent on the patient's age and metabolic profile |
| Ottonelli et al., 2025 [16] | clinical | improvement of ocular surface parameters: prolonged TBUT and higher Schirmer I test scores | potential neurovascular mechanisms or direct modulation of tear secretion and anti-inflammatory action |
| Huang et al., 2025 [49] | clinical | significant reduction in the incidence of DED in patients using semaglutide compared to other obesity therapies | use of the systemic anti-inflammatory properties of semaglutide to protect the ocular surface |

**Tab. I.** Summary of studies evaluating the therapeutic potential of GLP-1 agonists in the treatment of dry eye disease.

parative studies with other therapies used in the treatment of obesity, including phentermine, topiramate, naltrexone, and bupropion [49, 50]. Particularly promising are the data regarding long-term semaglutide use in the context of age-related changes.

This drug has been shown to restore lacrimal gland function and structural integrity through reduction of oxidative stress in aging cells and inhibition of fibroblast-induced fibrosis [51]. It should be emphasized, however, that clinical findings remain inconsistent. A retrospective study from Taiwan reported a lower risk of DED among patients treated with SGLT2 inhibitors compared with GLP-1 RAs, a result that contrasts with several earlier reports [16, 48, 49–52].

**Disclosure**
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**Reprint requests to:**
Marzena Jargiło (e-mail: s85787@365.sum.edu.pl)
Student Research Club, Chair and Clinical Department of Ophthalmology,
Faculty of Medical Sciences in Katowice, Medical University of Silesia in Katowice
Ceglana 35, 40-514 Katowice