

Evaluating the Efficacy of Topical Insulin Compared with Preservative-Free Artificial Tears in Ocular Surface Restoration among Patients with Dry Eye Disease: A Randomized Controlled Trial

PJO – Official Journal of
Ophthalmological Society of Pakistan



This work is licensed under a Creative Commons Attribution-Non-Commercial 4.0 International License.

Shafiq Tanveer¹, Rasheed Ul Haq², Andaleeb Rabbi³, Nazli Gul⁴,
Imran Ahmad⁵

¹⁻⁵Department of Ophthalmology, Khyber Teaching Hospital, Peshawar

ABSTRACT

Purpose: To evaluate the efficacy of topical insulin (1 U/mL) compared with preservative-free artificial tears in improving ocular surface parameters in patients with Dry Eye Disease (DED).

Study Design: Randomized Controlled Trial.

Place and Duration of Study: Department of Ophthalmology, Khyber Teaching Hospital, from Peshawar from 14 April 2025 to 25 April 2026.

Methods: A total of 128 patients were enrolled in a prospective, randomized, participant-masked controlled trial. Patients meeting standardized DED criteria i.e., Schirmer test <10 mm, tear break-up time (TBUT) <10 seconds, ocular surface disease index (OSDI >20) were randomized 1:1 to topical insulin group (IDG) or carboxymethyl cellulose 0.5% artificial tears group (ATG), four times daily for 12 weeks. Primary outcome was the proportion achieving OSDI ≤20. Secondary outcomes were Schirmer test and TBUT. Repeated measures ANOVA and intention-to-treat analysis were performed.

Results: At 12 weeks, 89.06% of IDG patients achieved OSDI ≤20 versus 40.63% in the ATG (RR: 2.19, OR: 11.90). Schirmer test improvement was significantly greater in the IDG (4.75 ± 1.64 mm vs. 2.41 ± 1.24 mm), as was TBUT (4.34 ± 1.88 vs. 2.73 ± 2.28 seconds;). The insulin advantage was most pronounced in females, patients under 40, those with diabetes, and those with severe baseline OSDI >32. No major adverse effects were reported.

Conclusion: Topical insulin (1 U/mL) is significantly superior to artificial tears in improving tear production, tear film stability, and symptom burden in DED. These findings make it a cost-effective suitable option for DED in lower-middle income countries.

Keywords: Ocular Surface, Schirmer Test, Randomized Controlled Trial, Dry Eye Syndromes, Insulin.

How to Cite this Article: Tanveer S, Haq RU, Rabbi A, Gul N, Ahmad I. Evaluating the Efficacy of Topical Insulin Compared with Preservative-Free Artificial Tears in Ocular Surface Restoration among Patients with Dry Eye Disease: A Randomized Controlled Trial. 2026; 42(4):400-407. **Doi:10.36351/pjo.v42i4.2443**

Correspondence: Nazli Gul
Department of Ophthalmology, Khyber Teaching Hospital,
Peshawar
Email: drnazli83@gmail.com

Received: April 28, 2026
Revised: July 30, 2026
Accepted: August 25, 2026

INTRODUCTION

Dry eye disease (DED) is a long-standing, complex condition affecting the corneal tear film interface, characterized by disturbance of the normal balance of the tear film. Patients generally experience a range of eye symptoms, caused by tear film instability, increased tear osmolarity, inflammation, and essential neurosensory changes.¹ The Tear Film & Ocular Surface Society Dry Eye Workshop III (TFOS DEWS

III) report presents a more accurate classification by categorizing dry eye into aqueous-deficient and evaporative types. It stresses that, in most cases of evaporative dry eye, the primary underlying issue is meibomian gland dysfunction.² DED is common and increasingly received in clinical practice, with an estimated global prevalence of around 11.6%.³ Its frequency rises with age and is influenced by other factors such as prolonged screen use and underlying metabolic conditions, making it a significant challenge in ophthalmology.³

Conventional treatments, such as artificial tears, can help relieve symptoms by providing lubrication, but they rarely address the underlying epithelial dysfunction or restore the natural ocular surface integrity. In patients with diabetes mellitus, the condition is often more severe, as factors such as reduced corneal sensations, reduced levels of insulin in the tear film, and delayed epithelial healing contribute to a more chronic disease that is resistant to treatment.^{4,5,6} Pharmacological agents, such as cyclosporine A and Lifitegrast, are advanced treatment options that focus on inflammation, but have limited use as they take time to work, are expensive and have intolerable side effects, restricting their use in resource-limited environments such as Pakistan.⁷

Insulin, a pleiotropic peptide hormone, has emerged as a useful agent for the ocular surface. Insulin receptors and Insulin-like Growth Factor 1 Receptor (IGF-1R) are expressed on corneal epithelial cells, keratocytes, and within the tear film, where receptor activation stimulates the PI3K-Akt-mTOR cascade, promoting epithelial proliferation, migration, and goblet cell differentiation.^{8,9} Burgos-Blasco et al,¹⁰ reported significant improvements in corneal staining and symptoms with topical insulin in DED. Studies have demonstrated superior tear film parameters and inflammatory biomarker reductions with topical insulin versus artificial tears and saline.¹¹ Existing evidence nonetheless remains limited by small sample sizes and design heterogeneity.¹²

No well-designed randomized controlled trial has been conducted in Pakistan, where the burden of diabetes-associated DED is substantial and access to advanced therapies is limited. This study therefore aims to evaluate the efficacy of topical insulin (1 U/mL) compared with preservative-free artificial tears in improving ocular surface parameters in patients with DED over a 12-week period.

METHODS

This prospective, randomized, controlled clinical trial was conducted in accordance with CONSORT 2010 guidelines at the Outpatient Khyber Teaching Hospital, from Peshawar April 2025 to April 2026. Ethical clearance was obtained from the Institutional Review and Ethics Board (No: 579/DME/KMC), and the trial was prospectively registered at ClinicalTrials.gov (NCT06939959). The study adhered to the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrolment.

Patients aged ≥ 18 years of either gender were included if they met all three diagnostic criteria for DED: Schirmer's test (without anesthesia) < 10 mm at 5 minutes, fluorescein TBUT < 10 seconds, and OSDI score > 20 . Exclusion criteria comprised active ocular infection; severe ocular surface disease unrelated to DED, including cicatricial pemphigoid, Stevens–Johnson syndrome, and graft-versus-host disease; ocular surgery within the preceding six months; known hypersensitivity to insulin; current systemic insulin therapy; and inability to comply with follow-up.

Sample size was calculated using the two-proportion Z-test formula. Based on previously published literature reporting response rates of approximately 63% with preservative-free artificial tears,¹³ and assuming a clinically meaningful improvement to 85% with topical insulin, with a two-sided α of 0.05 and 80% power, the minimum calculated sample size was 55 participants per group. To account for a potential 10% loss to follow-up, the sample size was increased to 64 participants per group, resulting in a total of 128 participants.

Participants were allocated 1:1 using blocked randomization with variable block sizes; the sequence was generated by an independent biostatistician and concealed in sequentially numbered opaque sealed envelopes. This was a participant-masked trial: a second investigator, who was not involved in outcome assessment, prepared topical insulin according to a written standardized compounding protocol¹⁴ and dispensed both interventions in identical unlabeled single-use droppers of equal volume, ensuring that participants remained unaware of their treatment allocation throughout the twelve-week follow-up. The principal investigator, who conducted all clinical assessments, was not masked to treatment allocation. To mitigate the resultant risk of detection bias, all

objective measurements (Schirmer test and TBUT) were independently rechecked by a second colleague clinician who was unaware of the study hypothesis; any discrepancy exceeding 1 mm or 1 second was resolved by a third reading and consensus.

Artificial tear group (ATG) received preservative-free carboxymethylcellulose 0.5% artificial tears, one drop per eye four times daily for 12 weeks. Insulin drops group (IDG) received topical insulin 1 U/mL, prepared by diluting commercially available human regular insulin (100 U/mL) in sterile isotonic saline according to a standardized compounding protocol, administered identically. All pre-existing topical DED medications were discontinued with a minimum one-week washout before baseline assessment. Participants in Group II were counselled on refrigerated storage at 2–8°C.

The primary outcome was the proportion of patients achieving clinically meaningful symptomatic improvement, defined as OSDI ≤ 20 at 12 weeks. Secondary outcomes were TBUT and Schirmer's test, assessed at baseline, 4, 8, and 12 weeks. TBUT was measured at the slit lamp under cobalt-blue illumination after standardized fluorescein strip application, recorded as the means of three consecutive readings. Schirmer's test was performed without anesthesia using standard 5 × 35 mm filter paper strips. The eye with worse readings at baseline was selected for analysis. At each visit, anterior segment examination was done for adverse effects including corneal infiltrates, conjunctival hyperemia, and hypersensitivity signs.

Data was analyzed using IBM SPSS version 23.0. Normality was assessed by the Shapiro-Wilk test.

Continuous variables were expressed as mean $\pm$ SD and categorical variables as frequencies and percentages. Baseline comparability was assessed by independent samples t-test and Chi-square test. Longitudinal changes were analyzed by repeated measures ANOVA with Greenhouse-Geisser correction where sphericity was violated on Mauchly's test. The primary binary outcome was compared by Chi-square test with relative risk, odds ratio, absolute risk reduction, and NNT calculated with 95% confidence intervals. Subgroup analyses examined effect modification by sex, age group (<40 vs. ≥ 40 years), diabetes status, and baseline disease severity. An intention-to-treat analysis was performed, with missing data managed using last-observation-carried-forward (LOCF). A two-sided p-value ≤ 0.05 was considered statistically significant throughout.

RESULTS

A total of 128 participants were enrolled and equally randomized into the IDG (n=64) and ATG (n=64). Two participants were lost to follow-up from the IDG; intention-to-treat analysis with LOCF was applied. The overall cohort comprised 65 (50.8%) males and 63 (49.2%) females, with a mean age of 36.63 ± 12.98 years. Among participants, 78 (60.9%) were employed and 45 (35.2%) had known diabetes mellitus. Baseline demographic and clinical characteristics were well-matched between groups, with no statistically significant differences observed (Table 1). Baseline mean Schirmer test was 6.10 ± 1.31 mm, mean TBUT was 6.48 ± 1.59 seconds, and mean OSDI score was 46.24 ± 16.29 .

Table 1: Baseline demographic and clinical characteristics of study participants.

Variable	IDG (n=64)	ATG (n=64)	p-value
Age (years)	35.39 ± 12.74	37.25 ± 13.29	0.579§
Schirmer test (mm)	6.36 ± 1.30	6.11 ± 1.17	0.255§
TBUT (sec)	6.48 ± 1.70	6.47 ± 1.49	0.956§
OSDI score	44.67 ± 16.70	47.81 ± 15.85	0.277§
Sex			
Male	34	31	0.596*
Female	30	33	
Employment			
Employed	41	37	0.469*
Unemployed	23	27	
Education			
Educated	34	31	0.596*
Uneducated	30	33	
Socioeconomic status			
Satisfactory	36	32	0.479*
Unsatisfactory	28	32	
Known diabetic			
Yes	22	23	0.853*
No	42	41	

§ Independent samples t-test; * Chi-square test. IDG = Insulin Drops Group; ATG = Artificial Tears Group.

Table 2: Longitudinal outcome measures by group across the 12-week follow-up period.

Outcome	Time	IDG (mean $\pm$ SD)	ATG (mean $\pm$ SD)	p	η^2
Schirmer test (mm)	Baseline	6.36 $\pm$ 1.30	6.11 $\pm$ 1.17	<0.001	0.561
	4 weeks	8.02 $\pm$ 1.35	6.35 $\pm$ 1.37		
	8 weeks	10.50 $\pm$ 1.55	7.31 $\pm$ 1.74		
	12 weeks	11.11 $\pm$ 1.40	8.52 $\pm$ 1.52		
TBUT (sec)	Baseline	6.48 $\pm$ 1.70	6.47 $\pm$ 1.49	<0.001	0.135
	4 weeks	8.77 $\pm$ 1.54	7.11 $\pm$ 1.04		
	8 weeks	9.73 $\pm$ 1.25	7.97 $\pm$ 0.96		
	12 weeks	10.83 $\pm$ 1.18	9.20 $\pm$ 1.83		
OSDI score	Baseline	44.67 $\pm$ 16.70	47.81 $\pm$ 15.85	0.032	0.031
	4 weeks	33.03 $\pm$ 12.18	37.31 $\pm$ 11.58		
	8 weeks	22.87 $\pm$ 8.58	30.66 $\pm$ 11.36		
	12 weeks	15.44 $\pm$ 7.67	23.81 $\pm$ 12.29		

p-values reflect the group $\times$ time interaction from repeated measures ANOVA. IDG = Insulin Drops Group; ATG = Artificial Tears Group.

Within-group analysis using repeated measures ANOVA demonstrated statistically significant improvement in all outcome measures over 12 weeks in both groups ($p < 0.001$). A considerable time $\times$ treatment interaction was observed ($p < 0.01$), confirming that the rate and magnitude of improvement over time differed significantly between groups, with the IDG demonstrating progressively greater improvement across all time points (Table 2).

In the IDG, mean improvement at 12 weeks was 4.75 ± 1.64 mm in Schirmer test, 4.34 ± 1.88 seconds in TBUT, and 29.23 ± 14.21 points in OSDI (all $p < 0.001$). In the ATG, the corresponding improvements were 2.41 ± 1.24 mm, 2.73 ± 2.28 seconds, and 24.00 ± 16.70 points respectively (all $p < 0.001$). Effect sizes indicated a large treatment effect for Schirmer test ($\eta^2 = 0.561$), moderate for TBUT ($\eta^2 = 0.135$), and small for OSDI ($\eta^2 = 0.031$).

The proportion of patients achieving clinically meaningful improvement (OSDI < 20) at 12 weeks was 89.06% (57/64) in the IDG versus 40.63% (26/64) in the ATG ($\chi^2 = 32.93$, $p < 0.001$). The relative risk of improvement was 2.19 (95% CI: 1.61–2.98), the odds ratio was 11.90 (95% CI: 4.69–30.16), absolute risk reduction was 48.43%, and the number needed to treat (NNT) was 2. The mean OSDI difference between groups at 12 weeks was 8.375 (95% CI: 4.79–11.96; $p < 0.001$).

Post hoc subgroup analysis demonstrated differential treatment responses. Among females, the

IDG showed significantly greater improvement than the ATG ($p < 0.001$), whereas no significant between-group difference was observed in males ($p = 0.75$). Younger participants, particularly those under 40 years of age, showed a significantly better response to insulin ($p = 0.003$). However, in patients aged 40 years and above, insulin did not offer any meaningful advantage ($p = 0.747$). Diabetic patients showed a significantly greater response in the IDG versus ATG ($p = 0.007$); no significant difference was observed in non-diabetic patients ($p = 0.561$). Patients with severe baseline disease (OSDI > 32) showed a marked advantage for insulin ($p = 0.001$), and even those with OSDI ≤ 32 demonstrated a statistically significant benefit ($p = 0.019$). No major adverse effects were reported in either group during follow-up.

DISCUSSION

Topical insulin has gained increasing attention over the past decade as a potential treatment for ocular surface disease. However, there is still no well-established randomized controlled trial directly comparing its effectiveness with standard treatments, particularly in dry eye populations from lower-middle-income countries. To the best of our knowledge, this is the first randomized controlled trial from Pakistan comparing topical insulin with preservative-free artificial tears. Our findings show that insulin is both statistically and clinically superior across all outcome measures at 12 weeks. Patients in the insulin group

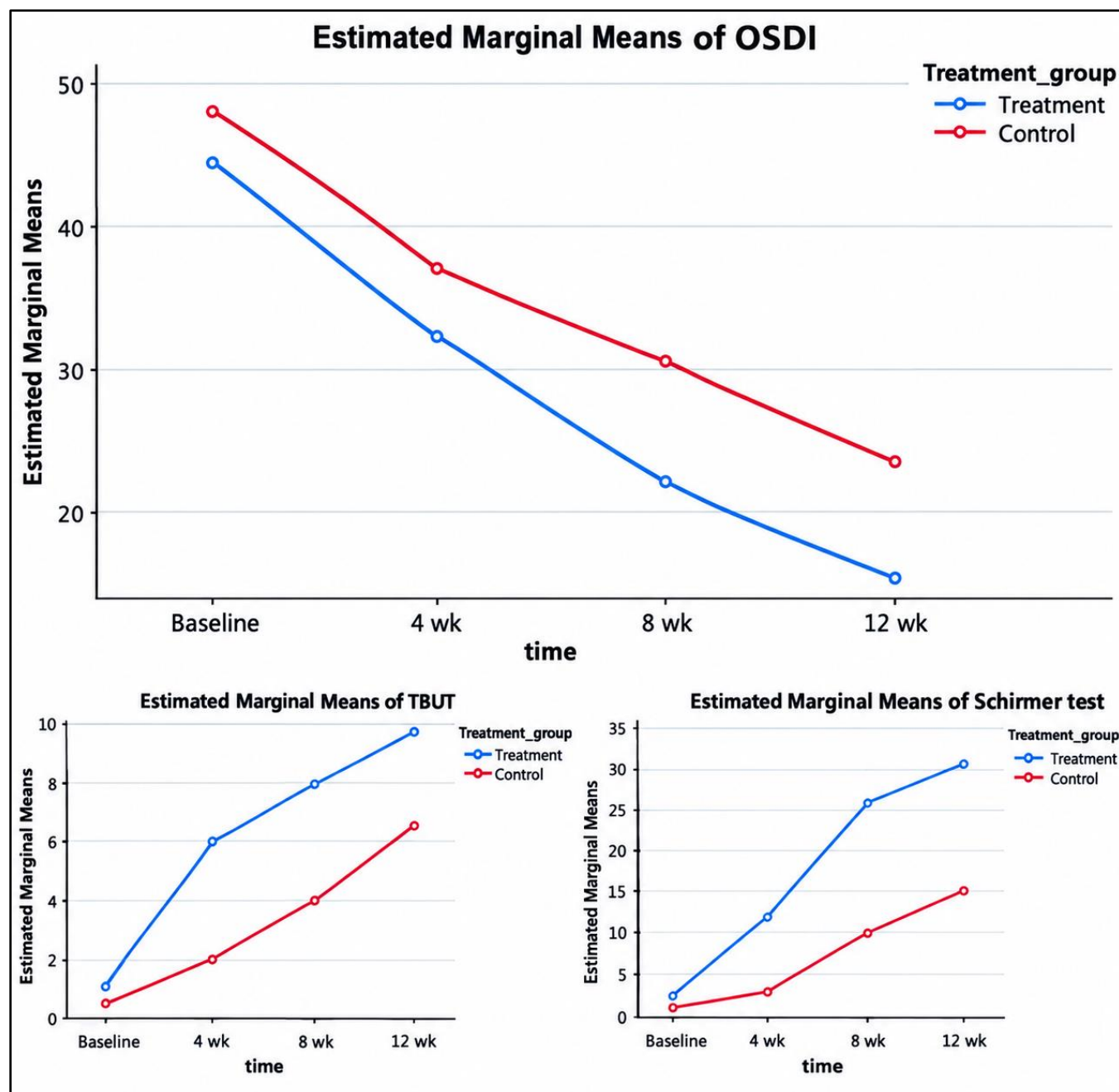


Figure 1: Estimated marginal means of the ocular surface disease index (OSDI) score, Schirmer test and tear film breakup time (TBUT), measured at baseline, 4 weeks, 8 weeks, and 12 weeks. The insulin drops group (blue line) demonstrated a greater reduction in OSDI score over the follow-up period compared with the artificial tear group (red line). Both groups showed progressive improvement in Schirmer test and TBUT values; however, the magnitude of improvement was consistently greater in the insulin drops group.

were more than twice as likely to achieve symptomatic relief compared with those receiving artificial tears (89.06% vs. 40.63%; NNT=2). Insulin also led to significantly greater improvements in tear secretion and tear film stability as evident by TBUT. The treatment effect was more pronounced in female patients, those with diabetes mellitus, younger

individuals, and patients presenting with more severe disease at baseline. No major adverse effects were observed in either group. These results are supported by a strong biological basis. Cid-Bertomeu P et al, demonstrated the presence of insulin in the human tear film and identified insulin receptors (IR) and Insulin-like Growth Factor 1 receptors (IGF-1R) on both

corneal and conjunctival epithelium, providing a possible mechanism for its therapeutic effect.¹⁵ Activation of these receptors by the PI3K-Akt-mTOR signaling pathway helps in the epithelial cell proliferation, the migration of these cells, and differentiation of their goblet cells. It is also shown that in chronic hyperglycemia, the relative lack of insulin inhibits the function of lacrimal acinar cells and also reduces meibum secretion from the meibomian glands.¹⁶ Collectively, these processes can be used to present a clear biological explanation regarding the better outcomes in the insulin-treated group (IDG).¹⁷

Aqueous tear production improved by 4.75 ± 1.64 mm in the IDG versus 2.41 ± 1.24 mm in the ATG at 12 weeks, with a large treatment effect ($\eta^2=0.561$). This finding aligns with the work of Atikah et al., who reported that topical insulin produced significantly greater improvement in Schirmer test values compared with both artificial tears and saline in patients with diabetic dry eye after four weeks of treatment.¹¹ TBUT improvement was similarly more in the IDG (4.34 ± 1.88 vs. 2.73 ± 2.28 seconds; $\eta^2=0.135$). This reflects insulin's ability to help restore goblet cell function and improve the stability of the mucin layer through Wnt/ β -catenin signaling pathways.¹⁸ In contrast to this, artificial tears provide temporary lubrication without addressing the underlying epithelial pathology. Pucker et al, in his review confirmed that artificial tears yield significant improvements within groups but lack a mechanism that modifies the disease process, and a large multicenter RCT demonstrated that no formulation of an artificial tear is better than another, showing the ceiling effect inherent to lubricant-based therapy.^{19,20}

The proportion achieving OSDI <20 was 89.06% in the IDG versus 40.63% in the ATG, yielding an RR of 2.19, OR of 11.90, and NNT of 2. The inter-group OSDI divergence widened progressively across the 4-, 8-, and 12-week time points, suggesting cumulative and potentially disease-modifying effects rather than merely symptomatic benefit. This contrasts with another study, where between-group OSDI differences were non-significant at four weeks, reinforcing that the therapeutic gain of topical insulin is time-dependent.¹³ These findings partially contrast with the Phase I/II RCT in Sjögren's disease-related DED, where insulin nano emulsion failed to demonstrate a significant between-group advantage, likely reflecting the autoimmune-driven glandular destruction inherent to

that population and the study's shorter 30-day follow-up.²¹

Subgroup analysis revealed that females responded significantly more to insulin ($p<0.001$), while no meaningful advantage was observed in males ($p=0.75$). This aligns with the well-known effect of estrogen on the meibomian gland lipid synthesis, which downregulates the meibum production, making ocular surface interface more responsive to hormonal changes in females. It is also recognized that declining androgens impair lacrimal gland trophic support, which further predisposes women to more severe tear film dysfunction.²² Participants younger than 40 years responded significantly better to insulin ($p=0.003$), which may reflect age-related attenuation of the ocular surface growth factors. Patel Ret al, demonstrated that tear IGF-1 levels decline with advancing age which leads to worsening clinical signs, explaining reduced receptor-mediated responsiveness to insulin in older patients.²³

The increased response of diabetic patients to topical insulin ($p=0.007$) is biologically rational. Chronic hyperglycemia activates the polyol and NF- κ B pathways which depletes the insulin levels in the tear film, and it also impairs lacrimal gland and corneal epithelial function through mechanisms that can be reversed by topical instillation of insulin.²⁴ Atikah et al, also states that topical insulin leads to a significantly greater reduction in inflammatory markers such as IL-1 α , IL-6, and MMP-9 compared with artificial tears in patients with DED.¹¹ In terms of disease severity, patients with more severe symptoms (OSDI >32) showed considerably higher benefit from insulin ($p=0.001$). Even those with milder to moderate disease (OSDI ≤ 32) also experienced a statistically significant improvement ($p=0.019$). This suggests that the therapeutic effect of insulin is seen at every level of disease severity to certain extent, which is in line with the findings reported by Burgos-Blasco et al.¹⁰

We did not observe any major adverse effects in any of the group. This further confirms the safety of topical insulin as previously reported by Radulescu et al, who documented that it is generally well tolerated.²⁵ The only side effect they observed was mild, transient discomfort upon instillation and no cases of systemic hypoglycemia were observed, as systemic absorption through the conjunctiva was none at therapeutic doses.²⁵

This study has some limitations including the single-center trial, lack of assessor masking, though

partially addressed through independent confirmation of objective measurements, the 12-week follow-up time which cannot draw any conclusions about long-term use of the treatment and post-hoc and exploratory sub-group analysis which needs confirmation by adequately powered, prospectively designed trials in the future.

CONCLUSION

This study demonstrates higher effectiveness of topical insulin over artificial tears in improving dry eye symptoms, tear secretion and tear film stability in DED. This improvement over time gets better which indicates a disease-modifying effect of insulin, in contrast to artificial tears, which acts only as a temporizing agent. The treatment specifically benefited the patients with diabetes, female gender, younger individuals, and those with more severe disease at baseline, reinforcing the biological explanation for the variation in response among these subgroups.

Topical insulin is cost-effective, has simple preparation, and has a favorable safety profile, which makes it a practical treatment option, especially in resource-limited settings and populations with a high burden of DED.

Funding: This study was not funded by any organization.

Patient's Consent: Researchers followed the guidelines set forth in the Declaration of Helsinki.

Conflict of Interest: Authors declared no conflict of interest.

Ethical Approval: The study was approved by the Institutional review board/Ethical review board (579/DME/KMC)

REFERENCES

1. **Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al.** TFOS DEWS II Definition and Classification Report. *Ocul Surf.* 2017;**15**(3):276-283. Doi: 10.1016/j.jtos.2017.05.008.
2. **Stapleton F, Argüeso P, Asbell P, Azar D, Bosworth C, Chen W, et al.** TFOS DEWS III: Digest. *Am J Ophthalmol.* 2025;**279**:451-553. Doi: 10.1016/j.ajo.2025.05.040. Erratum in: *Am J Ophthalmol.* 2026;**288**:350-351. Doi: 10.1016/j.ajo.2026.04.007.
3. **Papas EB.** The global prevalence of dry eye disease: A Bayesian view. *Ophthalmic Physiol Opt.* 2021;**41**(6):1254-1266. Doi: 10.1111/opo.12888.
4. **Jones L, Downie LE, Korb D, Benitez-Del-Castillo JM, Dana R, Deng SX, et al.** TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;**15**(3):575-628. Doi: 10.1016/j.jtos.2017.05.006.
5. **Ljubimov AV.** Diabetic complications in the cornea. *Vision Res.* 2017;**139**:138-152. Doi: 10.1016/j.visres.2017.03.002.
6. **Huang T, Wang D, Jiang D, Lu X, Lin L, Zhang Y, et al.** Diabetic dry eye: advances in pathogenesis, diagnostic strategies, and therapeutic approaches. *Front Med (Lausanne).* 2026;**13**:1756568. Doi: 10.3389/fmed.2026.1756568.
7. **Kawahara A.** Treatment of Dry Eye Disease (DED) in Asia: Strategies for Short Tear Film Breakup Time-Type DED. *Pharmaceutics.* 2023;**15**(11):2591. Doi: 10.3390/pharmaceutics15112591.
8. **Chen K, Li Y, Zhang X, Ullah R, Tong J, Shen Y.** The role of the PI3K/AKT signaling pathway in the corneal epithelium: recent updates. *Cell Death Dis.* 2022;**13**(5):513. Doi: 10.1038/s41419-022-04963-x.
9. **Peterson C, Chandler HL.** Insulin facilitates corneal wound healing in the diabetic environment through the RTK-PI3K/Akt/mTOR axis in vitro. *Mol Cell Endocrinol.* 2022;**548**:111611. Doi: 10.1016/j.mce.2022.111611.
10. **Burgos-Blasco B, Diaz-Valle D, Rego-Lorca D, Perez-Garcia P, Puebla-Garcia V, Fernandez-Vigo JI, et al.** Topical insulin, a novel corneal epithelial regeneration agent in dry eye disease. *Eur J Ophthalmol.* 2024;**34**(3):719-725. Doi: 10.1177/11206721231206790.
11. **Atikah A, Suzana M, Wan Haslina WAH, Norshamsiah MD, Mushawiahti M, Birinder KSS, et al.** Randomized controlled trial on effects of topical insulin compared to artificial tears and normal saline on tear inflammatory mediator levels and clinical parameters in diabetics with dry eye disease. *Cont Lens Anterior Eye.* 2025;**48**(2):102346. Doi: 10.1016/j.clae.2024.102346.
12. **Krolo I, Behaegel J, Termote K, de Bruyn B, De Schepper M, Oellerich S, et al.** The role of topical insulin in ocular surface restoration: A review. *Surv Ophthalmol.* 2024;**69**(5):805-817. Doi: 10.1016/j.survophthal.2024.04.003.
13. **Aniah Azmi N, Bastion MC.** Short-Term Results of Trial of Topical Insulin for Treatment of Dry Eyes in Diabetics. *Eye Contact Lens.* 2020;**46** Suppl 1:S25-S32. Doi: 10.1097/ICL.0000000000000623.

14. **Vicario-de-la-Torre M, Puebla-García V, Ybañez-García L, López-Cano JJ, González-Cela-Casamayor MA, Brugnera M, et al.** Topical Insulin Eye Drops: Stability and Safety of Two Compounded Formulations for Treating Persistent Corneal Epithelial Defects. *Pharmaceutics*. 2024;**16**(5):580. Doi: 10.3390/pharmaceutics16050580.
15. **Cid-Bertomeu P, Vilaltella M, Martínez M, Mir M, Huerva V.** Topical insulin for ocular surface disease. *J Ocul Pharmacol Ther*. 2024;**40**(4):204-214. Doi:10.1089/jop.2024.0016.
16. **Jiang M, Zhang K, Zhang Z, Zeng X, Huang Z, Qin P, et al.** PI3K/AKT/mTOR Axis in Cancer: From Pathogenesis to Treatment. *Med Comm* (2020). 2025;**6**(8):e70295. Doi: 10.1002/mco2.70295.
17. **Zhou Q, Yang L, Wang Q, Li Y, Wei C and Xie L.** Mechanistic investigations of diabetic ocular surface diseases. *Front Endocrinol*. 2022;**13**:1079541. Doi: 10.3389/fendo.2022.1079541
18. **Abdi P, Ghaffari R, Azad N, Al-Shaheeb A, Latifi G, Soltani Shahgoli S, et al.** Topical insulin for refractory persistent corneal epithelial defects. *Sci Rep*. 2024;**14**(1):12459. Doi: 10.1038/s41598-024-63091-y.
19. **Pucker AD, Ng SM, Nichols JJ.** Over the counter (OTC) artificial tear drops for dry eye syndrome. *Cochrane Database Syst Rev*. 2016;**2**(2):CD009729. Doi: 10.1002/14651858.CD009729.pub2.
20. **Aragona P, Benítez-Del-Castillo JM, Coroneo MT, Mukherji S, Tan J, Vandewalle E, et al.** Safety and Efficacy of a Preservative-Free Artificial Tear Containing Carboxymethylcellulose and Hyaluronic Acid for Dry Eye Disease: A Randomized, Controlled, Multicenter 3-Month Study. *Clin Ophthalmol*. 2020;**14**:2951-2963. Doi: 10.2147/OPTH.S256480.
21. **Marzola MM, Gutierrez DR, Cintra BC, Murashima AAB, Dalmolin LF, Garcia DM, et al.** Insulin Nanoemulsion Eye Drops for the Treatment of Dry Eye Disease in Sjögren's Disease: A Randomized Clinical Trial Phase I/II. *Vision* (Basel). 2025;**9**(3):54. Doi: 10.3390/vision9030054.
22. **Kaštelan S, Hat K, Tomić Z, Matejić T, Gotovac N.** Sex Differences in the Lacrimal Gland: Implications for Dry Eye Disease. *Int J Mol Sci*. 2025;**26**(8):3833. Doi: 10.3390/ijms26083833.
23. **Patel R, Zhu M, Robertson DM.** Shifting the IGF-axis: An age-related decline in human tears IGF-1 correlates with clinical signs of dry eye. *Growth Horm IGF Res*. 2018;**40**:69-73. Doi: 10.1016/j.ghir.2018.02.001.
24. **Weng J, Ross C, Baker J, Al-Furaih S, Shamloo K, Sharma A.** Diabetes-Associated Hyperglycemia Causes Rapid-Onset Ocular Surface Damage. *Invest Ophthalmol Vis Sci*. 2023;**64**(14):11. Doi: 10.1167/iovs.64.14.11.
25. **Bievel Radulescu R, Ferrari S, Stanca HT, Ponzin D.** Topical insulin as a novel treatment for persistent epithelial defects and other ocular surface disorders: a systematic review. *Graefes Arch Clin Exp Ophthalmol*. 2025;**263**(9):2427-2445. Doi: 10.1007/s00417-025-06840-7.

Authors Designation and Contribution

Shafiq Tanveer; Trainee Medical Officer: *Concepts, Design, Literature Search, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Rasheed Ul Haq; Trainee Medical Officer: *Concepts, Literature Search, Data Acquisition, Data Analysis, Statistical Analysis, Manuscript Preparation.*

Andaleeb Rabbi; Trainee Medical Officer: *Concepts, Design, Literature Search, Data Acquisition, Manuscript Preparation, Manuscript Editing, Manuscript Review.*

Nazli Gul; Associate Professor: *Concepts, Design, Data Analysis, Statistical Analysis, Manuscript Preparation, Manuscript Review.*

Imran Ahmad; Associate Professor: *Concepts, Design, Data Acquisition, Manuscript Preparation, Manuscript Review.*

