RESEARCH PAPER

Effects of Diquafosol Sodium On Tear Film Homeostasis in Dry Eye Disease: A Systematic Review On Meibomian Gland Dysfunction

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ABSTRACT

Background: Dry eye disease (DED) is a complex, multifaceted disorder often linked to dysfunction of the meibomian glands, which disrupts the lipid component of the tear film, thereby promoting its instability and accelerating evaporation. Diquafosol sodium, a P2Y2 receptor agonist, has emerged as a potential therapy that enhances tear film dynamics; however, its effect on the lipid layer remains incompletely understood.

Objective: To systematically evaluate the efficacy of diquafosol sodium in enhancing the lipid layer depth of the tear film and optimising the performance of the meibomian glands in individuals affected by DED.

Methods: A systematic review was undertaken in accordance with PRISMA 2020. PubMed/MEDLINE, Cochrane CENTRAL, Scopus, and Web of Science were searched for records published between January 2013 and May 2026. Eligible studies administered topical diquafosol sodium and reported at least one tear film outcome, including lipid layer thickness, tear film break-up time or meibomian gland function. Risk of bias was assessed with RoB 2 for randomised studies and ROBINS-I for non-randomised studies, and certainty of evidence with GRADE. Data were synthesised narratively.

Results: Four studies met the eligibility criteria: two randomised trials and two non-randomised studies. Diquafosol produced a rapid increase in tear film lipid layer thickness after a single drop, rising from 49.4 ± 16.2 nm to 70.6 ± 28.2 nm at 30 minutes ($P < 0.001$) in one randomised trial, and by 12.6 ± 2.0 nm at 20 minutes ($P < 0.001$) in a second, in which normal saline, sodium hyaluronate and gatifloxacin produced no significant change. Noninvasive break-up time improved for at least 90 minutes ($P < 0.001$), outlasting the measurable lipid layer increase, while tear meniscus height was unchanged. Resting lipid layer thickness measured before instillation did not change over three months of therapy ($P = 0.791$). Uncontrolled studies reported improvement in meibum quality, meiboscore, break-up time and ocular surface staining. Certainty of evidence was low for the acute lipid layer and tear film stability outcomes and very low for all others.

Conclusion: Topical diquafosol sodium produces a rapid, largely transient increase in tear film lipid layer thickness and improves tear film stability, supported by two randomised trials using objective masked interferometry, although certainty in this finding is low. Whether the effect is sustained during continued treatment remains unresolved. Evidence that diquafosol improves meibomian gland function derives entirely from uncontrolled studies and is of very low certainty. Adequately powered randomised trials of at least three months, with a concurrent control arm and masked assessment of meibomian gland outcomes, are required.

Keywords: *Diquafosol Sodium; Dry Eye Disease; Meibomian Gland Dysfunction; Tear Film; Lipid Layer Thickness; Ocular Surface*

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INTRODUCTION

Dry eye disease (DED) is a multifactorial disorder characterized by disruption of tear film homeostasis, leading to ocular discomfort, visual disturbance, inflammation, and impaired quality of life (1,2). Evaporative dry eye, the most common subtype, is primarily associated with meibomian gland dysfunction (MGD), which compromises the tear film lipid layer, increases tear evaporation, and accelerates ocular surface damage (2,5). Given the rising prevalence of DED, therapies targeting tear film stability rather than symptomatic relief alone have become increasingly important (3,4).

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MGD is characterized by obstruction of the meibomian glands and qualitative changes in meibum secretion, resulting in reduced lipid layer thickness (LLT), tear film instability, and worsening clinical symptoms (5,6,7). Since the lipid layer is essential for minimizing tear evaporation and maintaining ocular surface integrity, restoration of meibomian gland function and lipid layer stability has become a major therapeutic goal in evaporative DED (4,8,9).

Diquafosol sodium is a selective P2Y2 receptor agonist that stimulates water and mucin secretion from conjunctival epithelial and goblet cells, thereby enhancing tear film homeostasis. Unlike conventional artificial tears, diquafosol promotes endogenous tear production and may also improve lipid layer stability by facilitating meibum distribution and supporting meibomian gland function (11,12,13). Clinical studies have reported improvements in tear breakup time (TBUT), ocular symptoms, lipid layer thickness, and meibomian gland function following topical diquafosol therapy, although the magnitude of these effects remains inconsistent across studies (17,18,19).

Despite growing evidence, published studies differ considerably in patient characteristics, disease severity, treatment protocols, and reported outcomes, making the overall therapeutic effect of diquafosol difficult to interpret. Furthermore, previous reviews have primarily focused on general dry eye outcomes rather than specifically evaluating tear film parameters in patients with MGD. Therefore, this systematic review aimed to evaluate the effects of topical diquafosol sodium on tear film parameters in patients with dry eye disease, with particular emphasis on lipid layer thickness and outcomes related to meibomian gland dysfunction.

METHODS

Study Design and Reporting Guidelines

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) statement. The review aimed to comprehensively evaluate the effects of topical diquafosol sodium on tear film parameters in patients with dry eye disease, with particular emphasis on lipid layer thickness and outcomes related to meibomian gland dysfunction (Figure 1). The protocol was registered prospectively with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD420261446336), and the review is reported in accordance with the PRISMA 2020 statement.

Information Sources and Search Strategy

A comprehensive literature search was performed in PubMed/MEDLINE, Cochrane CENTRAL, Scopus, and Web of Science for records published from January 2013 to May 2026. The searches were run on May to August 2026. The search period was intentionally expanded because several pivotal clinical studies investigating the effects of diquafosol on meibomian gland dysfunction, lipid layer thickness, and tear film stability were published before 2020. Controlled vocabulary (Medical Subject Headings [MeSH]) and free-text keywords were combined using Boolean operators. The principal search terms included: ("diquafosol" OR "diquafosol sodium" OR "P2Y2 receptor agonist") AND ("dry eye disease" OR "keratoconjunctivitis sicca" OR "evaporative dry eye") AND ("meibomian gland dysfunction" OR "MGD" OR "tear film" OR "lipid layer thickness" OR "tear film break-up time" OR "TBUT" OR "ocular surface"). The complete search strategy was adapted for each database. In addition to electronic database searching, the reference lists of eligible studies and relevant review articles were manually screened to identify additional potentially eligible publications.

Eligibility Criteria

Studies were considered eligible if they fulfilled the following criteria: (1) randomized controlled trials, prospective studies, retrospective studies, or observational studies involving human participants; (2) patients diagnosed with dry eye disease, including studies involving meibomian gland dysfunction as a predefined subgroup or study population; (3) topical diquafosol sodium administered as the intervention; (4) comparison with placebo, artificial tears, sodium hyaluronate, conventional therapy, or baseline measurements; (5) reporting at least one tear film-related outcome, including lipid layer thickness, tear film break-up time (TBUT), meibomian gland function, meibography findings, Schirmer test, corneal fluorescein staining, ocular surface staining, or patient-reported symptom scores (OSDI). Only English-language articles published between January 2013 and May 2026 were included. Studies were excluded if they were reviews, meta-analyses, editorials, conference abstracts without full text, case reports, animal experiments, laboratory studies, or studies that did not evaluate clinical outcomes following topical diquafosol therapy. Where a study reported cohorts in which diquafosol was co-administered with other ocular therapies, only cohorts receiving diquafosol without concomitant ocular treatment were used, because the effect of diquafosol cannot be isolated where other treatments acting on the same outcomes were given concurrently. This rule was applied to all included studies and was added to the registered protocol as an amendment before submission.

Study Selection

All records were organised and duplicates removed prior to evaluation. Two reviewers independently screened titles and abstracts to identify relevant studies. Full texts of selected articles were then assessed using predefined criteria. Any differences in judgement were resolved through discussion, ensuring a consistent and reliable selection process across all included studies for final analysis. Disagreements were resolved through consensus. When necessary, a third reviewer was consulted to resolve persistent disagreements.

Data Extraction

In this study, two reviewers independently extracted data using a standardized data extraction form. Extracted

information included first author, publication year, country, study design, sample size, participant characteristics, intervention details, comparator, treatment duration, outcome measures, and principal findings. Particular attention was given to tear film parameters, including lipid layer thickness, tear film break-up time, meibomian gland function, meibography findings, Schirmer test, corneal fluorescein staining, and symptom scores. Any discrepancies were resolved by discussion until consensus was reached.

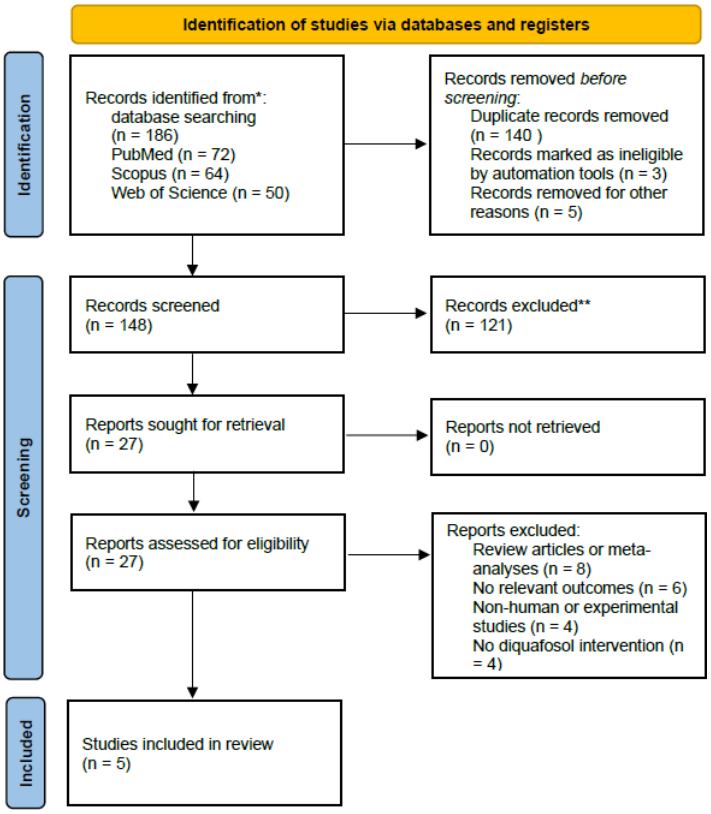

Figure 1. Prisma Flowchart

Risk of Bias Assessment

Risk of bias was assessed independently by two reviewers, with disagreements resolved by discussion. Randomised studies were assessed with the revised Cochrane risk-of-bias tool for randomised trials (RoB 2) across five domains and rated as being at low risk of bias, as raising some concerns, or as being at high risk of bias. Non-randomised studies were assessed with the ROBINS-I tool across seven domains and rated as being at low, moderate, serious or critical risk of bias. Assessments were made for the effect of assignment to intervention. Because the two randomised studies used non-standard allocation structures, a paired-eye design with the fellow eye as concurrent control in one and a four-period crossover in the other, the additional signalling questions for these designs were considered, in particular the potential for carry-over between periods and between eyes. Domain-level and overall judgements are presented in Figure 2, with supporting justifications in Tables 2 and 3, and were carried through to the interpretation of the synthesis

Data Synthesis

Owing to substantial heterogeneity in study populations, intervention protocols, outcome definitions, and reporting methods, quantitative meta-analysis was considered inappropriate. Therefore, findings were synthesized narratively. Results were grouped according to clinically relevant outcome domains: lipid layer thickness, tear film stability (TBUT), meibomian gland function, ocular surface staining, Schirmer test, patient-reported symptoms. Whenever possible, results from studies involving meibomian gland dysfunction were analyzed separately from studies involving the broader dry eye disease population to better characterize the potential role of diquafosol in evaporative dry eye.

Certainty of Evidence

The certainty of the evidence for each outcome was assessed using the GRADE approach, considering risk of bias, inconsistency, indirectness, imprecision and publication bias. Evidence from randomised trials began at high certainty and evidence from non-randomised studies at low certainty, and was rated down where a domain was not met. Certainty was categorised as high, moderate, low or very low and is reported with the reasons for each judgement in Table 4. Because quantitative pooling was not appropriate, imprecision was judged from the size of the contributing samples and the width of the reported intervals rather than from a pooled confidence interval. Publication bias could not be assessed formally, since funnel plot asymmetry and related tests require substantially more studies than were available.

Outcome Measures

The primary outcome of this review was change in lipid layer thickness following topical diquafosol treatment. Secondary outcomes included tear film break-up time, meibomian gland function, meibography findings, corneal fluorescein staining, Schirmer test, ocular surface disease index (OSDI), and other clinically relevant tear film parameters reported by the included studies.

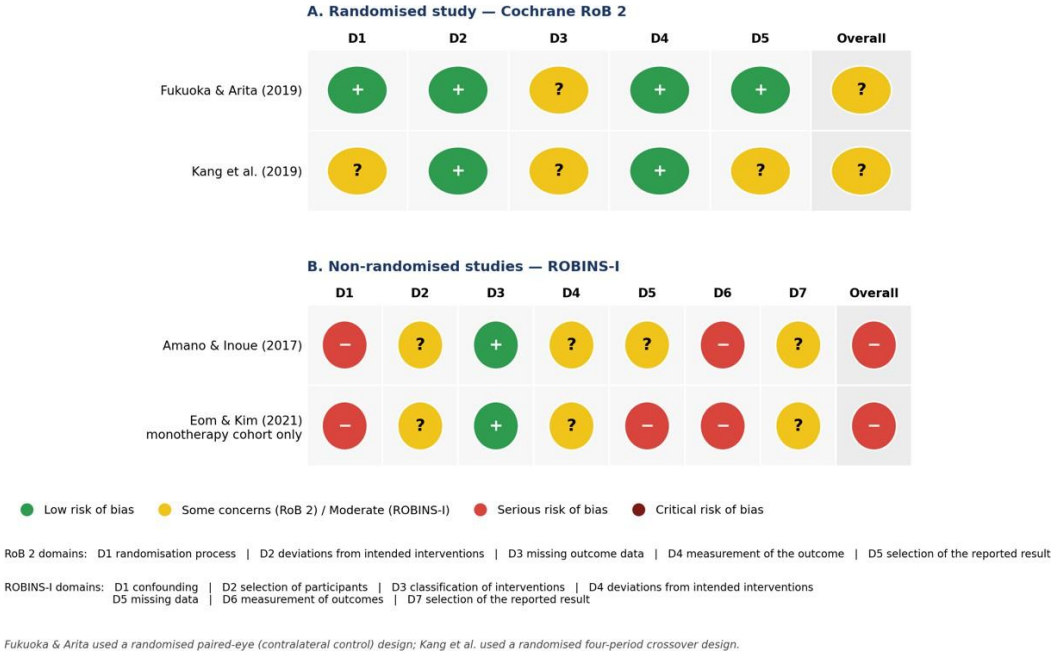

Figure 2. Risk of bias assessment. (A) Randomised studies assessed with the Cochrane RoB 2 tool. (B) Non-randomised studies assessed with ROBINS-I.

Study	Design	n	Population	Intervention	Comparator	Outcomes	Key findings
Fukuoka & Arita (2019, Japan)	Randomised, masked, paired-eye clinical study; single administration with 90-minute follow-up	47 patients (94 eyes); mean age 48.1 ± 13.0 years	DED with bilateral MGD; baseline LLT ≤ 75 nm, FBUT ≤ 5 s or Schirmer ≤ 5 mm, lid margin abnormality and plugged gland orifices	Single drop of 3% diquafosol sodium	Single drop of preservative-free artificial tears in the contralateral eye	LLT (LipiView), NIBUT, tear meniscus height, tear interferometric pattern (DR-1α), VAS symptoms, adverse events	LLT rose significantly at 30 min ($P < 0.001$) and 60 min ($P = 0.042$) but not at 90 min; artificial tears produced no change (between-group $P < 0.001$). NIBUT improved for at least 90 min (all $P < 0.001$). Tear meniscus height unchanged. No serious adverse events.
Amano & Inoue (2017, Japan)	Prospective, uncontrolled, single-centre study; 3-month treatment period	13 patients completed (14 enrolled, 1 withdrew for ocular pain); mean age 69.5 ± 8.3 years	DED and MGD by Japanese MGD Working Group and Japanese dry eye criteria	3% diquafosol sodium six times daily for 3 months	Within-subject baseline (no control arm)	LLT before and 20 min after instillation, meibum score, meiboscore, lid margin signs, tear BUT, fluorescein staining, Schirmer I, DEQS and MGD questionnaires	Pre-instillation LLT unchanged over 3 months ($P = 0.791$); the acute post-drop rise was significant only at 3 months ($P = 0.039$). Meibum score ($P = 0.011$), meiboscore ($P = 0.036$), lid margin signs, tear BUT and staining all improved. Symptom scores did not reach significance.
Kang et al. (2019, South Korea)	Randomised, masked, four-period crossover study; single instillation with assessment at 20 minutes	124 participants (124 eyes); mean age 28.9 ± 6.3 years	DED (TBUT < 5 s, corneal staining > 1); baseline meiboscore 0.78 ± 0.66 and meibum expressibility 1.60 ± 0.82, described by the authors as a mild obstructive MGD pattern	Single drop of 3% diquafosol sodium	Normal saline, 0.1% sodium hyaluronate and 0.3% gatifloxacin, each at a separate visit	LLT (LipiView) at baseline and 20 min after instillation	LLT rose by 12.6 ± 2.0 nm at 20 min ($P < 0.001$). Normal saline, sodium hyaluronate and gatifloxacin produced no significant change. Diquafosol was the only solution tested that increased LLT.

Eom & Kim (2021, South Korea) - monotherapy cohort	Multicentre prospective observational study at 20 institutions; 8-week treatment period. Only the monotherapy cohort, receiving diquafosol without concomitant ocular therapy, was used	196 analysed of 244 in the cohort full analysis set; mean age 44.5 ± 16.1 years	Dry eye level I–III by Korean Corneal Disease Study Group criteria; Sjögren syndrome and severe blepharitis (meibum quality or expressibility grade 3) excluded	3% diquafosol sodium six times daily for 8 weeks as sole ocular therapy	Within-cohort baseline; no randomisation and no control arm	TBUT, corneal and conjunctival staining (NEI scheme), OSDI, meibum quality, meibum expressibility, patient-reported outcomes, adverse events. LLT was not measured	TBUT, corneal and conjunctival staining and OSDI all improved over 8 weeks (all $P < 0.001$). Meibum quality improved by 0.25 ± 0.68 points ($P < 0.001$) and expressibility by 0.14 ± 0.62 points ($P = 0.002$). LLT was not measured.

DED, dry eye disease; MGD, meibomian gland dysfunction; LLT, tear film lipid layer thickness; NIBUT, noninvasive tear film break-up time; TBUT, tear film break-up time; FBUT, fluorescein break-up time; OSDI, Ocular Surface Disease Index. Values are mean ± standard deviation except for Kang et al., where they are mean ± standard error. Full numerical results are reported in the Results section.

RESULTS

Study Selection

The search identified 754 records: 254 from PubMed/MEDLINE, 173 from Cochrane CENTRAL, 162 from Scopus and 165 from Web of Science. After removal of 585 duplicates and 17 records removed for other reasons, 152 titles and abstracts were screened, of which 139 were excluded for lack of relevance, ineligible design or absence of a diquafosol intervention. Thirteen full-text articles were assessed for eligibility and nine were excluded: three reviews or meta-analyses, four reporting no relevant outcome and two administering no diquafosol intervention. Four studies were included in the qualitative synthesis (Figure 1).

Study Characteristics

Four studies met the eligibility criteria: two randomised trials, one uncontrolled prospective interventional study and one multicentre prospective observational study. Two were conducted in Japan and two in South Korea. Sample sizes ranged from 13 to 196 participants and mean age from 28.9 to 69.5 years. Two studies required both dry eye disease and meibomian gland dysfunction for entry; one enrolled patients with dry eye disease in whom a mild obstructive meibomian gland pattern was present; and one enrolled patients with dry eye disease of mild to moderate severity in whom severe meibomian gland disease was an exclusion criterion. Diquafosol was given as a single drop in two studies and six times daily for three months and eight weeks in the other two. Study characteristics and findings are summarised in Table 1.

Risk of Bias in Included Studies

Risk of bias varied substantially across the four included studies (Figure 2, Tables 2 and 3). Both randomised studies were judged as raising some concerns overall. In the paired-eye study the concern arose from the exclusion of ten of 57 enrolled participants after enrolment, one criterion for which was a baseline lipid layer thickness above the eligibility threshold; all other domains were at low risk. In the crossover study the concerns arose from incomplete reporting of the randomisation method, absence of participant flow across the four visits, and the absence of a registered protocol together with selective presentation of lipid layer thickness alone, although several other ocular surface measures had been recorded at baseline. In both studies the primary outcome was measured by automated interferometry with masked assessors, so measurement bias is unlikely. The two non-randomised studies were judged at serious risk of bias, principally because neither had a comparator and because meibomian gland outcomes were graded on semi-quantitative scales by unmasked assessors.

Effect of Diquafosol on Tear Film Lipid Layer Thickness

Three of the four included studies measured lipid layer thickness, in each case with the LipiView interferometer, and each demonstrated an increase after diquafosol instillation. In the randomised paired-eye study, lipid layer thickness rose from 49.4 ± 16.2 nm before instillation to 70.6 ± 28.2 nm at 30 minutes (adjusted $P < 0.001$) and 63.9 ± 30.0 nm at 60 minutes ($P = 0.042$), returning towards baseline by 90 minutes (62.0 ± 26.2 nm, $P = 0.11$). Preservative-free artificial tears instilled into the contralateral eye produced no significant change at any assessment point, and the between-group difference in treatment effect was significant ($P < 0.001$) (17).

The randomised crossover study produced concordant results in a larger sample. Twenty minutes after a single drop, lipid layer thickness rose from 61.50 ± 2.57 to 73.27 ± 2.67 nm, a mean increase of 12.6 ± 2.0 nm ($P < 0.001$). Normal saline, 0.1% sodium hyaluronate and 0.3% gatifloxacin produced mean changes of 1.2 ± 2.2, 1.5 ± 2.0 and 0.5 ± 3.2 nm respectively, none of which was significant. Diquafosol was therefore the only agent tested that increased the lipid layer, which argues against the increase being a non-specific consequence of instilling a drop (19).

The single study with a treatment period long enough to test durability qualifies this picture. Over three months of six-times-daily therapy, lipid layer thickness measured before instillation did not change (81.8 nm at baseline versus 79.7 nm at three months, $P = 0.791$). What reached significance was the acute rise measured 20 minutes after a drop, which was +12.2, +11.5, +9.5 and +17.0 nm at

baseline and at one, two and three months, and which was significant only at the three-month visit (P = 0.039) (18). Taken together, the available evidence supports an acute and largely transient increase in lipid layer thickness after diquafosol instillation. It does not demonstrate a sustained rise in resting lipid layer thickness during continued therapy, since the only study to examine this found none.

Effect on Tear Film Stability

Improvement in tear film stability was the most consistently reported finding. In the randomised paired-eye study, noninvasive break-up time rose from 3.0 ± 1.8 s before instillation to 6.1 ± 2.9, 6.6 ± 2.7 and 6.1 ± 2.8 s at 30, 60 and 90 minutes (all adjusted P < 0.001), while artificial tears produced no change; the between-group treatment effect was significant (P < 0.001). The improvement persisted at 90 minutes, by which point the lipid layer increase was no longer significant, and tear meniscus height was unaffected in both arms (P = 0.96), indicating that the effect is attributable neither to lipid layer thickness alone nor to tear volume (17).

Over longer treatment periods, fluorescein break-up time rose from 3.3 to 7.5 s after three months of therapy (P < 0.0001) (18), and tear film break-up time rose from 3.92 ± 2.35 s to 5.53 ± 2.40 s over eight weeks in the monotherapy cohort of the observational study (P < 0.001) (20). Because neither study included a control arm, regression to the mean and observation effects cannot be excluded. Qualitative interferometry supported these findings: among eyes classified as evaporative type before instillation, the interferometric pattern improved in 62.5%, 80.0% and 57.5% of eyes at 30, 60 and 90 minutes after diquafosol, compared with 13.9%, 13.9% and 5.6% after artificial tears (P < 0.001 at each time point) (17).

Effect on Meibomian Gland Function

Two studies assessed meibomian gland function after sustained therapy, and no randomised study assessed this outcome. After three months of six-times-daily diquafosol, meibum score fell from 2.3 to 1.8 (P = 0.011) and total meiboscore from 2.6 to 2.2 (P = 0.036); lid margin signs also improved, with telangiectasia falling from 7.3 to 2.8 per eye and plugged gland orifices from 6.3 to 1.8 per eye (both P < 0.001) (18). In the monotherapy cohort of the observational study, meibum quality improved by 0.25 ± 0.68 points (95% CI 0.15 to 0.35, P < 0.001) and meibum expressibility by 0.14 ± 0.62 points (95% CI 0.05 to 0.23, P = 0.002) over eight weeks (20). These changes are modest in absolute terms, were obtained without a control group in both studies, and rest on semi-quantitative grading scales applied by unmasked assessors, which the investigators of one study explicitly identified as a limitation. Whether diquafosol acts directly on meibomian gland epithelium remains unsettled, since a related P2Y2 agonist had no effect on cultured human meibomian gland epithelial cells (16).

Ocular Surface Staining and Tear Production

Fluorescein staining fell from 1.5 to 0.4 after three months (P < 0.0001) and Schirmer I values rose from 7.5 to 10.1 mm (P = 0.002) (18). In the monotherapy cohort, corneal staining fell from 2.24 ± 1.92 to 0.97 ± 1.16 and conjunctival staining from 1.73 ± 2.06 to 0.72 ± 1.26 over eight weeks (both P < 0.001) (20). Lipid layer thickness was not measured in that study.

Effect on Patient-Reported Outcomes

Findings for symptoms were less consistent than for objective signs. In the randomised paired-eye study, visual analogue scores improved significantly more with diquafosol than with artificial tears for ocular fatigue (P = 0.005), dryness (P = 0.014), itching (P = 0.001), redness (P = 0.007) and heavy sensation (P < 0.001), but not for discharge, foreign body sensation, pain, epiphora or glare (17). In the monotherapy cohort, OSDI fell from 41.01 ± 21.47 to 25.30 ± 19.43 over eight weeks (P < 0.001), and 74.0% of respondents across the whole study rated their symptoms better or much better at week 8 (20). By contrast, in the three-month uncontrolled study neither the DEQS ocular symptom score (P = 0.065) nor the MGD questionnaire score (P = 0.081) reached significance, although both moved in the direction of improvement (18).

Adverse Events

No serious adverse events were reported in the randomised paired-eye study (17). In the three-month study, one of 14 enrolled patients withdrew because of ocular pain immediately after the first instillation, which resolved without sequelae (18). In the observational study, 132 of 450 subjects (29.3%) experienced 193 adverse events, of which 97% were mild or moderate; six subjects reported 12 severe events, all judged unlikely to be related to the study drug (20). No included study was designed or powered to detect harm.

Certainty of Evidence

No outcome reached moderate certainty (Table 4). Certainty was low for the acute increase in lipid layer thickness and for acute tear film stability, both of which rest on randomised evidence with objective masked measurement, after downgrading for risk of bias and for indirectness or imprecision. Certainty was very low for resting lipid layer thickness after three months, for tear film stability over weeks to months, for meibomian gland function, for ocular surface staining, for patient-reported symptoms and for adverse events, each of which derives wholly or largely from non-randomised studies at serious risk of bias.

DISCUSSION

This systematic review examined the effect of topical diquafosol sodium on the tear film in patients with dry eye disease and meibomian gland dysfunction, with particular attention to the lipid layer. Four studies met the eligibility criteria: two randomised trials and two non-randomised studies. The principal finding is that diquafosol produces a rapid increase in tear film lipid layer thickness after a single instillation, together with an improvement in tear film stability that outlasts the measurable lipid layer change. The evidence does not, however, establish that this translates into a sustained rise in resting lipid layer

thickness during continued therapy, nor that diquafosol restores meibomian gland function.

The acute lipid layer effect is the most secure finding of this review and rests on two randomised trials using automated interferometry with masked assessors (17,19). Its most persuasive feature is the comparator structure of the crossover trial, in which normal saline, 0.1% sodium hyaluronate and 0.3% gatifloxacin were each administered to the same participants and none produced a significant change in lipid layer thickness, whereas diquafosol did (19). Because instilling any drop transiently disturbs the tear film, this design argues against the increase being a non-specific consequence of instillation. The paired-eye trial reached the same conclusion against preservative-free artificial tears in the fellow eye (17), and a comparable acute rise had previously been demonstrated in healthy eyes (22). Certainty in this finding is nonetheless low, reflecting some concerns in both trials and the indirectness of a surrogate measure assessed within an hour of a single drop in exclusively East Asian populations.

A finding that merits emphasis is the dissociation between the two acute effects. Noninvasive break-up time remained significantly improved at 90 minutes, by which point the increase in lipid layer thickness was no longer significant, while tear meniscus height was unchanged throughout (17). Improvement in tear film stability is therefore attributable neither to lipid layer thickness alone nor to an increase in tear volume. Diquafosol stimulates secretion of aqueous fluid and membrane-associated mucins through P2Y2 receptor activation (11,13,14), and a single drop increases tear fluid secretion in normal eyes (23), and the mucin component may contribute to tear film stability after the lipid effect has waned. This mechanistic separation is the aspect of diquafosol's action least well characterised by existing evidence and is a natural target for future work.

Whether the acute effect accumulates into a durable change is unresolved, and the single study able to address it argues against a simple interpretation. Over three months of six-times-daily treatment, lipid layer thickness measured before instillation did not change ($P = 0.791$); what reached significance was the acute post-instillation rise, and only at the three-month visit (18). One reading is that diquafosol acts as a repeated short-acting stimulus to meibum delivery rather than as an agent that restores baseline lipid layer thickness. A second is that the study, with 13 patients and no control group, was simply unable to detect a modest durable change. These readings cannot be distinguished with the present evidence, and the term “lipid layer recovery” should be avoided until a controlled study with a treatment period of at least three months has measured resting lipid layer thickness directly.

Evidence that diquafosol improves meibomian gland function is the weakest component of this review, and it is important to be explicit about why. Both studies reporting this outcome were uncontrolled, both graded meibum quality, expressibility and gland dropout on semi-quantitative scales applied by unmasked assessors, and in one the grading was performed by different examiners across 20 institutions without any reported inter-observer reliability (18,20). No randomised study in this review assessed meibomian gland function at all. The improvements reported are also modest in absolute terms, amounting to a quarter of a point on a four-point scale for meibum quality over eight weeks (20). Certainty for this outcome is very low, and the appropriate statement is that uncontrolled studies report improvement, not that diquafosol improves gland function. A biological pathway is nonetheless plausible: P2Y2 receptors have been localised to meibomian gland ductal epithelium (11,12), and diquafosol instillation increased intracellular lipid droplets in murine meibomian gland acinar cells (15), although a related P2Y2 agonist had no effect on cultured human meibomian gland epithelial cells (16). An earlier clinical study of patients with obstructive meibomian gland dysfunction treated for at least four months likewise reported improvement in meibum grade and tear film break-up time, but was also uncontrolled (21).

These findings should be read alongside the broader diquafosol literature. A systematic review of eight randomised trials in 1,516 patients concluded that diquafosol is a safe option for dry eye disease (24), and a more recent meta-analysis of 19 randomised trials in 2,697 patients found it superior to artificial tears across conventional endpoints (25). Neither, however, addressed the lipid layer or meibomian gland function as primary outcomes, because most randomised trials of diquafosol report tear film break-up time, ocular surface staining and symptom scores rather than interferometric measures. The contribution of the present review is therefore not to establish efficacy in dry eye disease, which is already better supported elsewhere, but to examine specifically whether diquafosol acts on the lipid component of the tear film and on the glands that produce it. Read together, the wider literature establishes that diquafosol benefits patients with dry eye disease, while this review indicates that its lipid layer effect is acute and that its effect on gland function remains unproven.

From a clinical perspective, the implication is narrower than the earlier literature might suggest. Diquafosol can reasonably be considered in evaporative dry eye associated with meibomian gland dysfunction, where it improves tear film stability and produces a short-lived increase in lipid layer thickness. It should not, on present evidence, be presented to patients as a treatment that restores meibomian gland function, and it is not a substitute for interventions that act directly on the glands, such as lid hygiene, warm compression, thermal pulsation or intense pulsed light (4). The frequent dosing used in the included studies, six times daily, is also relevant to adherence in routine practice.

This review has several strengths. The search covered four databases including Cochrane CENTRAL and spanned more than a decade, capturing the interferometric literature that a window restricted to recent years would have

missed. Every included study was appraised from its full text, and all reported values were extracted from the published articles rather than from abstracts. Risk of bias was assessed with instruments matched to study design, using ROBINS-I rather than a summary scale for the non-randomised studies, and the certainty of the evidence was rated with GRADE. Cohorts in which diquafosol was co-administered with other ocular therapies were excluded from the synthesis, so no reported effect is confounded by concurrent treatment acting on the same outcomes.

Several limitations must be acknowledged. Only four studies met the eligibility criteria and only two were randomised, and both randomised trials assessed a single instillation, so no randomised evidence exists for any outcome beyond 90 minutes. All four studies were conducted in Japan or South Korea, and the participants of one had a mean age of 28.9 years with only a mild obstructive meibomian gland pattern, which limits generalisability, particularly since lipid layer thickness is itself associated with symptom severity and gland status in older cohorts (10). The study contributing the largest sample excluded patients with meibum quality or expressibility of grade 3, so the most severe meibomian gland disease is not represented in the evidence on that outcome; that study also mixed treatment-naive patients with patients who discontinued previous therapy without reporting the proportions. Meta-analysis was not appropriate given the heterogeneity of designs, populations and assessment intervals, so no pooled effect estimate is available. Publication bias could not be assessed formally, and it is relevant that three of the four included studies were funded or supported by the manufacturer of the study drug. Finally, this review was registered retrospectively, and the eligibility rule concerning co-administered therapy was added to the protocol as an amendment during the review rather than specified at the outset.

Future research should address the questions this review leaves open rather than repeating what is already established. A randomised controlled trial with a treatment period of at least three months, a concurrent control arm, and resting lipid layer thickness measured before instillation as a prespecified primary outcome would determine whether the acute effect accumulates. Meibomian gland outcomes should be prespecified and assessed by masked observers using standardised meibography with reported inter-observer reliability. Trials in populations outside East Asia, in patients with severe meibomian gland disease, and in direct comparison with lipid-based artificial tears and gland-directed physical treatments would clarify where diquafosol belongs in the management of evaporative dry eye.

CONCLUSION

Topical diquafosol sodium produces a rapid increase in tear film lipid layer thickness and an improvement in tear film stability within an hour of instillation. This finding is supported by two randomised trials using objective, masked interferometry, and in one of them diquafosol was the only agent, among normal saline, sodium hyaluronate and gatifloxacin, to raise the lipid layer; certainty in this finding is nonetheless low. Whether the effect is maintained during continued treatment is unresolved: the only study to measure resting lipid layer thickness after three months of therapy found no change, but it enrolled 13 patients and had no control group. Evidence that diquafosol improves meibomian gland function derives entirely from uncontrolled studies at serious risk of bias, with unmasked assessment of semi-quantitative grading scales, and is of very low certainty; no randomised study has assessed this outcome. Diquafosol therefore has a demonstrable short-term effect on the lipid component of the tear film, but the present evidence does not establish that it restores meibomian gland function or produces a durable increase in lipid layer thickness. Adequately powered randomised trials with a treatment period of at least three months, a concurrent control arm, prespecified meibomian gland outcomes and masked assessment are required.

Risk of bias varied substantially across the four included studies (Figure 2, Tables 2 and 3). Both randomised studies were judged as raising some concerns overall. In the paired-eye study the concern arose from the exclusion of ten of 57 enrolled participants after enrolment, one criterion for which was a baseline lipid layer thickness above the eligibility threshold; all other domains were at low risk. In the crossover study the concerns arose from incomplete reporting of the randomisation method, absence of participant flow across the four visits, and the absence of a registered protocol together with selective presentation of lipid layer thickness alone, although several other ocular surface measures had been recorded at baseline. In both studies the primary outcome was measured by automated interferometry with masked assessors, so measurement bias is unlikely. The two non-randomised studies were judged at serious risk of bias, principally because neither had a comparator and because meibomian gland outcomes were graded on semi-quantitative scales by unmasked assessors.

Table 2. Risk of bias in the randomised studies (Cochrane RoB 2)

Domain	Fukuoka & Arita (2019) -randomised, masked, paired-eye	Kang et al. (2019) -randomised four-period crossover
D1. Randomisation process	Low. Permuted-block randomisation (block size 4) with sequentially numbered opaque sealed envelopes; sequence generated by an independent allocation manager. Baseline ocular parameters did not differ between eyes.	Some concerns. Participants were randomly assigned to four sequence groups and the treated eye randomly selected, but neither sequence generation nor allocation concealment is described, and baseline data are reported only for the whole cohort.

D2. Deviations from intended interventions	Low. Single investigator-administered drop; participants and researchers masked; outcome window 90 minutes.	Low. All four solutions given in counterbalanced order at monthly intervals, providing ample washout for a 20-minute outcome; investigators masked.
D3. Missing outcome data	Some concerns. 47 of 57 enrolled participants (82.5%) analysed; exclusions included baseline LLT above the eligibility threshold, a post-enrolment decision, though non-differential in a paired-eye design.	Some concerns. All 124 participants appear in the analysis, but no participant flow across the four visits is reported and no losses are stated.
D4. Measurement of the outcome	Low. LLT by automated LipiView interferometry and NIBUT by DR-1α, with masked assessors.	Low. LLT quantified automatically by LipiView interferometry with masked investigators.
D5. Selection of the reported result	Low. Prospectively registered (UMIN000024041) before recruitment; endpoints prespecified; a priori sample size calculation; Bonferroni adjustment applied.	Some concerns. No registration, protocol or sample size calculation. Several ocular surface measures recorded at baseline but only LLT reported; paired t-tests without adjustment for multiplicity.
Overall	Some concerns	Some concerns

Risk of bias varied substantially across the four included studies (Figure 2, Tables 2 and 3). Both randomised studies were judged as raising some concerns overall. In the paired-eye study the concern arose from the exclusion of ten of 57 enrolled participants after enrolment, one criterion for which was a baseline lipid layer thickness above the eligibility threshold; all other domains were at low risk. In the crossover study the concerns arose from incomplete reporting of the randomisation method, absence of participant flow across the four visits, and the absence of a registered protocol together with selective presentation of lipid layer thickness alone, although several other ocular surface measures had been recorded at baseline. In both studies the primary outcome was measured by automated interferometry with masked assessors, so measurement bias is unlikely. The two non-randomised studies were judged at serious risk of bias, principally because neither had a comparator and because meibomian gland outcomes were graded on semi-quantitative scales by unmasked assessors.

Table 3. Risk of bias in the non-randomised studies (ROBINS-I)

Domain	Amano & Inoue (2017) -single-arm before-and-after	Eom & Kim (2021) -monotherapy cohort
D1. Confounding	Serious. No comparator, so change over three months cannot be separated from natural fluctuation or regression to the mean. Co-intervention was well controlled: no other ophthalmic solution, lid hygiene or warm compression was used.	Serious. No control group. Confounding by co-intervention is absent in this cohort, but confounding by indication remains, since patients manageable on diquafosol alone were plausibly less severe; the cohort also mixes treatment-naive patients with those who discontinued previous therapy.
D2. Selection of participants	Moderate. Consecutive patients at a single hospital over a defined period, with follow-up beginning at the start of treatment.	Moderate. Follow-up began at the start of treatment with a fixed assessment schedule, but cohort membership was a clinician decision rather than protocol-driven.
D3. Classification of interventions	Low. Intervention clearly defined and adherence recorded at every visit.	Low. Unambiguous: 3% diquafosol six times daily with no concomitant ocular therapy.
D4. Deviations from intended interventions	Moderate. Adherence recorded only in broad self-reported categories; all participants reported at least 75%.	Moderate. Real-world observational conduct over eight weeks with no systematic adherence measurement.
D5. Missing data	Moderate. One of 14 enrolled patients withdrew; numbers analysed varied by visit; no imputation or sensitivity analysis.	Serious. 196 of 244 in the cohort analysis set (80.3%) analysed. Reasons for loss are reported only for the study as a whole and include adverse events and loss to follow-up.
D6. Measurement of outcomes	Serious. Masking not possible in a single-arm study; meibum score, meiboscore and lid margin signs graded on semi-quantitative scales by unmasked clinicians.	Serious. Assessors not masked; meibum quality and expressibility graded on 0–3 scales by different examiners across 20 institutions with no inter-observer reliability reported.
D7. Selection of the reported	Moderate. Registered (UMIN000018510), but eight LLT comparisons reported with no	Moderate. Primary endpoint prespecified and cohort-level data reported in full, but

result	adjustment for multiplicity.	numerous secondary outcomes across time points without adjustment for multiplicity.
Overall	Serious	Serious

Risk of bias varied substantially across the four included studies (Figure 2, Tables 2 and 3). Both randomised studies were judged as raising some concerns overall. In the paired-eye study the concern arose from the exclusion of ten of 57 enrolled participants after enrolment, one criterion for which was a baseline lipid layer thickness above the eligibility threshold; all other domains were at low risk. In the crossover study the concerns arose from incomplete reporting of the randomisation method, absence of participant flow across the four visits, and the absence of a registered protocol together with selective presentation of lipid layer thickness alone, although several other ocular surface measures had been recorded at baseline. In both studies the primary outcome was measured by automated interferometry with masked assessors, so measurement bias is unlikely. The two non-randomised studies were judged at serious risk of bias, principally because neither had a comparator and because meibomian gland outcomes were graded on semi-quantitative scales by unmasked assessors.

Table 4. Summary of Findings: topical 3% diquafosol sodium for dry eye disease with meibomian gland dysfunction

Outcome	Studies and participants	What the evidence shows	Certainty	Reasons for the rating
Lipid layer thickness -acute (20–60 min after a single drop)	2 randomised trials; 171 participants	LLT rose from 49.4 ± 16.2 to 70.6 ± 28.2 nm at 30 min ($P < 0.001$) with no change after artificial tears (between-group $P < 0.001$); and by 12.6 ± 2.0 nm at 20 min ($P < 0.001$), while saline, sodium hyaluronate and gatifloxacin produced no significant change.	Low	Downgraded once for risk of bias (some concerns in both trials) and once for indirectness (single-drop effect on a surrogate measure, exclusively East Asian populations).
Lipid layer thickness -resting, after 3 months	1 non-randomised study; 13 participants	Pre-instillation LLT unchanged after three months (81.8 vs 79.7 nm, $P = 0.791$). The acute post-instillation rise persisted and was largest at three months (+17.0 nm, $P = 0.039$).	Very low	Non-randomised starting point; downgraded for serious risk of bias and for imprecision. A null result from 13 patients cannot exclude a real effect.
Tear film stability - acute (NIBUT within 90 min)	1 randomised trial; 47 participants	NIBUT rose from 3.0 ± 1.8 s to 6.1 ± 2.9, 6.6 ± 2.7 and 6.1 ± 2.8 s at 30, 60 and 90 min (all $P < 0.001$), with no change after artificial tears. Tear meniscus height unchanged ($P = 0.96$).	Low	Downgraded once for risk of bias and once for imprecision (a single trial of 47 participants).
Tear film stability - over 8 weeks to 3 months	2 non-randomised studies; 209 participants	Fluorescein break-up time rose from 3.3 to 7.5 s over three months ($P < 0.0001$); TBUT rose from 3.92 to 5.53 s over eight weeks ($P < 0.001$). Neither study had a control group.	Very low	Non-randomised starting point; downgraded for serious risk of bias in both studies. No randomised evidence exists beyond 90 minutes.
Meibomian gland function	2 non-randomised studies; 209 participants	Meibum score fell from 2.3 to 1.8 ($P = 0.011$) and meiboscore from 2.6 to 2.2 ($P = 0.036$) over three months. Meibum quality improved by 0.25 ± 0.68 and expressibility by 0.14 ± 0.62 points over eight weeks. No randomised study assessed this outcome.	Very low	Non-randomised starting point; downgraded for serious risk of bias, with all grading applied by unmasked assessors, and for imprecision.
Ocular surface staining	2 non-randomised studies; 209	Fluorescein staining fell from 1.5 to 0.4 over three months ($P <$	Very low	Non-randomised starting point;

	participants	0.0001); corneal staining fell from 2.24 to 0.97 over eight weeks (P < 0.001).		downgraded for serious risk of bias in both studies.
Patient-reported symptoms	1 randomised trial and 2 non-randomised studies; 256 participants	Diquafosol improved 5 of 11 visual analogue symptom scores more than artificial tears. OSDI fell from 41.01 to 25.30 over eight weeks (P < 0.001), but DEQS (P = 0.065) and MGD questionnaire (P = 0.081) did not reach significance at three months.	Very low	Downgraded for risk of bias, for inconsistency across and within studies, and for imprecision.
Adverse events	1 randomised trial and 2 non-randomised studies	No serious adverse events in the randomised trial. One of 14 patients withdrew for ocular pain in the three-month study. In the observational study 132 of 450 subjects (29.3%) reported 193 events, 97% mild or moderate.	Very low	Downgraded for risk of bias and twice for imprecision: few events, short follow-up, and no study designed to detect harm.

Risk of bias varied substantially across the four included studies (Figure 2, Tables 2 and 3). Both randomised studies were judged as raising some concerns overall. In the paired-eye study the concern arose from the exclusion of ten of 57 enrolled participants after enrolment, one criterion for which was a baseline lipid layer thickness above the eligibility threshold; all other domains were at low risk. In the crossover study the concerns arose from incomplete reporting of the randomisation method, absence of participant flow across the four visits, and the absence of a registered protocol together with selective presentation of lipid layer thickness alone, although several other ocular surface measures had been recorded at baseline. In both studies the primary outcome was measured by automated interferometry with masked assessors, so measurement bias is unlikely. The two non-randomised studies were judged at serious risk of bias, principally because neither had a comparator and because meibomian gland outcomes were graded on semi-quantitative scales by unmasked assessors.

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AUTHOR CONTRIBUTIONS
The study's conception and design were a collaborative effort of all authors. FPR undertook the literature search, screening, and data extraction. H provided supervision throughout the study and offered critical revisions of the manuscript to ensure its intellectual rigour. JS played a key role in interpreting the data and drafting the manuscript. The final version was reviewed and approved by all authors.

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CONFLICT OF INTEREST
The authors declare that there is no conflict of interest regarding the publication of this paper.

ETHICAL APPROVAL
Ethical approval was deemed unnecessary for this study, as it constitutes a systematic review of previously published data.

DATA AVAILABILITY
Further information may be requested from the corresponding author, while all data generated or analyzed in the course of this study are included within this published article.

ARTIFICIAL INTELLIGENCE DISCLOSURE
Artificial intelligence tools were used to assist with language refinement and manuscript preparation. During revision, an artificial intelligence tool was also used to verify the reference list and to extract outcome data from the full text of the included studies. Errors in the reference list of an earlier version, including citations that could not be verified against published records, were identified and corrected as a result. All references in the present version were checked against the published articles, and all reported numerical results were extracted from the full text of the included studies. The authors take full responsibility for the content of the manuscript.

ABBREVIATIONS
DED: Dry Eye Disease
MGD: Meibomian Gland Dysfunction

TBUT: Tear Break-Up Time

OSDI: Ocular Surface Disease Index

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