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Adjunctive Oral Vitamin D Supplementation Enhances Tear Secretion in Patients with Refractive Errors and Dry Eye Syndrome: A Double-Blind Randomized Controlled Trial

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ABSTRACT: Refractive errors often coexist with dry eye syndrome (DES), exacerbated by vitamin D deficiency through impaired tear film stability and inflammation. This trial assessed whether adjunctive oral vitamin D enhances the efficacy of artificial tears in refractive error-associated DES. A double-blind randomized controlled trial enrolled 45 adult patients (aged 17–45 years) with refractive errors and confirmed DES at the Refraction Ophthalmology Outpatient Clinic of a tertiary teaching hospital. Participants were randomized 1:1 to artificial tears monotherapy (Group A, n=23) or combination therapy with 1000 IU oral cholecalciferol daily plus artificial tears (Group B, n=22) for four weeks. Primary outcomes were serum 25-hydroxyvitamin D [25(OH)D] levels and DES parameters including Schirmer's test, tear break-up time (TBUT), meibomian gland evaluation (MGE), and Ocular Surface Disease Index (OSDI). After dropouts, 39 patients were analyzed (monotherapy n=21, combination n=18). Monotherapy showed a paradoxical vitamin D category shift (normal: 52.38% to 38.10%; $p<0.001$) with stable Schirmer test 1 (4.76% abnormal; $p=0.048$ bilaterally); Schirmer test 2, TBUT, MGE, and OSDI were non-significant. Combination therapy improved vitamin D status ($p<0.001$), Schirmer test 1 (22.22% to 11.11%; $p=0.039$), and Schirmer test 2 (44.44% to 27.78%; $p=0.007$). No significant intergroup differences in dry eye severity ($p=0.541$ baseline; $p=0.647$ post-intervention); significant within-group severity reduction for combination therapy (mild DES: 61.11% to 83.33%; $p=0.045$) versus monotherapy ($p=0.133$). Adjunctive oral vitamin D supplementation to artificial tears significantly improves vitamin D status and tear secretion in refractive error-associated DES, with superior within-group dry eye severity reduction compared to monotherapy.

1. INTRODUCTION

Refractive errors, encompassing myopia, hyperopia, and astigmatism, constitute a predominant etiology of uncorrected visual impairment globally, contributing to approximately 49% of cases and 20% of blindness (Hashemi et al., 2018). In xxxx, the Rapid Assessment of Avoidable Blindness (RAAB) survey (2014–2016) underscores uncorrected refractive errors as a major

modifiable risk factor, trailing only cataracts in prevalence (Ismandari, 2018). Progressive axial elongation, particularly among myopic children, has been associated with accelerated refractive shift and an increased risk of long-term complications (Hou et al., 2018). These optical aberrations precipitate blurred vision that inadvertently compromises tear film dynamics through diminished blink frequency, particularly during near tasks. Concomitant dry eye syndrome (DES) amplifies this burden as a multifactorial disorder of tear film instability, reduced secretion, and evaporative loss, engendering ocular surface inflammation, discomfort, and refractive correction intolerance (Madrid-Costa et al., 2019).

Vitamin D deficiency—prevalent in 40–70% of DES cohorts—exacerbates this burden via impaired immunomodulation. Experimental evidence indicates that vitamin D suppresses T-lymphocyte mitogenesis and modulates B-cell differentiation (Rigby et al., 1984; Chen et al., 2007), while 25-hydroxyvitamin D [25(OH)D] further attenuates pro-inflammatory cytokines, including interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- α), and bolsters antimicrobial peptide expression on the ocular surface, with documented benefit in refractory DES (Bae et al., 2016). Epidemiologic data further link hypovitaminosis D to refractive anomalies, notably myopia, potentially through axial elongation and ciliary muscle hypo-responsiveness (Tideman et al., 2016; Malik et al., 2020). Oral vitamin D supplementation has additionally been shown to improve tear break-up time, Schirmer scores, and symptom burden as measured by the Ocular Surface Disease Index (Yang et al., 2018). However, the synergistic interplay between vitamin D repletion and lubricative therapies in refractive error-associated DES remains underexplored, particularly in resource-limited settings. This trial interrogates whether adjunctive oral cholecalciferol potentiates artificial tears' efficacy in refractive error-associated DES.

2. MATERIALS AND METHODS

This study was approved by the Health Research Ethics Committee of Universitas Hasanuddin and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment. This double-blind, prospective, randomized controlled clinical trial (RCT) was conducted at the Refraction Ophthalmology Outpatient Clinic of a tertiary teaching hospital, from August 2022 until the required sample size was achieved.

2.1 Study Population and Sampling

The population comprised adult patients with refractive errors. Samples were selected by consecutive sampling. Inclusion criteria: (1) adults aged 17–45 years with refractive errors and confirmed DES. Exclusion criteria: (1) ocular infection; (2) prior ocular surgery; (3) routine vitamin D supplementation within three months; (4) hormonal contraceptive use; (5) pregnancy; (6) gastrointestinal surgery history. Dropout criteria: (1) non-adherence; (2) therapy-related complications; (3) missed follow-up.

2.2 Sample Size Calculation

The minimum sample size was estimated using Federer's formula: $(n - 1)(t - 1) \geq 15$, where $t = 2$, yielding $n \geq 16$ per group (total ≥ 32). Accounting for 10% dropout, the final sample was set at 60 participants (30 per group).

2.3 Interventions

Participants were randomized 1:1 into two double-blind groups by computer-generated random blocks. Group A (monotherapy) received artificial tears (sodium chloride 0.9% and potassium chloride 0.2%; one drop four times daily). Group B (combination therapy) received the same artificial tears plus oral cholecalciferol 1000 IU daily (one tablet post-meal for 30 days). Compliance was assessed via patient diaries and residual tablet counts at week four.

2.4 Outcome Measures

Primary outcomes were serum 25(OH)D levels (ELISA; insufficiency <30 ng/mL, normal 30–100 ng/mL, hypervitaminosis >100 ng/mL) and DES parameters: TBUT (<10 seconds = abnormal), Schirmer's test 1 and 2 (≤ 10 mm = abnormal), OSDI (0–12 normal, 13–22 mild, 23–32 moderate, >33 severe), and MGE (Meiboscore grade 0–3). Secondary outcomes included DES severity shifts per TFOS DEWS II criteria. Assessments were performed at baseline and week four by masked examiners.

2.5 Statistical Analysis

Data were analyzed using IBM SPSS Statistics version 28. Normality was assessed via Shapiro-Wilk test. Parametric data used paired/unpaired t-tests; non-parametric data used Wilcoxon signed-rank/Mann-Whitney U tests. Categorical variables used chi-square or Fisher's exact tests. Significance was set at $p < 0.05$.

3. RESULTS AND DISCUSSION

3.1 Baseline Characteristics

A total of 45 patients were enrolled; six were lost to follow-up, yielding 39 analyzable cases (monotherapy n=21, combination n=18), as shown in **Figure 1**. Baseline and clinical characteristics are presented in **Table 1**. The majority were female (28, 71.79%), with most aged 21–30 years. Baseline dry eye severity was predominantly mild (24, 61.54%). Serum 25(OH)D was normal in 43.59%, with equal proportions of insufficiency and hypervitaminosis (28.21% each). Astigmatism predominated as the leading refractive error (66.67% OD, 71.79% OS), with no hyperopia cases. Pre- and post-intervention chi-square analyses showed no significant association between refractive error type and dry eye severity (all $p > 0.05$; OD pre: $p = 0.746$, OS pre: $p = 0.817$, OD post: $p = 0.139$, OS post: $p = 0.662$).

Table 1. Combined baseline demographics, clinical characteristics, visual acuity, and refractive error distribution (n=39).

Characteristics	n (%)
DEMOGRAPHICS (N=39)	
Age group (years)	
17–20	11 (28.21)
21–30	19 (48.72)
31–40	9 (23.08)
Sex	
Male	11 (28.21)
Female	28 (71.79)
Treatment group	
Artificial tears monotherapy	21 (53.85)
Combination (artificial tears + oral vitamin D)	18 (46.15)
DRY EYE AND VITAMIN D STATUS	
Dry eye severity at baseline	
Mild	24 (61.54)
Moderate	14 (35.90)
Severe	1 (2.56)
Serum vitamin D category†	
Insufficiency (<30 ng/mL)	11 (28.21)
Normal (30–100 ng/mL)	17 (43.59)
Hypervitaminosis (>100 ng/mL)	11 (28.21)
VISUAL ACUITY AND REFRACTIVE ERROR	OD / OS*, n (%)
UCVA* distance vision impairment (WHO criteria)	
Good (>20/40)	15 (38.46) / 17 (43.59)
Mild (20/40–20/60)	6 (15.38) / 5 (12.82)
Moderate (20/60–20/200)	5 (12.82) / 4 (10.26)
Severe (20/200–3/60)	7 (17.95) / 9 (23.08)
Blindness (<3/60)	6 (15.38) / 4 (10.26)
Refractive error type	
Myopia	13 (33.33) / 11 (28.21)

Characteristics	n (%)
Hyperopia	– / –
Astigmatism	26 (66.67) / 28 (71.79)

*OD = oculus dexter (right eye); OS = oculus sinister (left eye); UCVA = uncorrected visual acuity. †Serum vitamin D categorized as 25-hydroxyvitamin D [25(OH)D]: insufficiency <30 ng/mL; normal 30–100 ng/mL; hypervitaminosis >100 ng/mL.

3.2 Changes in Serum Vitamin D and Ocular Surface Parameters

Serum 25(OH)D distributions pre- and post-intervention are shown in Table 2. In the monotherapy group, the normal proportion decreased from 52.38% to 38.10% post-intervention, with increased insufficiency (28.57% to 38.10%) and hypervitaminosis (19.05% to 23.81%; $p < 0.001$). In the combination group, insufficiency decreased (38.89% to 33.33%) and normal levels increased (33.33% to 44.45%; $p < 0.001$).

Table 2. Serum 25(OH)D category distribution pre- and post-intervention by treatment group.

Category†	Monotherapy (n=21)			Combination Therapy (n=18)		
	Pre, n (%)	Post, n (%)	p-value	Pre, n (%)	Post, n (%)	p-value
Insufficiency	6 (28.57)	8 (38.10)	<0.001*	7 (38.89)	6 (33.33)	<0.001*
Normal	11 (52.38)	8 (38.10)		6 (33.33)	8 (44.45)	
Hypervitaminosis	4 (19.05)	5 (23.81)		5 (27.78)	4 (22.22)	

*Chi-square test, $p < 0.001$, statistically significant. †25(OH)D = 25-hydroxyvitamin D.

Ocular surface evaluations are detailed in Table 3. Monotherapy showed bilateral stability in Schirmer test 1 abnormality rates (4.76% pre and post, $p = 0.048$); Schirmer test 2 ($p = 0.228$), TBUT (100% abnormal post-intervention, not applicable for statistical comparison), MGE ($p = 0.071$), and OSDI ($p = 0.053$) were non-significant. Combination therapy showed significant improvements in Schirmer test 1 (22.22% to 11.11%, $p = 0.039$ bilaterally) and Schirmer test 2 (44.44% to 27.78%, $p = 0.007$ bilaterally). TBUT remained 100% abnormal; MGE ($p = 0.051$) and OSDI showed no significant changes.

Table 3. Ocular surface parameter evaluations pre- and post-intervention for both treatment groups.

Parameter	Side	Monotherapy (n=21)			Combination Therapy (n=18)		
		Pre Abnormal n (%)	Post Abnormal n (%)	p-value	Pre Abnormal n (%)	Post Abnormal n (%)	p-value
Schirmer Test 1	OD†	1 (4.76)	1 (4.76)	0.048*	4 (22.22)	2 (11.11)	0.039*
	OS†	1 (4.76)	1 (4.76)	0.048*	4 (22.22)	2 (11.11)	0.039*
Schirmer Test 2	OD	4 (19.05)	5 (23.81)	0.228	8 (44.44)	5 (27.78)	0.007*
	OS	4 (19.05)	5 (23.81)	0.228	8 (44.44)	5 (27.78)	0.007*
TBUT†	OD	20 (95.24)	21 (100)	N/A	18 (100)	18 (100)	N/A
	OS	20 (95.24)	21 (100)	N/A	18 (100)	18 (100)	N/A
MGE† (Loss <1/3)	OD	6 (28.57)	2 (9.52)	0.071	5 (27.78)	3 (16.67)	0.051

Parameter	Side	Monotherapy (n=21)			Combination Therapy (n=18)		
		Pre Abnormal n (%)	Post Abnormal n (%)	p-value	Pre Abnormal n (%)	Post Abnormal n (%)	p-value
	OS	6 (28.57)	2 (9.52)	0.071	5 (27.78)	3 (16.67)	0.051
OSDI† (Moderate)	–	6 (28.57)	4 (19.05)	0.053	4 (22.22)	3 (16.67)	1.000

*Chi-square test, $p < 0.05$, statistically significant. †OD = oculus dexter (right eye); OS = oculus sinister (left eye); TBUT = tear break-up time; MGE = meibomian gland evaluation; OSDI = Ocular Surface Disease Index.

3.3 Dry Eye Severity Comparison Pre- and Post-Intervention

Intergroup and within-group dry eye severity comparisons are presented in Table 4. Baseline severity was comparable across groups (chi-square $p = 0.541$). Post-intervention, both groups shifted toward mild severity (90.48% monotherapy, 83.33% combination; intergroup $p = 0.647$). Within-group analysis revealed a significant severity reduction in the combination group (mild DES: 61.11% to 83.33%, $p = 0.045$), but not in monotherapy (61.90% to 90.48%, $p = 0.133$).

Table 4. Dry eye severity distribution: intergroup comparison (Part A) and within-group comparison (Part B) pre- and post-intervention (chi-square test).

Severity	Monotherapy (n=21), n (%)	Combination (n=18), n (%)	p-value (intergroup)
A. Intergroup comparison (chi-square test)			
Pre-intervention			
Mild	13 (61.90)	11 (61.11)	0.541
Moderate	8 (38.10)	6 (33.33)	
Severe	–	1 (5.56)	
Post-intervention			
Mild	19 (90.48)	15 (83.33)	0.647
Moderate	2 (9.52)	3 (16.67)	
Severe	–	–	
B. Within-group comparison (chi-square test)			
Severity	Pre, n (%)	Post, n (%)	p-value (within-group)
Monotherapy			
Mild	13 (61.90)	19 (90.48)	0.133
Moderate	8 (38.10)	2 (9.52)	
Severe	–	–	
Combination Therapy			

Severity	Monotherapy (n=21), n (%)	Combination (n=18), n (%)	p-value (intergroup)
Mild	11 (61.11)	15 (83.33)	0.045*
Moderate	6 (33.33)	3 (16.67)	
Severe	1 (5.56)	—	

*p<0.05, statistically significant.

3.4 Discussion

This study predominantly enrolled female participants (71.79%) with refractive errors and DES, consistent with prior epidemiologic reports of higher DES prevalence among women, particularly those of reproductive and perimenopausal age (Stapleton et al., 2017; Zhang et al., 2020). Astigmatism was the leading refractive error identified (66.67% right eye, 71.79% left eye), consistent with population-based estimates identifying astigmatism as the most common ametropia among both children and adults (Hashemi et al., 2018). Comparable associations between uncorrected refractive error and dry eye symptomatology have also been reported in occupational cohorts with high near-work demands (Dhungel and Shrestha, 2017). Occupational factors, including prolonged visual display terminal use, may further exacerbate DES via reduced blink rate, as demonstrated in cohorts with high screen exposure (Bazeer et al., 2019).

Baseline serum 25(OH)D was normal in 43.59% of participants, with balanced proportions of insufficiency and hypervitaminosis (28.21% each), differing from prior meta-analytic estimates in which the majority of DES patients demonstrated serum levels below 20 ng/mL (Askari et al., 2020). Hypovitaminosis D is understood to drive DES via impaired immunomodulation, supported by the demonstrated expression of vitamin D receptors and local hydroxylase activity within corneal epithelium and other ocular barrier tissues (Rolando and Barabino, 2023; Alsalem et al., 2014). Deficiency has additionally been shown to heighten oxidative stress, disrupting meibomian gland function and tear film stability through reactive oxygen species accumulation and consequent lipid peroxidation (Dogru et al., 2018).

The paradoxical vitamin D category shift observed in the monotherapy group—wherein the proportion with normal levels declined despite no supplementation—may reflect natural fluctuation in gastrointestinal absorption influenced by molecular form, food matrix, and host factors such as age, adiposity, and genetic polymorphisms (Maurya and Aggarwal, 2017). In the combination arm, daily cholecalciferol supplementation for 30 days significantly improved vitamin D status and was accompanied by improvement in basal and reflex tear secretion, corroborating findings from comparable supplementation trials in deficient cohorts (Watts et al., 2020; Sridhar and Tripathy, 2020).

Mechanistically, activated vitamin D is understood to suppress key inflammatory mediators—including TNF- α and interleukins 1, 2, 6, 8, and 12—while inducing the anti-inflammatory cytokine IL-10, thereby restoring tear film homeostasis (Bae et al., 2016; Rolando and Barabino, 2023; Dogru et al., 2018). Current guidance recommends specific serum 25(OH)D thresholds and supplementation regimens of 8–12 weeks for optimal ocular surface response; the non-significant improvements observed in OSDI and meibomian gland parameters in this trial likely reflect the comparatively short four-week intervention period (Holick et al., 2011; Askari et al., 2020; Watts et al., 2020).

Beyond inflammatory modulation, vitamin D may influence axial length regulation in myopic eyes, with longitudinal data linking low vitamin D status to accelerated axial elongation and altered tear film parameters in myopic cohorts (Saka et al., 2010; Hazra et al., 2022). Oral bioavailability of vitamin D to the ocular surface may nonetheless be constrained by corneal avascularity, a feature of normal corneal anatomy and physiology that limits direct systemic delivery to avascular ocular tissues (American Academy of Ophthalmology, 2020–2021).

Limitations of this study include the short follow-up duration, fixed supplementation dose precluding dose-response analysis, and single-center design. Multicenter trials with extended follow-up, variable dosing regimens, and molecular assays of ocular vitamin D receptor expression are warranted to further validate adjunctive vitamin D supplementation in refractive error-associated DES.

4. CONCLUSION

Adjunctive oral vitamin D supplementation significantly improves tear secretion and dry eye severity in patients with refractive errors. These findings support routine assessment of vitamin D status in the management of DES alongside conventional lubricative therapy. Prospective validation with extended follow-up, dose titration, and assessment of ocular vitamin D receptor pharmacodynamics is warranted.

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AUTHOR CONTRIBUTIONS

Conceptualisation: I.N. Iskandar, P. Syawal. Methodology: I.N. Iskandar, R.B. Ladju. Formal analysis: I.N. Iskandar, R.B. Ladju, M.N. Zuhair. Investigation and data curation: I.N. Iskandar, H. Eka, M. A. Ismail. Supervision: P. Syawal, H. Eka, M. A. Ismail, J. Sirajuddin. Writing –original draft: I.N. Iskandar, M.N. Zuhair. Writing –review and editing: all authors. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST

The authors declare no financial or non-financial conflicts of interest.

ETHICS STATEMENT

This study was approved by the Health Research Ethics Committee of Universitas Hasanuddin and was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants prior to enrollment.

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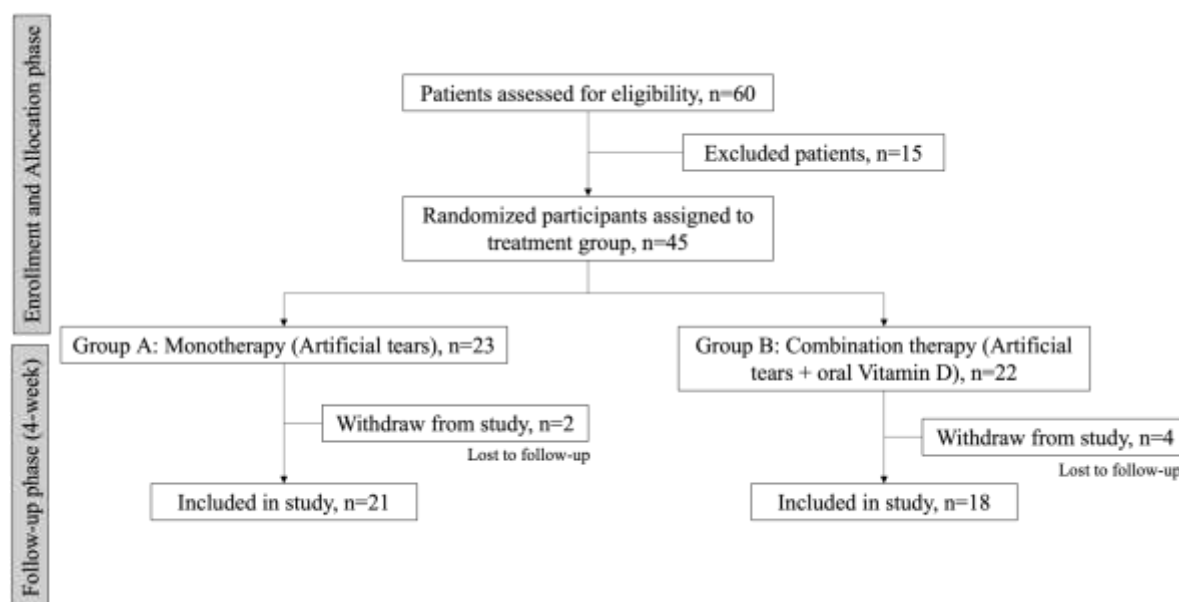


Figure 1. Flow diagram of participant recruitment, randomization, and follow-up. Of 60 patients assessed for eligibility, 45 were randomized (Group A: monotherapy n=23; Group B: combination therapy n=22). Five participants were lost to follow-up (Group A: n=2; Group B: n=3), yielding 39 analyzable cases (Group A: n=21; Group B: n=18) at four weeks.