

ORIGINAL ARTICLE

The prevalence of ocular dryness associated with systemic isotretinoin in acne patients in Iraq

Mohammed Al-Daraji¹, Saad H. Salman¹, Ali Abbas Hassan Fazaa¹, Ahmed Flayyih Hasan^{2,3}

¹COLLEGE OF MEDICINE, IBNSINA UNIVERSITY OF MEDICAL AND PHARMACEUTICAL SCIENCES, BAGHDAD, IRAQ

²BIOTECHNOLOGY RESEARCH CENTER, AL-NAHRAIN UNIVERSITY, BAGHDAD, IRAQ

³DEPARTMENT OF MEDICAL LABORATORY TECHNIQUES, COLLEGE OF HEALTH AND MEDICAL TECHNOLOGY, AL-FARABI UNIVERSITY, BAGHDAD, IRAQ

ABSTRACT

Aim: This research was conducted to assess the prevalence of ocular dryness during the course of systemic isotretinoin in acne patients in Iraq.

Materials and Methods: 64 acne patients using systemic isotretinoin in doses ranging from 20mg to 60 mg were enrolled in this study. All patients had been checked for ocular dryness by using Schirmer's test before starting therapy and after each month regularly for 6 times.

Results: 64 acne patients were included in this study with a high percentage of the female gender (81.75%) with a mean age of 21.2 ± 3.4 . The mean duration of systemic isotretinoin is 4.3 months while the mean total cumulative dose is 5.8 grams. About 31.25% among the participants have developed ocular dryness, and the most frequent grade is grade III (50%). 70% of patients that have ocular dryness use lubricant eye drops. However, no significant correlations were seen between dosage, gender, duration, age, and TCD with ocular dryness.

Conclusions: This research reveals that ocular dryness may occur during the course of systemic isotretinoin. This research contributes to the raise the awareness of the effects of isotretinoin use on the health of the ocular surface. However, no significant correlations were seen between dosage, gender, duration, age, and TCD with ocular dryness.

KEY WORDS: Schirmer's test, ocular, dry eye, systemic isotretinoin

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INTRODUCTION

Acne vulgaris is the most common dermatological disease adolescents, mainly occur in persons aged 11–30 years [1, 2]. Acne is mainly classified as mild, moderate, and severe. Acne in the face can cause severe inflammatory responses, which may lead to scarring in the face, making the patients look for reasonable management and helping them to overcome the psychosocial impact and psychological burden [3].

Systemic isotretinoin was approved to be utilized in acne, especially in severe, resistant, and nodular types in 1982 [4]. Most pathophysiological factors involved in acne are typically targeted by systemic isotretinoin producing a high satisfaction outcome [5, 6].

Isotretinoin therapy is associated with a variety of side effects ranging in consequences and severity. Mucocutaneous effects are more common adverse effect such as xerosis and cheilitis [7].

There are several reports of ocular side effects ranging in severity from less severe effects such as dry eye diseases and corneal surface alterations e.g. ocular irri-

tation, visual field defects and dark adaptation abnormalities to extremely rare and serious adverse effects include optic neuritis, retinal toxicity and corneal opacities, which may lead to permanent damage of ocular tissue if unrecognized [8, 9]. These ocular adverse effects have been reported within days to years of isotretinoin therapy initiation [10]. Ocular side effects are suspected to be dose dependent and become tolerable with a change in dosing and symptomatic management these notes are reported in some cases [11].

However, these ophthalmological side effects, such as dry eye disease, blepharitis, and conjunctivitis [12]. Systemic administration of isotretinoin may cause change in the structure and function of the meibomian gland and suppress the production of lipids, causing rapid tear evaporation [13]. In addition, it alters the epithelium of conjunctiva, influencing the morphology of goblet cells and affecting mucin production [14]. The alteration of the mucin and lipid layers causes instability of the tear film, leading to dry eye by evaporation, increased osmolarity, and dry eye symptoms [15]. It is important

Table 1. Demographic character of the participants

Character	Number	[%]
Total	64	100
Gender	Male	12
	Female	52
Age (years)	(21.2± 3.7)	
Weight (kg)	(58.42± 7.8 kg)	

Source: Authors own work

Table 2. Duration and dosage of isotretinoin

Duration and dosage	Number	[%]	TCD(g)	M	SD
Duration of isotretinoin	3 month	14	21.9		
	4 month	28	43.75		
	6 month	24	37.5		
Dosage	20 mg	11	17.18	1.8	
	40 mg	35	54.68	4.8	
	60 mg	18	28.12	10.8	
Months used				4.3	1.52
Total cumulative dose(g)				5.8	4.58

Note: M: mean, SD: Standard Deviation, TCD: Total cumulative dose

Source: Authors own work

for dermatologists to be aware and educate patients about the possible ophthalmologic adverse effects of systemic isotretinoin [16].

AIM

This study was conducted to assess the prevalence of ocular dryness in acne patients in Iraq who were undergoing systemic isotretinoin treatment and raise their awareness about the adverse effect of systemic isotretinoin on ocular dryness.

MATERIALS AND METHODS

64 patients participated in this study having moderate to severe acne with a mean age of 21.2± 3.7 receiving 20-60 mg of systemic isotretinoin with regular follow up for 6 months durations by an ophthalmologist to evaluate their ocular dryness using Schirmer’s test (Most commonly applied in clinical tests for dry-eye disease evaluation, treatment, and management. It is thought that inserting a strip of filter paper into the inferior fornix and measuring the length of the wetted portion after 5 minutes provides a direct assessment of tear production rate).

Schirmer’s test has four grades to estimate the ocular dryness that begin with normal (Grad 1), mild (Grade 2), moderate (Grade 3) and severe (Grade 4).

All the patients undergo a checkup before the beginning of the treatment and every month during the course.

The patients who had these criteria had been excluded as follows:

- 1. Patients that had previous eye surgery.
- 2. Any systemic diseases.
- 3. Contact lens use.
- 4. Dry eye disease.

ETHICAL APPROVAL

This study was done in an outpatient clinic of dermatology and ophthalmology in Baghdad city from April 2023 to April 2024. The study was approved by The Institutional Review Board/Ethical Review Board (EAC1452). All patients read and signed the informed consent when they were included in the study.

RESULTS

64 participants were included in this study, female participants represent 81.25%.The mean age of participants was 21.2± 3.7 years and their mean weight was 58.42± 7.8 kg (Table 1, Fig. 1).

Regarding the duration of systemic isotretinoin, 37.5% of the participants used it for 6 months and 43.75% for 4 months while 21.9% used it for 3 months. Concerning the daily dosage of systemic isotretinoin, 54.68% of the patients used 40 mg, which is the commonest dose of isotretinoin while 28.12% used 60 mg and the rest of the participants were using 20mg among the course 7.18% (Table 2, Fig 2-3).

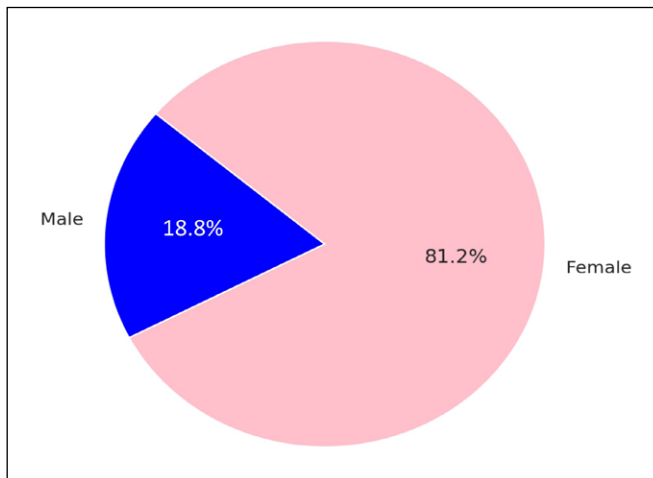


Fig. 1. Gender distribution

Source: Own materials

The total cumulative dose (TCD) of the participants using 20 mg/kg/day was 1.8 g for 3 months, 4.8 gram was for participants that had been using 40 mg/kg/day for 4 months and 10.8 g for participants using 60 mg/kg/day for 6 months (Table 2). Most of the participants that are using systemic isotretinoin had a grad 1 (68.75%), while the other participants had a grad 2, 3, and 4 (31.25).

The number of participants that had a change in the ocular dryness when they were using systemic isotretinoin as a follow-up (a G2 of ocular dryness is 4, 10 had a G3, and 6 of them had a G4) as shown in table 3 and figure 4.

REPEATED-MEASURES ANOVA FOR SCHIRMER'S TEST

A repeated-measures ANOVA was conducted with Time (baseline, Month 1, Month 2, ..., Month 6) as the with-

in-subject factor and Isotretinoin Dose (20 mg/day, 40 mg/day, 60 mg/day) as a between-subject factor. Additional covariates included Gender and Age. Mauchly's test of sphericity was satisfied ($p = 0.08$), indicating no violation of sphericity in table 4 and figure 5.

- **Main Effect of Time:** Statistically significant ($p < 0.001$), indicating that tear production changed across the six-month period.

- **Dose:** Did not reach statistical significance ($p = 0.068$) but showed a notable trend.

- **Time × Dose Interaction:** Significant ($p = 0.001$), suggesting that changes in Schirmer's scores over time differed by dose group.

Post-hoc Pairwise Comparisons (Bonferroni-adjusted) revealed that the largest decreases in Schirmer's scores occurred between baseline and Month 3 (mean difference = 6.2 mm, $p < 0.001$) and that the 60 mg/day group showed significantly lower scores at Month 4 and Month 5 compared to the 20 mg/day group ($p < 0.01$).

Ordinal Logistic Regression for Dryness Grade

An ordinal logistic regression model (proportional odds model) was fitted to dryness grade (1 = Normal, 2 = Mild, 3 = Moderate, 4 = Severe) with Time, Dose, Age, Gender, and Total Cumulative Dose (TCD) as predictors. Dryness grade measurements were taken at each monthly visit, and patient ID was included as a random effect to account for repeated measures (Table 5, Fig 6).

DISCUSSION

The objective of our research was to investigate the prevalence of the eye dryness with the use of systemic isotretinoin, which is measured by Schirmer's test in Iraqi patients.

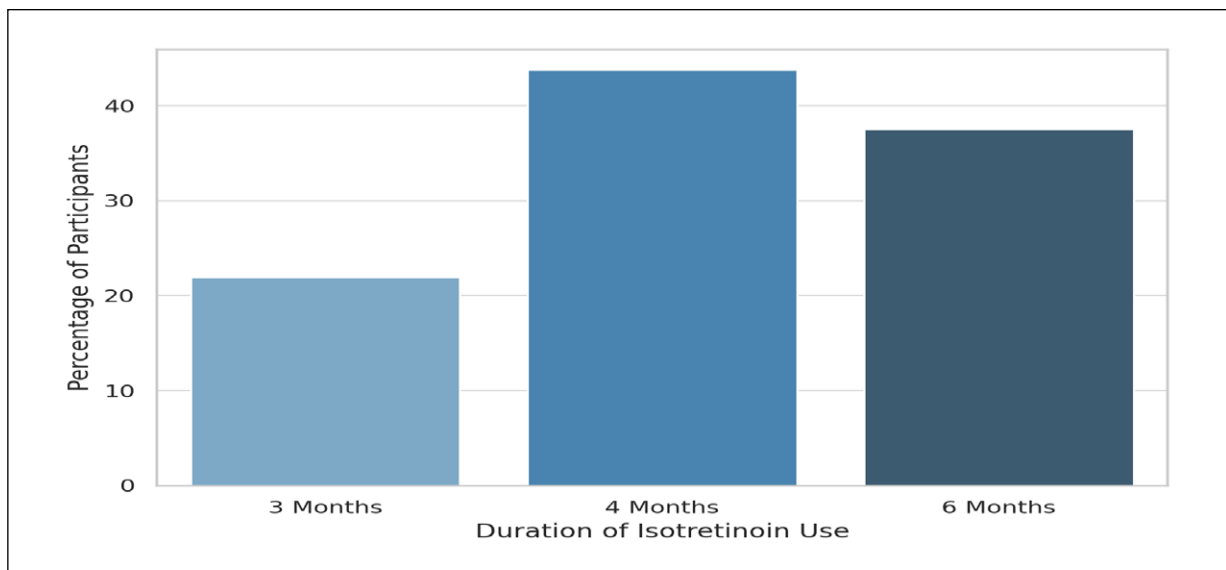


Fig. 2 Duration of isotretinoin use

Source: Own materials

Table 3. Prevalence of ocular dryness in patients using systemic isotretinoin in Iraq

Grade	Number	[%]
1	44	68.75
2	4	6.25
3	10	15.62
4	6	9.37

Source: Authors own work

Table 4. Repeated-measures ANOVA results for Schirmer's test

Source	SS	Df	MS	F	p-value	Partial η^2
Time	3,620.1	5	724.0	11.57	< 0.001	0.21
Dose	920.4	2	460.2	2.78	0.068	0.08
Gender	380.2	1	380.2	2.31	0.135	0.04
Time $\times$ Dose	2,040.6	10	204.1	3.84	0.001	0.15
Error	12,100.3	186	65.05	—	—	—

Source: Authors own work

Table 5. Ordinal logistic regression for dryness grade

Predictor	Coefficient (β)	Standard Error	p-value	Odds Ratio (95% CI)
Time (per month)	0.32	0.09	0.001	1.37 (1.14–1.64)
Dose (Ref = 20 mg)				
40 mg	0.28	0.12	0.025	1.32 (1.03–1.70)
60 mg	0.51	0.15	0.001	1.67 (1.24–2.23)
TCD (per gram)	0.04	0.03	0.145	1.04 (0.98–1.12)
Age (years)	–0.01	0.02	0.572	0.99 (0.96–1.02)
Gender (Ref = Male)	0.19	0.14	0.178	1.21 (0.91–1.62)

Source: Authors own work

Before the treatment course began, all the participants didn't experience any eye symptoms. With respect to the duration and dosage of isotretinoin usage, the majority of participants utilize systemic isotretinoin for 4–6 months (81.25%). The most frequently prescribed daily dosage was 40 mg (54.68%).

Our study had tested effect of systemic isotretinoin on ocular dryness in acne patients in Iraq, depending on the duration of isotretinoin use and TCD. The results showed that most of the participants were using 40 mg/kg/day with TCD of 4.8 gram (54.68%), and the highest TCD that was used by the participants is 10.8 gram (28.12%).

About the cease of isotretinoin use, all of the participants hadn't quit using it. This implies that the majority of people in our study kept their isotretinoin intake during the course of the research.

It emphasizes the potential ocular side effects of isotretinoin and the development of symptoms. It assures the importance of addressing and monitoring ocular dryness during systemic isotretinoin treatment to ensure the visual health and well-being of the patients. This provides evidence of the findings of Jarab et al. (2022) [17].

Basheikh et al. (2020), they observed a comparable pattern of lubricant eye drop usage during isotretinoin treatment [18]. As in our study, during the treatment of systemic isotretinoin, about 31.25% of participants had ocular dryness (grades 2, 3, 4) and they needed the lubricant eye drops, about 50% used eye drop lubricant when they needed it and 20% used eye drop lubricant most of the time. Grade 2 (30%) did not use lubricant eye drops at all.

A significant proportion of participants used lubricant eye drops; this indicates the necessity of proactive management of ocular symptoms to assure patient comfort and reduce the risk of ocular side effects during isotretinoin treatment.

The most frequent doses that cause ocular dryness among participants are 40 mg in a 4 month duration, which might be due to a known side effect of systemic isotretinoin on mucosal body membranes or unrevealed causes that need to be investigated more. Most of the participants that developed an ocular dryness had occurred during the third month due to the effect of isotretinoin on mucosal membrane with great individual variation.

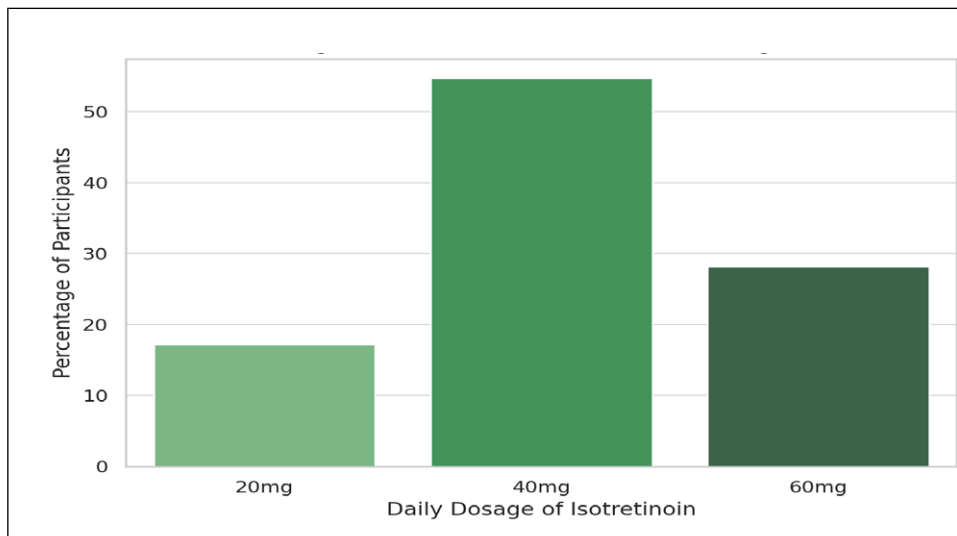


Fig. 3. Dosage distribution of isotretinoin
Source: Own materials

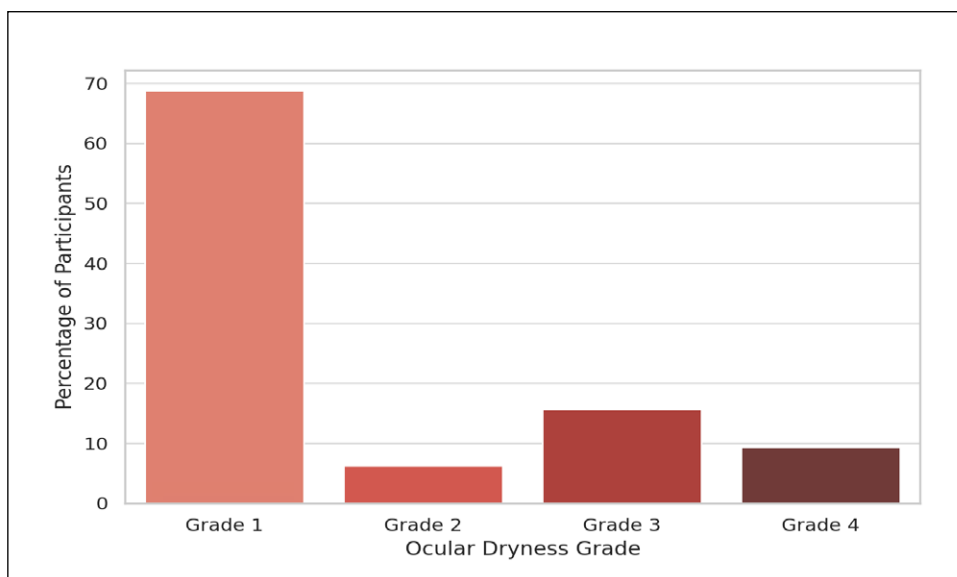


Fig. 4. Prevalence of ocular dryness
Source: Own materials

During the course of the systemic isotretinoin, we did not observe a correlation between TCD of systemic isotretinoin and ocular dryness among the participants. This could be related to the small sample size, the younger age group of the participants, and excluding the patients that already have an ocular dry eye disease.

Table 4 presents the results of the repeated-measures ANOVA on Schirmer's test scores, indicating a significant main effect with time and a significant Time $\times$ Dose interaction. The finding indicates that tear production varied significantly throughout the six months of treatment, with this variation being affected by the daily dose of isotretinoin. Especially, patients who were given higher doses experienced a more significant decrease in Schirmer's scores beginning approximately the third month, which is the time when isotretinoin's known mucocutaneous side effects spread to the ocular surface. Although the dose effect per se did not attain conventional statistical significance, the interaction term refers to the way the importance of dosage becomes

greater with the passage of time. The results of this study corroborate the clinical observation that the manifestation of increased dryness frequently arises during the advanced stages of isotretinoin treatment and can potentially be alleviated through the implementation of proactive management approaches, including the earlier application of lubricating eye drops.

The lack of a significant influence of gender or age in the ANOVA analysis is consistent with previous research indicating that ocular dryness associated with isotretinoin is predominantly influenced by pharmacological factors rather than demographic variables. Despite this, the descriptive statistics showed a quantitatively greater reduction in tear production in female subjects, suggesting that although not statistically significant, female patients can somehow perceive or experience dryness differently. These findings underscore the necessity for ongoing ocular evaluation independent of patient demographics, particularly when high daily doses of isotretinoin are prescribed.

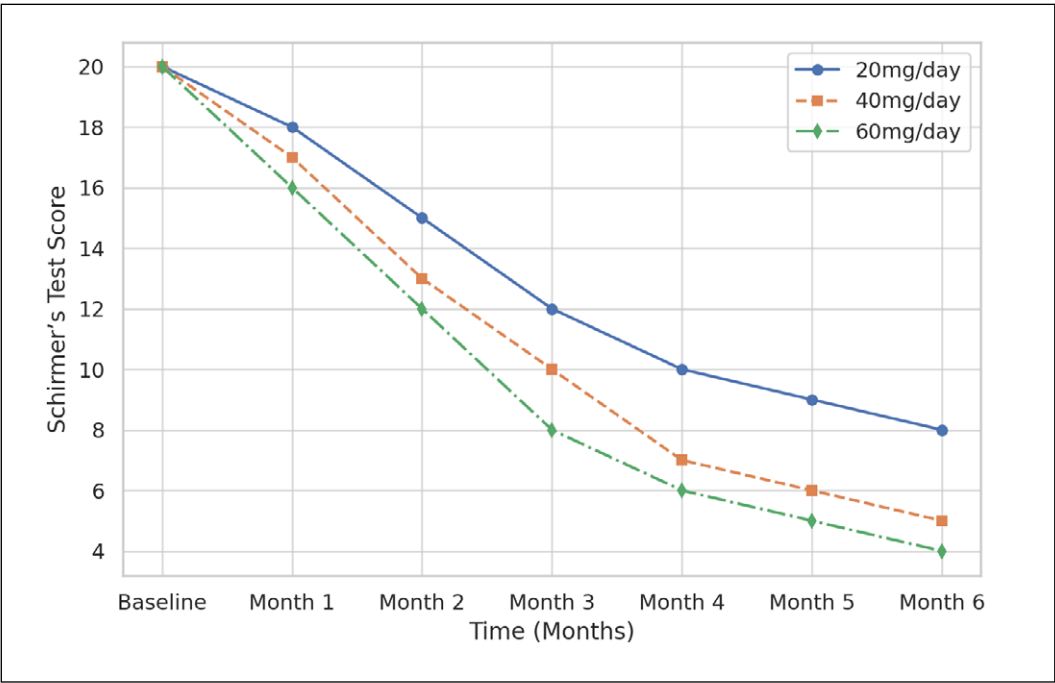


Fig. 5. Schirmer's test scores over time by dose group
Source: Own materials

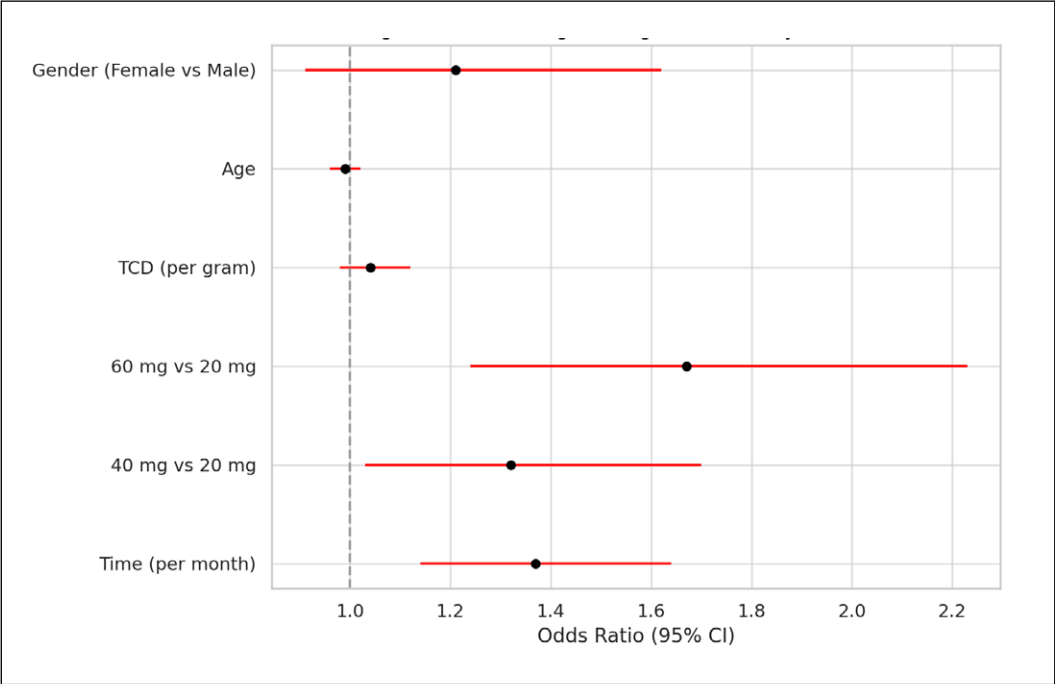


Fig. 6. Ordinal logistic regression for dryness grade
Source: Own materials

Table 5 presents the ordinal logistic regression, which models dryness grade (ranging from mild to severe) as the dependent variable. The positive coefficient sign for time shows that with every month increase in therapy duration, patients were more likely to move to a higher dryness severity grade. Furthermore, the dose-response effect was more pronounced in this model than in repeated-measures ANOVA: both 40 mg and 60 mg daily doses were associated with a significantly higher probability of allocation to a more dryness category than the 20 mg daily dose. From a clinical standpoint, this assists in informing that increased isotretinoin doses heighten the risk of more severe ocular dryness,

substantiating individualized dosing schedules and frequent monitoring. Importantly, total cumulative dose (TCD) was not statistically significantly associated with dryness grade. While TCD is a significant variable for the majority of side effects, there is a chance that regimens with shorter duration and greater dose are more effective on the ocular surface compared to the sum of isotretinoin over time absorbed. Similarly, the lack of a major effect of gender and age in this model suggests that dryness severity is mainly driven by the dosage-time interaction, and not by demographic characteristics alone. This finding also supports the need for clinicians to prioritize ocular

health assessments and patient counseling, especially when prescribing isotretinoin in moderate-to-high doses for extended durations.

CONCLUSIONS

In our study, we found that the prevalence of among the participants that had ocular dryness during the course of systemic isotretinoin is about 30% in Iraqi patients. These findings highlight the significance of evaluating and tracking the condition of the eye

surface during isotretinoin treatment on an individual basis. This research contributes to being aware of the effects of isotretinoin use on the health of the ocular surface. However, no significant correlations were seen between gender, dosage, duration, TCD, and age with ocular dryness. Although we exclude those patients that have ocular eye disease, it's important to discover the effect of isotretinoin on their ocular health. Additional research is required to verify and expand upon those findings, with an emphasis on diverse populations and larger sample sizes.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

CORRESPONDING AUTHOR

Ahmed Flayyih Hasan

Biotechnology Research Center,

Al-Nahrain University, Baghdad, Iraq

e-mail: ahmed_flayyih@nahrainuniv.edu.iq

ORCID AND CONTRIBUTIONSHIP

Mohammed Al-Daraji: 0009-0002-8456-7698 **B** **C**

Saad H. Salman: 0009-0002-7845-7126 **A**

Ali Abbas Hassan Fazaa: 0009-0009-2701-2793 **D** **E**

Ahmed Flayyih Hasan: 0009-0007-9208-5046 **A** **B** **D**

A – Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article

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