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ORIGINAL RESEARCH

Oral Isotretinoin-Associated Ocular Effects and Risk Factors: A Cross-Sectional Study

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Purpose: Oral isotretinoin is a derivative of vitamin A, used to treat acne vulgaris. One of its effects is altering the corneal surface and ocular glands, resulting in eye dryness and various other symptoms. This study aimed to analyze the impact of systemic isotretinoin treatment on ocular health and investigate the potential risk factors contributing to ocular pathology.

Patients and Methods: This cross-sectional study was conducted on 489 participants in the Jazan region using a convenience sampling method. An online questionnaire composed of five sections, including the Arabic version of the validated Ocular Surface Disease Index (OSDI), was used to assess the presence of ocular symptoms associated with isotretinoin usage as well as the potential contributing risk factors.

Results: A significant association was established between oral isotretinoin use and specific eye symptoms, including a gritty feeling in the eye (66.4%), sore eyes (68.6%), blurry vision (75.9%), and the need for moisturizing drops (35%). OSDI severity varied according to isotretinoin usage status, with severe OSDI grades reported in 56.9% of current users, 51.2% of those who stopped < 2 months ago, and 38.8% of those who stopped ≥ 2 months ago. Furthermore, significant risk factors associated with worse OSDI grades included contact lens use and isotretinoin dose, with contact lens use being associated with a 17.5-point increase in OSDI scores, while each 10 mg increase in isotretinoin dose was linked to a 0.20-point rise in OSDI score.

Conclusion: This study emphasizes the importance of assessing individual risk factors before starting isotretinoin therapy and monitoring ocular health in patients undergoing therapy. Clinicians should be aware of preventive methods and should consider high-risk patients to an ophthalmologist for interventions, such as punctal plugs, that can reduce complications. Further research targeting specific populations with shared risk factors is needed to validate these findings.

Keywords: retinoids, ocular pathology, eye dryness, Saudi Arabia

Introduction

Oral isotretinoin, also known as 13-cis-retinoic acid, is a natural derivative of vitamin A in the body. It was approved by the Food and Drug Administration (FDA) in 1982 as a pharmaceutical treatment for acne vulgaris. Although the precise mechanism of the drug's action remains unclear, its exceptional efficacy in improving acne symptoms has garnered widespread attention.[1] Accumulating evidence indicates that oral isotretinoin effectuates by reducing the size of sebaceous glands, regulating cell proliferation, and decreasing keratinization, consequently reducing sebum excretion in the skin and other systems through a similar mechanism.[1] However, the increasing usage of oral isotretinoin has raised concerns regarding its potential ophthalmological side effects attributed to alterations in the corneal surface or tear abnormalities, resulting in dry eyes and intolerance to contact lenses.[2]

The recent advancements in acne research using cell culture models and molecular techniques involving mammal sebocytes, sebocyte-like cells, and human sebaceous gland cell lines have improved our understanding of the disease's pathogenesis. Sebaceous glands are present throughout the body except for the palms, soles, and dorsum of the feet but

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are most concentrated in the face and scalp, the common sites of acne. These glands produce sebum, a mixture of complex oils that lubricate and protect the skin.[3] Meibomian glands (MGs) are sebaceous glands located at the eyelid margin, responsible for secreting essential lipids that prevent tear evaporation and maintain ocular surface (OS) homeostasis. The development of acne is strongly associated with increased sebum excretion and altered lipid composition and oxidant/antioxidant ratio of the skin surface lipids. These factors play a significant role in the pathogenesis of acne. Consequently, isotretinoin is commonly used to control acne by reducing sebaceous gland activity. However, a consequence of isotretinoin's action is the occurrence of MG dysfunction, leading to potential ocular side effects.[4]

Isotretinoin usage has also been linked to several alterations in the eye, especially the OS. Typically, the lipid layer of the MGs allows the tear film to remain adherent to the OS between each blink, thus avoiding rapid evaporation.[5] In vitro studies suggested that exposure to 13-cis retinoic acid inhibits cell proliferation, modifies gene expression, promotes inflammatory mediators and protease production, and increases apoptosis in MG, leading to meibomian gland dysfunction (MGD).[6] Also, patients receiving isotretinoin exhibit a decrease in density, a reduction in cell-to-cell contact, and an increase in the nucleus-cytoplasm ratio in the mucin-producing goblet cells of the conjunctival epithelium. This mucin layer has hydrophilic properties that facilitate a sufficient distribution of the aqueous layer. The modification of mucin formation combined with the MGD-induced disruption of the lipid layer leads to a vicious cycle of tear film instability, rapid evaporation, increased osmolarity, and worsened symptoms.[7]

Isotretinoin also causes notable alterations in the cornea, which is the eye's most anterior structure. According to a recent study, three months of continuous usage of isotretinoin caused a statistically significant decrease in corneal sensitivity, which might be linked to medication-induced dry eye disease (DED). Additionally, the sub-basal neural plexus in the corneas of DED-affected eyes has changed, resulting in decreased nerve fiber diameter and density. The latter causes long-term damage to the corneal nerves, a decline in sensitivity, and a loss in the blinking and tearing reflexes that protect the cornea, thereby further damaging the OS.[8] DED and blepharoconjunctivitis are the most common diseases related to isotretinoin use. The term DED refers to a multifactorial OS disorder in which the tear film's equilibrium is disturbed. Symptoms, such as pain, photophobia, dry eyes, foreign body sensation, and distorted vision, are linked to DED.[9] Blepharoconjunctivitis is a common ophthalmic condition that tends to exacerbate with the chronic use of isotretinoin in a dose-dependent manner. It is characterized by chronic inflammation of the eyelid margin with secondary conjunctival involvement characterized by scales and crusting of the eyelids, eyelashes, and papillary conjunctivitis.[10] Although only a few studies have focused on using isotretinoin, the drug has been related to retinal toxicity, neuro-ophthalmological diseases, impaired dark adaptation and color vision, and cataract formation in addition to OS damage.[11] Thus, the present study aimed to analyze the impact of oral isotretinoin treatment on ocular health and investigate the potential contributing risk factors that can increase the risk of ocular pathology.

Material and Methods

Study Design and Sample

This descriptive, cross-sectional study used a convenience sampling method and was conducted in the Jazan region. A self-administered online questionnaire composed of five sections was sent to the participants via social media platforms (WhatsApp, Twitter, Telegram, and Facebook). The sample size was calculated based on the total population aged ≥ 18 years in the Jazan region (919,267),[12] a confidence level of 95%, a population proportion of 0.5, and an error margin of ≤ 5%.

Data Collection Tools

The participants provided informed consent before filling out a questionnaire composed of five sections. The first section included questions about participants' demographics, such as age, gender, employment status, education level, monthly income, residency, and geographical area. The second section included the ocular surface disease index (OSDI), which evaluates the severity of dry eye disease among the study participants. It consisted of 12 questions, and the Arabic version of the questionnaire was used;[13] participants' answers were assessed on a scale of 0–100. The third section included questions about the isotretinoin doses taken by the participants, the duration of the treatment, and when they stopped the treatment. This section measured the participants' oral isotretinoin use grade across four categories: not using isotretinoin, stopped < 2 months ago, stopped ≥ 2 months ago, and current users. The four categories were created based on the results of previous studies that suggested that most ocular effects of isotretinoin tend to disappear or lessen in

severity within weeks of treatment cessation.[14–16] The fourth section included questions about the baseline clinical characteristics of the participants, such as eye symptoms before the treatment course, use of lubricant eye drops usage, and laser eye surgery. The fifth section included questions about the ocular symptoms experienced by participants during their treatment, such as discomfort, blurry vision, and changes in color vision.

Statistical Analysis

The collected data were coded, tabulated, and statistically analyzed using IBM SPSS Statistics (Statistical Package for Social Sciences) software version 28.0 (IBM Corp., Armonk, New York, USA, 2021). Quantitative data were tested for normality using the Shapiro–Wilk and Kolmogorov–Smirnov tests. The normally distributed data were described as mean ± standard deviation (SD) and compared using the analysis of variance (ANOVA) test. Qualitative data were described as numbers and percentages and compared using the chi-square and Fisher's exact tests, respectively. Bonferroni's test was used for post-hoc comparisons. A linear regression model was used to identify independent factors affecting the OSDI score. The level of significance was set at p-value ≤0.050.

Ethics Approval

This study was approved by Jazan University's Standing Committee for Scientific Research (reference number REC-45/08/1004, dated 03/03/2024). All procedures involving human participants adhered to the ethical standards established by the institutional and/or national research committee, the 1964 Helsinki Declaration, and its subsequent amendments.

Results

Demographic and Clinical Characteristics of Sample and Comparison According to Oral Isotretinoin Use

The present study included 489 participants, approximately 62.8% were female and 37.2% were male. The average age of the participants was 24.8 ± 5.2 years, and the average body mass index (BMI) was 23.3 kg/m². Most participants were single (80%). Moreover, many participants were students (60.3%), while the rest were workers (27.2%) and non-workers (12.5%). Approximately 2.9% of the participants reported allergies, 1% had hypertension, and 0.8% had diabetes mellitus. Additionally, 17.4% reported using contact lenses, and 4.3% had previously undergone a laser eye operation. Regarding oral isotretinoin, 33.7% of the participants had stopped using the drug ≥ 2 months ago, 8.8% had stopped using it < 2 months ago, 28.0% were currently using the drug, and 29.4% were not using isotretinoin (Figure 1). Strikingly, no significant differences were observed in the demographic and clinical characteristics according to oral isotretinoin usage, except for occupation (Table 1).

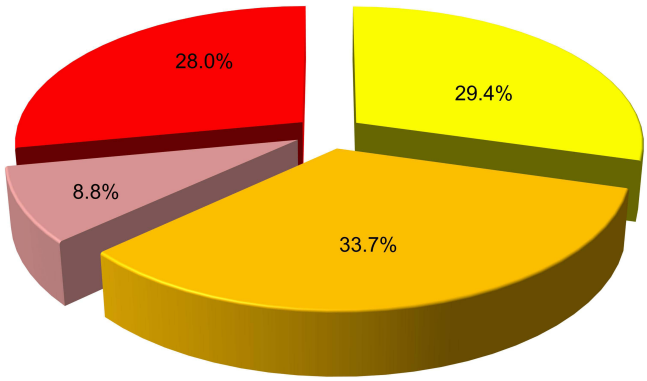

Figure 1 Oral isotretinoin usage in the studied sample. The segments are color-coded to represent different usage categories: yellow for no usage, Orange for Stopped ≥ 2 months ago, pink for Stopped < 2 months ago, and red for Current use.

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Table 1 Demographic and Clinical Characteristics of the Studied Sample and Comparison According to Oral Isotretinoin Use

Variables		All cases (Total = 489)	Oral isotretinoin use				
			None (Total = 144)	Stopped ≥ 2 months (Total = 165)	Stopped less < 2 months (Total = 43)	Current use (Total = 137)	*p*-value
Age (years)		24.8±5.2	24.5±5.2	24.3±4.4	25.4±6.5	25.4±5.5	^0.227
Gender	**Male**	182 (37.2%)	56 (38.9%)	52 (31.5%)	19 (44.2%)	55 (40.1%)	#0.276
	Female	307 (62.8%)	88 (61.1%)	113 (68.5%)	24 (55.8%)	82 (59.9%)	
BMI (kg/m^2)		23.3±5.4	23.4±5.6	22.9±5.4	24.1±7.3	23.4±4.5	^0.575
Marital status	**Married**	98 (20.0%)	23 (16.0%)	28 (17.0%)	10 (23.3%)	37 (27.0%)	#0.076
	Not married	391 (80.0%)	121 (84.0%)	137 (83.0%)	33 (76.7%)	100 (73.0%)	
Residence	**Urban**	257 (52.6%)	79 (54.9%)	91 (55.2%)	26 (60.5%)	61 (44.5%)	#0.146
	Rural	232 (47.4%)	65 (45.1%)	74 (44.8%)	17 (39.5%)	76 (55.5%)	
Education	**Below university**	87 (17.8%)	32 (22.2%)	22 (13.3%)	5 (11.6%)	28 (20.4%)	#0.114
	University	402 (82.2%)	112 (77.8%)	143 (86.7%)	38 (88.4%)	109 (79.6%)	
Occupation	**None**	61 (12.5%)	3 (2.1%)a	26 (15.8%)b	6 (14.0%)b	27 (19.7%)b	**#<0.001***
	Student	295 (60.3%)	114 (79.2%)a	94 (57.0%)b	21 (48.8%)b	66 (48.2%)b	
	Working	133 (27.2%)	27 (18.8%)a	45 (27.3%)a	16 (37.2%)a	44 (32.1%)a	
Comorbidity	**Hypertension**	5 (1.0%)	1 (0.7%)	0 (0.0%)	0 (0.0%)	4 (2.9%)	§0.079
	Diabetes mellitus	4 (0.8%)	2 (1.4%)	1 (0.6%)	1 (2.3%)	0 (0.0%)	§0.289
	Allergic conditions	14 (2.9%)	2 (1.4%)	8 (4.8%)	2 (4.7%)	2 (1.5%)	§0.154
Contact lenses usage		85 (17.4%)	29 (20.1%)	33 (20.0%)	6 (14.0%)	17 (12.4%)	#0.235
Previous laser eye operation		21 (4.3%)	4 (2.8%)	8 (4.8%)	2 (4.7%)	7 (5.1%)	#0.762
Oral isotretinoin use grades	**None**	144 (29.4%)					
	Stopped ≥ 2 months	165 (33.7%)					
	Stopped < 2 months	43 (8.8%)					
	Current use	137 (28.0%)					
		Total = 345	**Total = 0**	**Total = 165**	**Total = 43**	**Total = 137**	
Oral isotretinoin dose (mg)		25.8 ± 10.1		25.2 ± 9.9	24.2 ± 11.0	27.0 ± 10.1	^0.167

Note: Data presented as mean ± SD or number (%). Some percentages are calculated based on the total number of individuals in each subgroup ("None", "Stopped ≥ 2 months", "Stopped < 2 months", and "Current use"). Percentages for the "All cases" column are based on the total sample of 489 participants. ^ANOVA test. #Chi-square test. § Fisher's exact test. *Significant. Homogenous groups had the same symbol 'a, b' based on the post-hoc Bonferroni's test. Significant values are indicated in bold.

Ocular Effects of the Studied Sample and Comparison According to Oral Isotretinoin Use

Table 2 shows the relationship between oral isotretinoin usage and OSDI items. Some eye symptoms were found to be significantly associated with oral isotretinoin use, including a gritty feeling in the eye, sore eyes, and poor and blurry vision. However, sensitivity to light was not significantly associated with oral isotretinoin usage. 66.4% of the participants using oral isotretinoin reported a gritty feeling in their eyes, while 50% reported the same feeling without using isotretinoin. 68.6% of participants using isotretinoin reported painful or sore eyes, while 51.4% reported the same symptom without isotretinoin usage. Blurred and poor vision were reported by 79.6% and 75.9% of participants, respectively, who were currently using oral isotretinoin. Importantly, our results showed that limitations related to working with a computer or bank machine (ATM) and watching TV were significantly associated with the oral

Table 2 Ocular Effects of the Studied Sample and Comparison According to Oral Isotretinoin Usage

Variables		All cases	Oral isotretinoin use				
			None	Stopped ≥ 2 months	Stopped < 2 months	Current use	*p*-value
⌂**OSDI items**							
Experiencing:							
Eyes that are sensitive to light		242 (63.2%)	98 (68.1%)	101 (61.2%)	30 (69.8%)	87 (63.5%)	#0.541
Eyes that feel gritty		316 (64.6%)	72 (50.0%)a	84 (50.9%)a	28 (65.1%)ab	91 (66.4%)b	**#0.009***
Painful or sore eyes		275 (56.2%)	74 (51.4%)a	93 (56.4%)ab	28 (65.1%)ab	94 (68.6%)b	**#0.020***
Blurred vision		289 (59.1%)	82 (56.9%)a	93 (56.4%)a	27 (62.8%)ab	109 (79.6%)b	**#<0.001***
Poor vision		311 (63.6%)	84 (58.3%)a	81 (49.1%)a	28 (65.1%)ab	104 (75.9%)b	**#< 0.001***
Limiting performance:							
Reading		297 (60.7%)	84 (76.4%)	79 (65.8%)	23 (74.2%)	81 (73.6%)	#0.318
Driving at night		267 (72.0%)	68 (68.7%)	67 (59.3%)	20 (64.5%)	71 (65.1%)	#0.553
Working with a computer or bank machine (ATM)		226 (64.2%)	67 (60.4%)a	72 (57.6%)a	19 (67.9%)ab	93 (78.2%)b	**#0.004***
Watching TV		251 (65.5%)	59 (53.6%)a	68 (54.8%)a	25 (75.8%)ab	90 (77.6%)b	**#< 0.001***
Feeling uncomforted:							
Windy conditions		272 (66.8%)	70 (61.4%)a	78 (59.1%)a	27 (75.0%)ab	97 (77.6%)b	**#0.005***
Places or areas with low humidity (very dry)		250 (61.4%)	61 (54.5%)a	70 (53.4%)a	25 (71.4%)ab	94 (72.9%)b	**#0.002***
Areas that are air-conditioned		283 (69.5%)	72 (62.6%)a	88 (65.7%)ab	26 (74.3%)ab	97 (78.9%)b	**#0.030***
		Total = 489	**Total = 144**	**Total = 165**	**Total = 43**	**Total = 137**	
OSDI Grade	**Normal**	125 (25.6%)	45 (31.3%)	55 (33.3%)	7 (16.3%)	18 (13.1%)	**#< 0.001***
	Mild	71 (14.5%)</p	22 (15.3%)	25 (15.2%)	7 (16.3%)	17 (12.4%)	
	Moderate	77 (15.7%)	25 (17.4%)	21 (12.7%)	7 (16.3%)	24 (17.5%)	
	Severe	216 (44.2%)	52 (36.1%)	64 (38.8%)	22 (51.2%)	78 (56.9%)	
Other ocular problems							
Impaired visual field		82 (16.8%)	6 (4.2%)a	36 (21.8%)b	9 (20.9%)b	31 (22.6%)b	**#< 0.001***
Impaired color vision		54 (11.0%)	5 (3.5%)a	17 (10.3%)ab	8 (18.6%)b	24 (17.5%)b	**#< 0.001***
Needing moisturizing drops		120 (24.5%)	2 (1.4%)a	53 (32.1%)b	17 (39.5%)b	48 (35.0%)b	**#< 0.001***
Worsening eye status		99 (20.2%)	8 (5.6%)a	43 (26.1%)b	13 (30.2%)b	35 (25.5%)b	**#< 0.001***

Note: Data presented as mean ± SD or number (%). Some percentages are calculated based on the total number of individuals in each subgroup ("None", "Stopped ≥ 2 months", "Stopped < 2 months", and "Current use"). Percentages for the "All cases" column are based on the total sample of 489 participants. #Chi-square test. *Significant. Homogenous groups had the same symbol 'a, b' based on the post-hoc Bonferroni test. Significant values are indicated in bold.

administration of isotretinoin. Additionally, a statistically significant association was observed between isotretinoin usage and OSDI grades as well as feeling uncomfortable during windy conditions, in low humidity, or in air-conditioned areas (Table 2). Other statistically significant ocular complaints associated with isotretinoin usage were impaired visual field, impaired color vision, needing moisturizing drops, and worsening eye status. Impaired visual field was reported in 22.6%, impaired color vision in 17.5%, needing moisturizing drops in 35%, and worsening eye status in 25.5% (Figure 2). The OSDI grade was severe in 56.9%, moderate in 17.5%, mild in 12.4%, and normal in 13.1% of the current oral isotretinoin users. The percentage of severe grades of OSDI in those who stopped using isotretinoin < 2

months ago and stopped ≥ 2 months ago was 51.2% and 38.8% respectively. Moreover, the OSDI grade was severe in 36.1% of participants not using isotretinoin (Figure 3).

Oral Isotretinoin Use Among Other Variables and Risk Factors Affecting the OSDI Grades

Table 3 shows that neither age nor gender was associated with different OSDI grades. We also found that residence was not a risk factor for higher OSDI grades as urban and rural residents had similar OSDI grades, with no statistically significant association between residence and OSDI grades. However, the type of occupation was a predominant risk factor that was significantly associated with OSDI grades, as working was significantly more frequent in severe OSDI grades than in normal grades, while being a student was significantly less frequent in severe OSDI grades than in normal grades. Other risk factors investigated in this study are comorbid disorders such as hypertension, diabetes mellitus, and allergies, which were not associated with OSDI grade. Similarly, marital status, BMI, and type of education were not

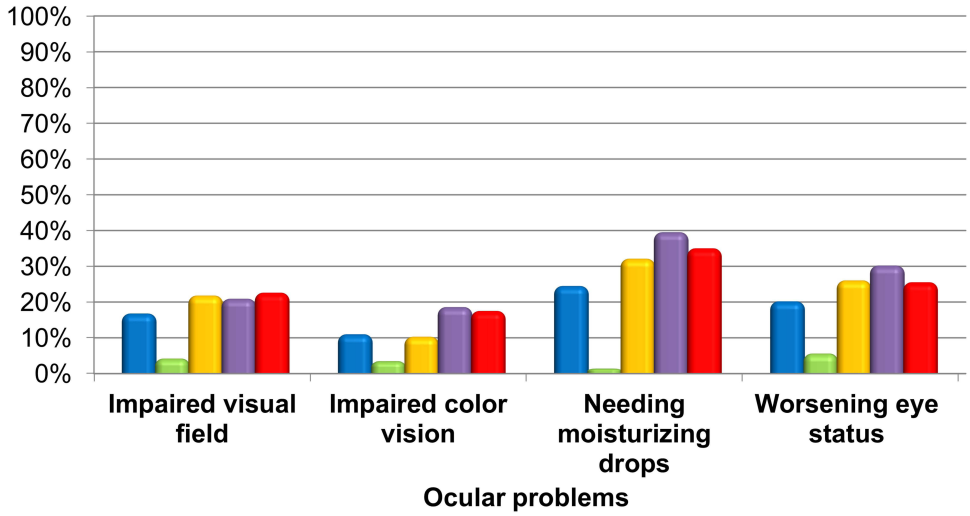

Figure 2 Comparison of oral isotretinoin use regarding other ocular problems. Bar colors represent different categories: Blue for all cases, Yellow for participants who stopped isotretinoin ≥ 2 months ago, Red for current users, Green for those with no history of isotretinoin use, and Purple for participants who stopped < 2 months ago.

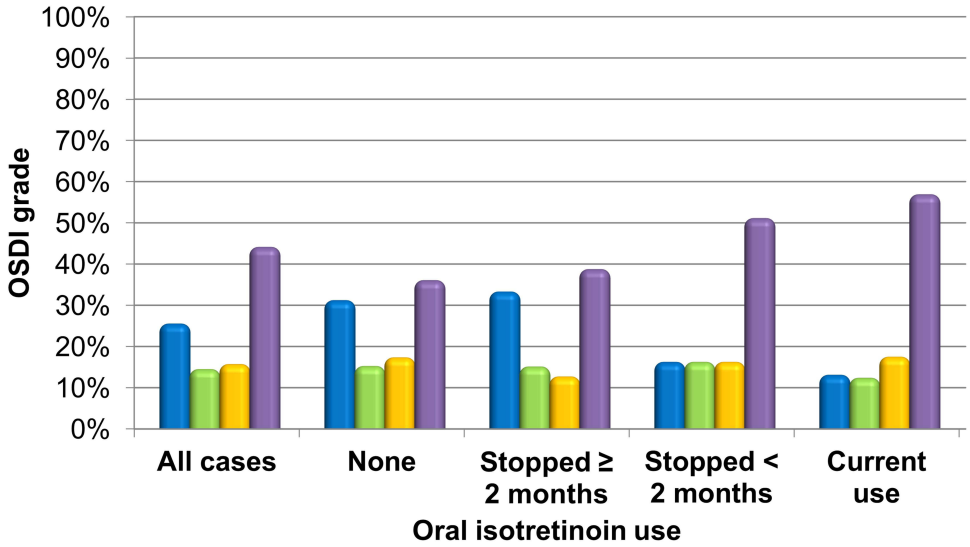

Figure 3 Comparison of oral isotretinoin use regarding OSDI grades. The bars are color-coded to indicate OSDI grades: blue for Normal, green for Mild, yellow for Moderate, and purple for Severe.

Table 3 Oral Isotretinoin Use Among Other Variables and Risk Factors Affecting the OSDI Grades

Variables		OSDI grades				
		Normal (Total = 125)	**Mild (Total = 71)**	**Moderate (Total = 77)**	**Severe (Total = 216)**	***p*-value**
Age (years)		24.4 ± 4.4	24.4±4.2	24.7±4.8	25.1±5.9	^0.614
Gender	**Male**	56 (44.8%)	23 (32.4%)	25 (32.5%)	78 (36.1%)	#0.200
	Female	69 (55.2%)	48 (67.6%)	52 (67.5%)	138 (63.9%)	
BMI (kg/m^2)		23.5 ± 7.2	23.1 ± 4.7	22.0 ± 4.2	23.7 ± 4.7	^0.129
Marital status	**Married**	18 (14.4%)	10 (14.1%)	21 (27.3%)	49 (22.7%)	#0.057
	Not married	107 (85.6%)	61 (85.9%)	56 (72.7%)	167 (77.3%)	
Residence	**Urban**	76 (60.8%)	36 (50.7%)	36 (46.8%)	109 (50.5%)	#0.177
	Rural	49 (39.2%)	35 (49.3%)	41 (53.2%)	107 (49.5%)	
Education	**Below university**	25 (20.0%)	13 (18.3%)	15 (19.5%)	34 (15.7%)	#0.753
	University	100 (80.0%)	58 (81.7%)	62 (80.5%)	182 (84.3%)	
Occupation	**None**	14 (11.2%)a	7 (9.9%)a	16 (20.8%)a	24 (11.1%)a	**#0.010***
	Student	86 (68.8%)a	48 (67.6%)ab	44 (57.1%)ab	117 (54.2%)b	
	Working	25 (20.0%)a	16 (22.5%)ab	17 (22.1%)ab	75 (34.7%)b	
Comorbidities	**Hypertension**	0 (0.0%)	0 (0.0%)	2 (2.6%)	3 (1.4%)	§0.224
	Diabetes mellitus	1 (0.8%)	1 (1.4%)	2 (2.6%)	0 (0.0%)	§0.090
	Allergic conditions	2 (1.6%)	2 (2.8%)	1 (1.3%)	9 (4.2%)	§0.547
Contact lenses use		8 (6.4%)a	12 (16.9%)ab	18 (23.4%)b	47 (21.8%)b	**#< 0.001***
Previous laser eye operation		5 (4.0%)	3 (4.2%)	3 (3.9%)	10 (4.6%)	§0.999
Oral Isotretinoin use	**None**	45 (36.0%)a	22 (31.0%)a	25 (32.5%)a	52 (24.1%)a	**#0.002***
	Stopped ≥ 2 months	55 (44.0%)a	25 (35.2%)ab	21 (27.3%)ab	64 (29.6%)b	
	Stopped < 2 months	7 (5.6%)a	7 (9.9%)a	7 (9.1%)a	22 (10.2%)a	
	Current use	18 (14.4%)a	17 (23.9%)ab	24 (31.2%)b	78 (36.1%)b	
		Total = 80	**Total = 49**	**Total = 52**	**Total = 164**	
Oral isotretinoin dose (mg)		23.1 ± 10.1a	22.4 ± 6.6a	25.8 ± 8.9ab	28.1 ± 10.8b	**^< 0.001***

Note: Data presented as mean ± SD or number (%). Percentages are calculated based on the total number of individuals within each OSDI grade (Normal, Mild, Moderate, Severe). ^ANOVA test. #Chi-square test. § Fisher's exact test. *Significant. Homogenous groups had the same symbol "a, b" based on the post-hoc Bonferroni test. Significant values are indicated in bold.

found to be statistically significant risk factors. Contact lens usage was one of the most important risk factors investigated in this study. Our results showed that contact lens usage was a statistically significant risk factor associated with the OSDI grade, with 23.4% and 21.8% having moderate and severe OSDI grades, respectively. (Figure 4). Interestingly, having a previous laser eye operation showed no correlation with OSDI grades. Furthermore, oral isotretinoin usage was significantly associated with OSDI grades; 36.0% of participants with normal OSDI grades were not oral isotretinoin users, and 36.1% of participants with severe OSDI grades were current users (Figure 5). Additionally, the dosage of oral isotretinoin was a major factor that showed a significant correlation with OSDI grades; the dose was significantly higher in severe OSDI grades than in normal and mild grades (Figure 6 and Table 3).

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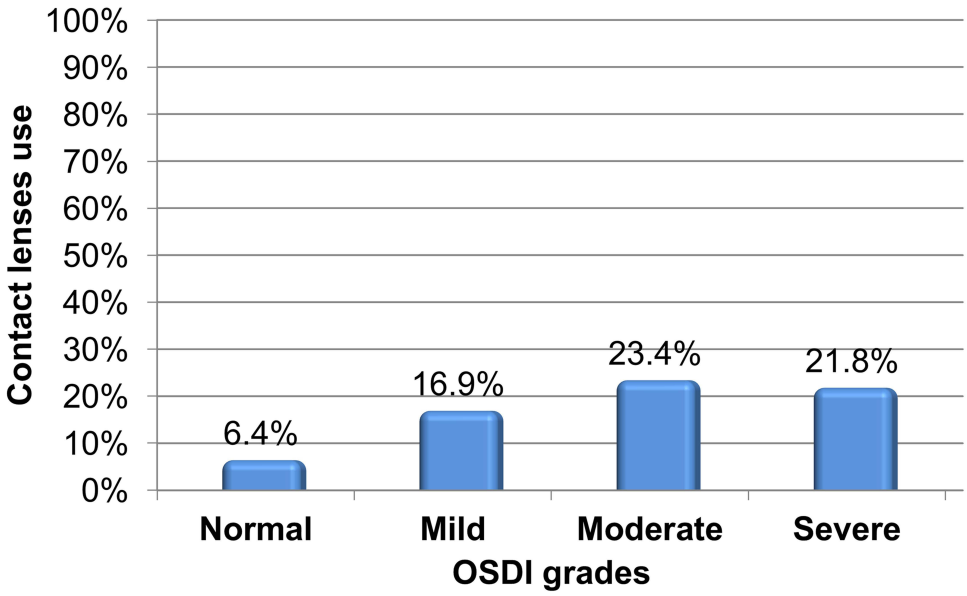

Figure 4 Comparison of OSDI grades regarding contact lens use.

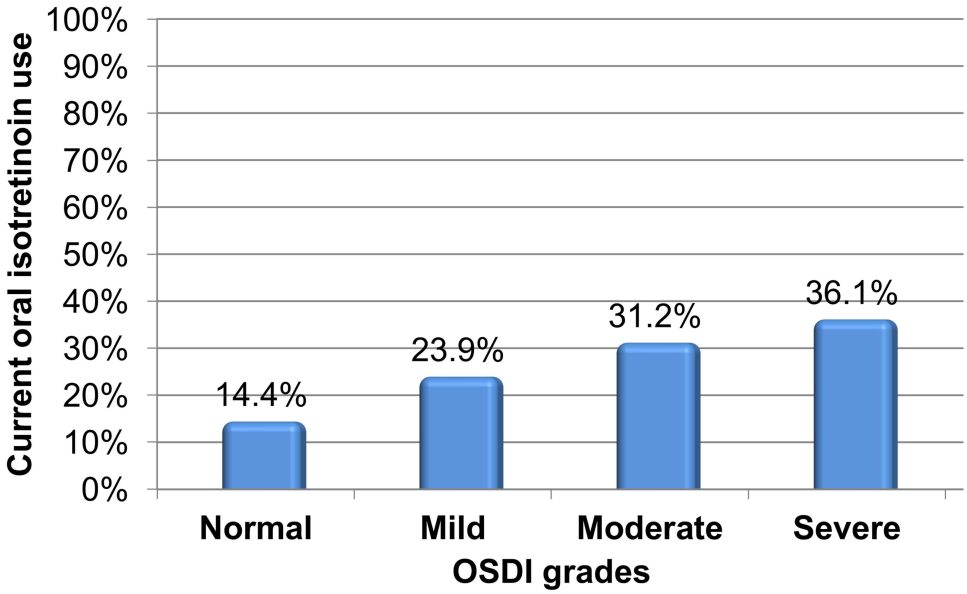

Figure 5 Comparison of OSDI grades regarding current oral isotretinoin use.

Linear Regression for Risk Factors Affecting OSDI Score Among the Studied Sample

Table 4 shows the results of linear regression for risk factors affecting OSDI score. After studying all demographic and clinical characteristics and oral isotretinoin use, contact lens usage was the risk factor most significantly associated with higher OSDI grades. Our results show that, on average, the OSDI scores of participants who used contact lenses were higher by 17.5 points than those who did not use contact lenses, holding other factors constant. Additionally, oral isotretinoin use was also a significant factor that increased OSDI scores among the studied sample, with higher oral isotretinoin use grades correlating with an 8.69-point increase in OSDI scores. Furthermore, the oral isotretinoin dose was significantly associated with a 0.20-point increase in the OSDI score for every 10 mg increase in dose. This model could explain 61.6% of the variability of OSDI scores among the studied sample (Table 4).

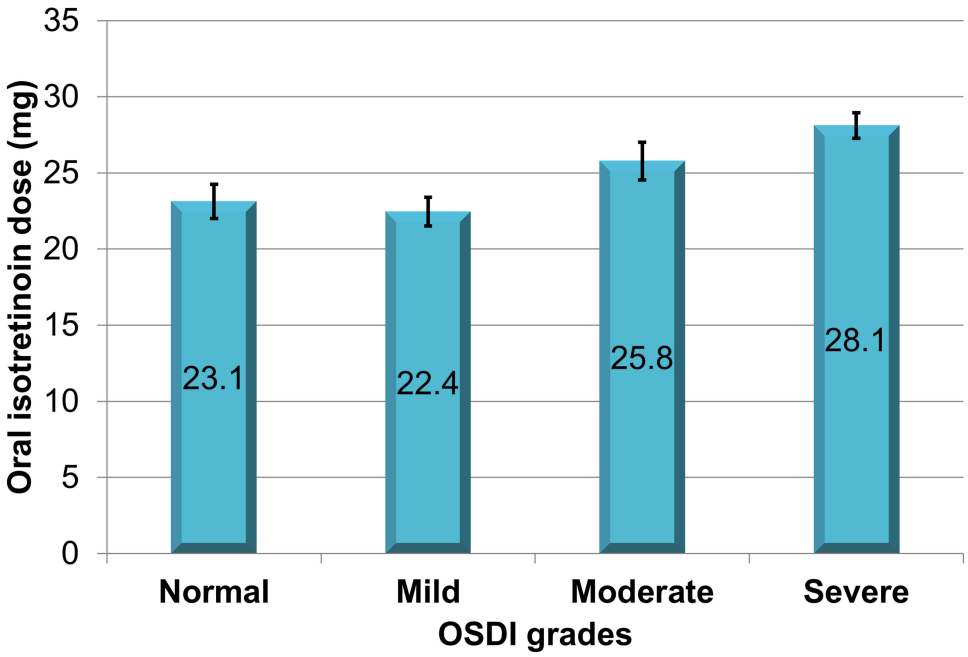

Figure 6 Comparison of OSDI grades regarding oral isotretinoin dose.

Discussion

Interpretation of Key Results

A key point to highlight is the significant association between isotretinoin use and OSDI grades. Table 2 shows this association with the higher percentages of complaints, such as gritty feeling in the eye, sore eyes, and blurry vision, as well as issues in those using computers and bank machines and watching TV among participants currently using oral isotretinoin. This raises concerns about whether using isotretinoin can affect the quality of life of patients and their ability to work or study effectively during the drug course. This is further emphasized by our finding that the type of occupation is a statistically significant risk factor associated with OSDI grades (Table 3). Therefore, special attention should be given to the occupation of the patients as a risk factor for worse OSDI grades, keeping in mind that such a risk factor may contribute to isotretinoin's ocular pathology, as oral isotretinoin is also associated with worse OSDI scores. Moreover, we observed that oral isotretinoin usage was significantly associated with severe ocular complaints such as impaired visual field and color vision. Thus, primary care doctors, dermatologists, and ophthalmologists need to be aware of the potential severe complications of isotretinoin. Additionally, we found that using oral isotretinoin was likely to increase the need for moisturizing drops. Hence, adding moisturizing drops to the treatment plan and educating patients on their effective usage can potentially prevent complications. Shifting the focus to the major risk factors associated with worse OSDI grades, these risk factors are likely to have a synergistic effect on ocular surface health, combined with the ocular effects

Table 4 Linear Regression for Risk Factors Affecting OSDI Score Among the Studied Sample

Factors	β	SE	*p*-value	95% CI	R^2
Contact lenses	17.50	2.77	**< 0.001***	12.05–22.95	61.6%
Oral isotretinoin use grades	8.69	0.86	**< 0.001***	7.00–10.38	
Oral isotretinoin doses (10 mg)	0.20	0.10	**0.044***	0.01–0.39	

Note: *Significant. CI: Confidence interval. R^2: Coefficient of determination. Significant values are indicated in bold.
Abbreviations: β, Regression coefficient; SE, Standard error.

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of isotretinoin, which is why we emphasize the importance of clinician awareness and risk factor management before, during and after isotretinoin treatment. Table 3 highlights the significant association between contact lens usage and ODSI grade, another major risk factor to consider before initiating oral isotretinoin therapy. Patient education on the proper usage of contact lenses could reduce their potential synergistic harmful effects on ocular health while on oral isotretinoin therapy. It's especially important to mention here that we have found the OSDI scores of participants who used contact lenses were higher by 17.5 points than those who did not use the lenses, as shown in Table 4, emphasizing the significance of contact lenses as a risk factor. Moreover, our results have shown a statistically significant correlation between the isotretinoin dose and the OSDI score, with a 0.20 increase in the OSDI score for every 10 mg increase in dose. Therefore, the dose is another factor to consider when outlining the treatment plan. Thus, clinicians may consider frequent evaluations of ocular health for patients taking high doses of oral isotretinoin.

Relating Findings to Existing Studies

Reviewing previous isotretinoin-related literature, we can conclude that some of the severe ocular effects reported by our participants, specifically, the impaired visual field and color vision, are not common effects reported in the literature, though they are documented infrequent complaints.[17] As we have shown that multiple risk factors can influence the OSDI grade and potentially lead to more adverse ocular effects during isotretinoin treatment, it is essential to assess the level of awareness among dermatologists and clinicians regarding the ocular effects of oral isotretinoin and the risk factors highlighted in this study. A study by Korkoman et al (2023) provided insights into dermatologists' knowledge and attitudes regarding the ocular side effects of isotretinoin in Saudi Arabia. The study indicated that while all surveyed dermatologists were aware that isotretinoin can cause dry eye, their knowledge of other potential ocular complications was limited. Only two-thirds of the clinicians recognized the risk of contact lens intolerance, and a small percentage believed it could lead to serious issues, such as ectopia lentis and retinoblastoma. As for preventive measures, most dermatologists did not routinely refer patients for ophthalmic exams before starting isotretinoin, and only 25% always prescribed lubricating eye drops.[18] This is especially significant considering that certain ophthalmological interventions, like punctal plugs, can potentially reduce the risk of high-risk patients.[19] Another study by Shajeri et al (2022) examined the knowledge, attitudes, and practices of the general public in Saudi Arabia regarding isotretinoin use. The results found that the majority of participants had limited knowledge about isotretinoin dosing and side effects. However, the study observed that females and those with higher educational levels tended to have greater knowledge about the medication. These findings mirrored the results of this study regarding the significant association between occupation and ocular health. The study also found that the public may lack a comprehensive understanding of the risks associated with isotretinoin, reinforcing the importance of patient education before initiating treatment.[20] Furthermore, our results did not reveal a significant correlation between age and OSDI score, which is consistent with the study by Alfouzan et al (2023).[16] Similarly, gender was not significantly associated with OS disease symptoms, which is also consistent with our results. On the other hand, no significant correlation was established between the dose and duration of isotretinoin use and OSDI grade, which contradicts our findings that revealed a significant correlation between the oral isotretinoin dosage and OSDI grades, with the dose being considerably larger in participants with severe OSDI grades compared to those with normal and mild grades. Regarding laser eye surgery, we have found no association between having previous laser eye surgery and OSDI grades, it is worth noting that previous studies have established the safety of LASIK and PRK for selected patients undergoing isotretinoin treatment.[21] Overall, our results, together with previous studies, highlight the need for improved education and monitoring practices surrounding isotretinoin use among healthcare providers and the general population.

Conclusion

This study sheds light on the potential complications of a commonly used drug, isotretinoin, which can cause serious ocular consequences. Thus, it is crucial for clinicians, especially dermatologists, to be aware of the risk factors associated with poorer ocular health and how to prevent these potential complications. Moreover, the current results highlight the importance of considering each patient's risk factors for ocular pathology before starting isotretinoin therapy. Clinicians and stakeholders may consider outlining reliable methods to monitor and evaluate the ocular health of high-risk patients while on isotretinoin therapy. Furthermore, clinicians should consult patients on effective preventive methods to reduce the incidence of complications. Dermatologists may consider prescribing Omega-3 Fatty Acids or referring high-risk

patients to an ophthalmologist and educating them regarding certain ophthalmological interventions, such as punctal plugs, which have been shown to improve ocular surface health and reduce their risk of complications.[19,22] Finally, it's important to address certain limitations of this study, such as the convenience sampling method. Further research focusing on specific populations with shared risk factors is essential to substantiate these findings.

Abbreviations

OSDI, ocular Surface Disease Index; MGs, meibomian glands; OS, ocular surface; MGD, meibomian gland dysfunction; DED, dry eye disease.

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Disclosure

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References

1. Paichitrojjana A, Paichitrojjana A. Oral isotretinoin and its uses in dermatology: a review. *Drug Des Devel Ther*. 2023;17:2573–2591. doi:10.2147/dddt.s427530
2. AlMasoudi RM, Bahaj RK, Kokandi AA. Patients' awareness of the ocular side effects of isotretinoin therapy: a study from Saudi Arabia. *Cureus*. 2022. doi:10.7759/cureus.24628
3. Makrantonaki E, Gancevičienė R, Zouboulis CC. An update on the role of the sebaceous gland in the pathogenesis of acne. *Dermatoendocrinol*. 2011;3(1):41–49. doi:10.4161/derm.3.1.13900
4. Gürlevik U, Kemeriz F, Yaşar E. The effect of isotretinoin on meibomian glands in eyes: a pilot study. *Int Ophthalmol*. 2022;42(7):2071–2078. doi:10.1007/s10792-021-02205-1
5. Gipson IK. The ocular surface: the challenge to enable and protect vision. *Invest Ophthalmol Vis Sci*. 2007;48(10):4391. doi:10.1167/iovs.07-0770
6. Ding J, Kam WR, Dieckow J, Sullivan DA. The influence of 13-CIS-retinoic acid on human meibomian gland epithelial cells. *Invest Ophthalmol Vis Sci*. 2013;54(6):4341. doi:10.1167/iovs.13-11863
7. Ruiz-Lozano RE, Hernandez-Camarena JC, Garza-Garza LA, Bustamante-Arias A, Colorado-Zavala MF, La Garza JAC. Isotretinoin and the eye: a review for the dermatologist. *Dermatol Ther*. 2020;33(6). doi:10.1111/dth.14029
8. Fouladgar N, Khabazkhoob M, Hanifnia AR, Yekta A, Mirzajani A. Evaluation of the effects of isotretinoin for treatment of acne on corneal sensitivity. *J Curr Ophthalmol*. 2018;30(4):326–329. doi:10.1016/j.joco.2018.06.005
9. Craig JP, Nichols KK, Akpek EK, et al. TFOS DEWS II Definition and Classification Report. *Ocul Surf*. 2017;15(3):276–283. doi:10.1016/j.jtos.2017.05.008
10. Blackman H, Peck GL, Olsen TG, Bergsma DR. Blepharoconjunctivitis: a side effect of 13-CIS-retinoic acid therapy for dermatologic diseases. *Ophthalmology*. 1979;86(5):753–8.1016/s0161–6420(79)35468–9.
11. Fraunfelder FT, Fraunfelder FW, Edwards R. Ocular side effects possibly associated with isotretinoin usage. *Am J Ophthalmol*. 2001;132(3):299–305. doi:10.1016/s0002-9394(01)01024-8
12. GASTAT Portal. Saudi Arabia: general Authority for Statistics; 2023. Available from: https://portal.saudicensus.sa/portal/public/1/15/101464?type=TABLE. Accessed December 10, 2024
13. Bakkar MM, Al Qadire M. Validation of the Arabic version of the Ocular Surface Disease Index Questionnaire. *Int J Ophthalmol*. 2021;14(10):1595–1601. doi:10.18240/ijo.2021.10.18
14. Kapała J, Lewandowska J, Placek W, Owczarczyk-Saczonek A. Adverse Events in Isotretinoin Therapy: a Single-Arm Meta-Analysis. *Int J Environ Res Public Health*. 2022;19(11):6463. doi:10.3390/ijerph19116463
15. Oner A, Ferahbas A, Karakucuk S, et al. Ocular Side Effects Associated with Systemic Isotretinoin. *J Toxicol Cutaneous Ocul Toxicol*. 2004;23(3):189–195.
16. Alfouzan YA, Alhammad RA, Alkhuzayem FA, et al. Isotretinoin-related eye dryness in acne patients in Qassim, Saudi Arabia. *Cureus*. 2023. doi:10.7759/cureus.49904
17. Lamberg O, Strome A, Jones F, et al. Ocular side effects of systemic isotretinoin - a systematic review and summary of case reports. *J DermatolTreat*. 2023;34(1):2213364. doi:10.1080/09546634.2023.2213364
18. Korkoman AJM, Alamri A, Zomia ASA, et al. Cross-sectional assessment of dermatologists' knowledge and attitude towards isotretinoin-related ocular side effects in Aseer, Saudi Arabia. *Cureus*. 2023. doi:10.7759/cureus.46335
19. Elhamaky TR. Efficacy of omega-3 fatty acids and punctal plugs in the prevention of isotretinoin-associated ocular surface disease. *Eur J Ophthalmol*. 2020;31(5):2339–2345. doi:10.1177/1120672120945655
20. Shajeri M, Sanguf M, Moafa M, et al. Assessment of knowledge, attitude, and practice in relation to use of isotretinoin among Jazan general population, Saudi Arabia. *Int J Med Dev Ctries*. 2022;1046–55.10.24911/ijmdc.51–1657383907.
21. Ortega-Usobiaga J, Llovet-Osuna F, Djodeyre MR, et al. Outcomes of Laser In Situ Keratomileusis and Photorefractive Keratectomy in Patients Taking Isotretinoin. *Am J Ophthalmol*. 2018;192:98–103.
22. Thomsen BJ, Chow EY, Sapijaszko MJ. The Potential Uses of Omega-3 Fatty Acids in Dermatology: a Review. *J Cutan Med Surg*. 2020;24(5):120347542092992. doi:10.1177/1203475420929925