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Most Common Isotretinoin Therapy Side Effects on Egyptian Acne Females in Dakahlia Governorate

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ABSTRACT

Background: Isotretinoin, an oral retinoid, is the most effective acne therapy. Isotretinoin has proven superior to other acne treatments. It is critical for clinicians to be aware of the side effects, toxicities, and management concerns associated with its usage. **Objective:** To evaluate the most common side effects while using isotretinoin therapy in acne in Egyptian female in Dakahlia. **Patients and methods:** Cohort, prospective, experimental study was conducted at Dermatology, Andrology and STDs outpatient clinic of Mansoura University Hospital on 80 female patients with acne who received isotretinoin therapy for three months, during the duration from February 2023 to October 2023. **Results:** After 1 month of treatment, the highest reported side effect was dry lip (92.5%), xerosis of skin at 35.0%, dry eyes increased to 28.8%, followed by dryness of mucous membrane (13.8%), hair loss (8.8%), facial erythema at 3.8%, sun sensitivity (2.5%), epistaxis (1.3%), irregular menses 5%, while mood changes and tiredness, headache, muscle ache, and abdominal pain were reported at 1.3% each. After 3 months, the most prevalent side effects were dry lips (100%), xerosis at 73.8%, dry eyes and mood changes reported (63.8%) for each, tiredness (52.5%), dryness of mucous membrane (51.3%), joint ache (47.5%), hair loss (42.5%), irregular menses (40%), muscle ache (37.5%), and facial erythema at 33.8%. **Conclusion:** The most common side effects were dry lips, dry eyes, irregular menses and hair loss. There was a significant relationship between higher dose of isotretinoin and severity of acne vulgaris with the presence of diarrhea. Isotretinoin appeared to have a bigger effect on lipids than on liver enzymes, and we suggested using isotretinoin with close monitoring.

Keywords: Isotretinoin Therapy Side Effects, Egyptian Acne Females, Dakahlia Governorate.

INTRODUCTION

Acne is a persistent inflammatory condition affecting the pilosebaceous unit, mostly due to elevated sebum production, follicular hyperkeratinization, bacterial colonization, and inflammation [(1)]. The intricate pathophysiology of acne includes the interplay of hormonal, microbiological, and immune components. However, the exact processes behind the genesis of acne are yet unknown [(2)]. One of the best medications for treating all types of acne vulgaris is oral isotretinoin, a vitamin A metabolite product [(3)]. For moderate acne that does not improve with traditional therapeutic approaches and nodulocystic acne, isotretinoin is the most effective therapy [(4)]. Use of isotretinoin has been linked to changes in lipid and liver profiles. There have been reports of elevated triglycerides (TGs) and liver enzymes in the serum [(5)].

The number of prescriptions for isotretinoin is rising, therefore it's critical that doctors understand the risks, toxicity, and management concerns associated with its usage. Cheilitis, dry mucous membranes, nasal bleeding, and dry skin are the adverse effects of systemic isotretinoin therapy that are most often documented worldwide [(6)]. The most dangerous is teratogenicity, which calls for strict control [(7)].

Isotretinoin may cause mental health issues such as suicidal thoughts and depression [(8)]. There is additional description of the effects on the gastrointestinal, respiratory, hematologic, neurological, and musculoskeletal systems [(9)]. Additionally, elevated levels of serum triglycerides, total cholesterol, and liver enzymes were noted [(10)]. The majority of idiosyncratic medication responses are believed to be brought on by chemically reactive metabolites, and idiosyncratic reactions frequently occur on the skin [(11)].

Difference in the incidence of side effects of isotretinoin was found in many studies, e.g., **Brzezinski *et al.* [(6)], Layton [(12)], and Brito *et al.* [(13)].** According to **Layton [(12)],** in Europe, cheilitis was the most common side effect (98%) followed by facial erythema (65%), dermatitis (65%), vestibulitis (50%), xerosis (50%), mucositis (40%), conjunctivitis (35%), epistaxis (35%), itching (25%), fragility of the skin (20%), and hair loss (5%). Achilles tendonitis, acne fulminans, depression, diarrhea, headaches, deafness, mood changes, night blindness, paronychia, urticaria, are vasculitis were reported as rare side effects.

According to **Brzezinski *et al.* [(6)],** in Poland and Romania, dry lips were the most prevalent side effect reported, occurring in 100% of individuals, followed by xerosis (94.97%), facial erythema (66.21%), epistaxis (47.26%), and muscular pains (38.78%). Other adverse effects were less observed as tiredness (20.73%), headaches (16.87%), joint aches (12.28%), mood change (9.50%), dry eyes (5.70%), hair loss (4.34%), vision changes (2.80%), and insomnia (2.78%).

Study of the frequency and severity of different side effects of oral isotretinoin in Egypt was not yet done. Our study was done to evaluate the most common side effects while using isotretinoin therapy

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in acne in Egyptian female population in Dakahlia Governorate.

PATIENTS AND METHODS

Cohort, prospective, experimental study was conducted at Dermatology, Andrology and STDs outpatient clinic of Mansoura University Hospital on 80 female patients with acne who received isotretinoin therapy for three months during the duration from February 2023 to October 2023.

Inclusion criteria:

- Egyptian females aged 15-35 years old, diagnosed with any type of acne vulgaris without history of systemic treatment in the last 3 months or topical treatment in the last month.
- Participants agreed to receive isotretinoin as the main mode of treatment.
- Married females agreed to use two methods of contraception during treatment.

Exclusion criteria:

- Female patients who were or might become pregnant during treatment.
- Lactating mothers.
- Alcohol intake.
- Patients with elevated lipid profile or liver enzymes (serum ALT or AST) prior to the study.
- Patients with chronic systemic medical illness or other dermatological disease.
- Patients with a history or clinical evidence of malignancy and autoimmune disease.

METHOD

All patients were subjected to:

1) Complete history taking:

- Personal history: Sociodemographic data about the patient.
- History of acne vulgaris including: onset, course, duration.
- Past medical history.

2) Complete cutaneous examination:

- Exclusion of any other dermatological disease.
- Determination of types and sites of acne lesions.
- The severity of acne was assessed directly by the global acne grading system (GAGS).

3) Investigational studies:

- **Routine laboratory investigations:**
  - **Complete blood count (CBC)**: hemoglobin concentration (Hb %), red blood cells (RBCs), white blood cells (WBCs), and platelet count.
  - **Lipid profile:** Included serum cholesterol, serum triglycerides**.**
  - **Liver Test Profile:** Included serum aspartate and alanine aminotransferases (AST and ALT).

4) Drug therapy:

Patients with moderate or severe acne with normal liver, renal function, and lipid profile received isotretinoin treatment at a dosage of 0.5-1.0 mg/kg/day for three months.

5) Outcome measurements:

- The GAGS was used to measure the degree of improvement in acne severity one month and three months following therapy.
- Assessment of patients' complaints from any clinical side effects such as dry lips, dry eyes, hair loss and myalgia was done after 1 month and 3 months treatment of isotretinoin.
- Cutaneous examination for dermatological side effects.
- This assessment was repeated at each visit, and persistence or resolution of symptoms was noted.
- Recording of any laboratory changes: CBC, liver enzymes and lipid profile 1 month then 3 months after treatment.
- CBC, Serum cholesterol, TGs, ALT, and AST were evaluated according to The **National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE)** (Table 1).
  - The NCI Common Nomenclature Criteria for Adverse Events v3.0 provides descriptive nomenclature for reporting adverse events (AEs). Each AE phrase is graded on a severity scale. CATEGORY is a comprehensive categorization of adverse events based on anatomy and/or pathophysiology.

Table (1): National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

CTCAE grade	Triglycerides mg/dL	Total cholesterol mg/dL	ALT or AST IU/L
Normal	≤150	≤200	≤40
Grade 1	150–375	201–300	41–100
Grade 2	376–750	301–400	101–200
Grade 3	751–1500	401–500	201–800
Grade 4	>1500	>500	>800

ALT: Alanine transaminase, AST: Aspartate aminotransferase.

Sample size:

Sample size calculation was based on the prevalence of chapped and dry lips (96%), which was reported as the most frequent side effect of isotretinoin in a previous study [14]. Open Epi Website (https://www.openepi.com/SampleSize/SSPropor.htm) was used to calculate the sample size with α error of 0.05 and absolute precision of. Therefore, the calculated sample size was 60 patients at least. After adding 20% to compensate for attrition, then the estimated sample size 72patients at least.

Ethical consideration:

The study protocol was submitted for clearance to Mansoura Medical College's Institution Research Board. The Local Ethical Committee of the Mansoura Faculty of Medicine authorized the study. Each participant or the caregivers of the children participants in this study provided written informed permission. Confidentiality and personal privacy were preserved throughout the study. The Helsinki Declaration was observed throughout the study's duration.

Statistical analysis

The SPSS program version 25.0 was used to statistically analyze and show all of the collected data in tables, graphs, and charts. Calculating mean±standard deviation (SD), medians, ranges, and percentages was the process of descriptive statistics. The normality of the data distribution was examined using the Kolmogorov-Smirnov test. Mann-Whitney U tests were used to evaluate the median differences of the data that were not normally distributed. When more than 20% of cells had an anticipated count of less than 5, the Monte-Carlo test was employed to investigate the relationship between the two qualitative variables. If more than two related groups differed on a dichotomous dependent variable, the Cochran's test was performed for comparison. A statistically significant p-value is one that is less than 0.05.

RESULTS

Table (2) shows the features of the studied patients. The cohort consisted of 80 patients with a mean age of 22.77 years. The mean dose of the treatment at the first month was 28.62 mg and was 25.38 mg at third month. The severity of acne vulgaris in the cohort varied, with 48.8% as moderate.

Table (2): Features of studied patients.

	All cohort n = 80	
Age (years)		
Mean ± SD	22.77 ± 3.27	
Median	22.0	
Min. – Max.	16.0 – 35.0	
Dose (mg) at first month		
Mean ± SD.	28.62 ± 9.64	
Median	30.0	
Min. – Max.	10.0 – 40.0	
Dose (mg) at third month		
Mean ± SD.	25.38 ± 10.78	
Median	20.0	
Min. – Max.	10.0 – 40.0	
Severity of acne		
Mild	7	8.8
Moderate	39	48.8
Severe	23	28.8
Very severe	11	13.8

Table (3) shows the comparison between the three studied periods regarding changes in laboratory parameters. The CBC changes were observed in 5.0% after 1 month and 3 months, with significant differences between 1st and 3rd months versus baseline CBC.

Regarding cholesterol changes, there was a significant difference among the three periods. The cholesterol changes were observed in 41.3% after 3 months, with significant difference between 3rd month versus baseline and 1st month. Triglyceride (TG) changes were observed in 8.8% after 3 months, with significant difference compared to baseline level. In terms of ALT and AST changes, there were no significant differences observed between the three periods. The presence of ALT and AST changes remained minimal throughout the study.

Table (3): Comparison between the three studied periods regarding laboratory changes n=80.

	Before treatment		After 1 month		after 3 months		Test	p1	Pairwise
	No.	%	No.	%	No.	%			
Hemoglobin (g/dL)							Q=6.400*	0.041*	p2=0.028* p3=0.028* p4=1.000
Normal	80	100.0	76	95.0	76	95.0			
Decrease	0	0.0	4	5.0	4	5.0			
Cholesterol change (mg/dL)									
Normal	79	98.8	72	90.0	47	58.8	Q=51.455*	<0.001*	p2=0.136 p3<0.001* p4<0.001*
Increased	1	1.3	8	10.0	33	41.3			
TG change (mg/dL)									
Normal	80	100.0	76	95.0	73	91.3	Q=10.571*	0.005*	p2=0.064 p3=0.001* p4=0.165
Increased	0	0.0	4	5.0	7	8.8			
ALT change (U/L)									
Normal	80	100.0	80	100.0	79	98.8	Q=2.000	0.368	–
Increased	0	0.0	0	0.0	1	1.3			
AST change (U/L)									
Normal	80	100.0	80	100.0	79	98.8	Q=2.000	0.368	–
Increased	0	0.0	0	0.0	1	1.3			

Q: Cochran's test, p1: Comparing the three studied periods, p2: Comparing before treatment and after 1 month, p3: Comparing before treatment and after 3 months, p4: Comparing after 1 month and after 3 months, *: Significant.

Tables (4) and (5) presents a comparison of local and systemic side effects of isotretinoin across three studied periods.

Before treatment, the most common side effect was hair loss (5.0%), dry eyes (3.8%), followed by irregular menses (2.5%). After 1 month of treatment, the highest reported side effect was dry lips (92.5%), xerosis of skin at 35.0%, dry eyes increased to 28.8%, followed by dryness of mucous membrane (13.8%).

After 3 months, the most prevalent side effects were dry lips (100%), xerosis at 73.8%, and dry eyes and mood changes reported (63.8%) for each. For dry eyes, dry lips, xerosis, facial erythema, epistaxis, hair loss, itching, exfoliation, sun sensitivity, dryness of mucous membrane, vision changes, mood changes, insomnia, tiredness, headache, joint ache, muscle aches, diarrhea, abdominal pain, irregular menses and paronychia, the percentage increased significantly from before treatment to after 1 month and after 3 months. However, there were no significant differences for skin fragility, urticarial, retinoid dermatitis, personality changes and hearing loss across study periods.

Table (4): Comparison between the three studied periods regarding dermatologic side effects n=80.

	Before treatment		After 1 month		after 3 months		Test	p1	Pairwise
	No.	%	No.	%	No.	%			
Dry lips							Q= 145.08*	<0.001*	p2<0.001* p3<0.001* p4=0.411
Absent	79	98.8	6	7.5	0	0.0			
Present	1	1.3	74	92.5	80	100.0			
Dry eyes									
Absent	77	96.3	57	71.3	29	36.3	Q=65.811*	<0.001*	p2=0.001* p3<0.001* p4<0.001*
Present	3	3.8	23	28.8	51	63.8			
Dryness of mucous membrane									
Absent	79	98.8	69	86.3	39	48.8	Q=61.905*	<0.001*	p2=0.059 p3<0.001* p4<0.001*
Present	1	1.3	11	13.8	41	51.3			
Xerosis of skin							Q=88.576*	<0.001*	p2<0.001* p3<0.001* p4<0.001*
Absent	80	100.0	52	65.0	21	26.3			
Present	0	0.0	28	35.0	59	73.8			
Itching									
Absent	80	100.0	80	100.0	58	72.5	Q=44.0*	<0.001*	p2=1.000 p3<0.001* p4<0.001*
Present	0	0.0	0	0.0	22	27.5			
Exfoliation									
Absent	80	100.0	80	100.0	74	92.5	Q=12.0*	0.002*	p2=1.000 p3=0.003* p4=0.003*
Present	0	0.0	0	0.0	6	7.5			
Retinoid dermatitis									
Absent	80	100.0	80	100.0	79	98.8	Q=2.000	0.368	–
Present	0	0.0	0	0.0	1	1.3			
Skin fragility									
Absent	80	100.0	80	100.0	80	100.0	–	–	–
Present	0	0.0	0	0.0	0	0.0			
Facial erythema							Q=48.667*	<0.001*	p2=0.480 p3<0.001* p4<0.001*
Absent	80	100.0	77	96.3	53	66.3			
Present	0	0.0	3	3.8	27	33.8			
Sun sensitivity									
Absent	80	100.0	78	97.5	54	67.5	Q=48.308*	<0.001*	p2=0.631 p3<0.001* p4<0.001*
Present	0	0.0	2	2.5	26	32.5			
Urticaria									
Absent	80	100.0	80	100.0	78	97.5	Q=4.000	0.135	–
Present	0	0.0	0	0.0	2	2.5			
Paronychia									
Absent	80	100.0	80	100.0	75	93.8	Q=10.0*	0.007*	p2=1.000 p3=0.006* p4=0.006*
Present	0	0.0	0	0.0	5	6.3			
Hair loss							Q=54.60*	<0.001*	p2=0.502 p3<0.001* p4<0.001*
Absent	76	95.0	73	91.3	46	57.5			
Present	4	5.0	7	8.8	34	42.5			
Personality changes									
Absent	80	100.0	80	100.0	80	100.0	–	–	–
Present	0	0.0	0	0.0	0	0.0			
Mood changes									
Absent	80	100.0	79	98.8	29	36.3	Q=100.04*	<0.001*	p2=0.864 p3<0.001* p4<0.001*
Present	0	0.0	1	1.3	51	63.8			
Insomnia									
Absent	80	100.0	80	100.0	77	96.3	Q= 6.0*	0.049*	p2=1.000 p3=0.034* p4=0.034*
Present	0	0.0	0	0.0	3	3.8			

Q: Cochran's test, p1: Comparing the three studied periods, p2: Comparing before treatment and after 1 month, p3: Comparing before treatment and after 3 months, p4: Comparing after 1 month and after 3 months, *: Significant.

Table (5): Comparison between the three studied periods regarding local and systemic changes n=80.

	Before treatment		After 1 month		after 3 months		Test	p1	Pairwise
	No.	%	No.	%	No.	%			
Epistaxis							Q=32.118*	<0.001*	p2=0.766 p3<0.001* p4<0.001*
Absent	80	100.0	79	98.8	63	78.8			
Present	0	0.0	1	1.3	17	21.3			
Vision changes									
Absent	80	100.0	80	100.0	71	88.8	Q=18.0*	<0.001*	p2=1.000 p3<0.001* p4<0.001*
Present	0	0.0	0	0.0	9	11.3			
Hearing loss									
Absent	80	100.0	80	100.0	80	100.0	-	-	-
Present	0	0.0	0	0.0	0	0.0			
Muscle aches									
Absent	80	100.0	79	98.8	50	62.5	Q=58.067*	<0.001*	p2=0.823 p3<0.001* p4<0.001*
Present	0	0.0	1	1.3	30	37.5			
Joint ache									
Absent	80	100.0	80	100.0	42	52.5	Q=76.0*	<0.001*	p2=1.000 p3<0.001* p4<0.001*
Present	0	0.0	0	0.0	38	47.5			
Tiredness									
Absent	80	100.0	79	98.8	38	47.5	Q=82.048*	<0.001*	p2=0.850 p3<0.001* p4<0.001*
Present	0	0.0	1	1.3	42	52.5			
Abdominal pain									
Absent	80	100.0	79	98.8	63	78.8	Q=32.118*	<0.001*	p2=0.766 p3<0.001* p4<0.001*
Present	0	0.0	1	1.3	17	21.3			
Diarrhea									
Absent	80	100.0	80	100.0	76	95.0	Q=8.0*	0.018*	p2=1.000 p3=0.014* p4=0.014*
Present	0	0.0	0	0.0	4	5.0			
Irregular menses									
Absent	78	97.5	76	95.0	48	60.0	Q=54.452*	<0.001*	p2=0.660 p3<0.001* p4<0.001*
Present	2	2.5	4	5.0	32	40.0			
Headache									
Absent	79	98.8	79	98.8	69	86.3	Q=20.0*	<0.001*	p2=1.000 p3<0.001* p4<0.001*
Present	1	1.3	1	1.3	11	13.8			

Q: Cochran's test, p1: Comparing the three studied periods, p2: Comparing before treatment and after 1 month, p3: Comparing before treatment and after 3 months, p4: Comparing after 1 month and after 3 months, *: Significant.

Table (6) shows that for dry eyes, vision changes, and headache, there were significant differences in the median age. Older age was significantly associated with higher incidence of dry eyes, vision changes, while younger age was significantly associated with higher incidence of headache.

Table (6): Relationship between age and different side effects after treatment (side effects in 1 +3 months).

	Age (years)			Test	p
	Mean ± SD.	Median	Min. – Max.		
Dry eyes					
Absent, n=28	21.29 ± 3.30	21.0	16.0 – 30.0	U=1035.0*	0.002*
Present, n=52	23.58 ± 2.99	23.0	18.0 – 35.0		
Vision changes					
Absent, n=71	22.52 ± 3.23	22.0	16.0 – 35.0	U=452.5*	0.041*
Present, n=9	24.78 ± 3.03	26.0	21.0 – 29.0		
Mood changes					
Absent, n=29	22.86 ± 3.52	22.0	16.0 – 35.0	U=757.0	0.860
Present, n=51	22.73 ± 3.15	22.0	16.0 – 30.0		
Insomnia					
Absent, n=77	22.66 ± 3.28	22.0	16.0 – 35.0	U=191.5	0.052
Present, n=3	25.67 ± 0.58	26.0	25.0 – 26.0		
Tiredness					
Absent, n=38	22.84 ± 3.46	22.0	16.0 – 35.0	U=804.0	0.954
Present, n=42	22.71 ± 3.13	22.0	16.0 – 30.0		
Headache					
Absent, n=69	23.10 ± 3.29	23.0	16.0 – 35.0	U=198.0*	0.011*
Present, n=11	20.73 ± 2.33	21.0	17.0 – 26.0		
Joint ache					
Absent, n=42	22.24 ± 2.63	22.0	16.0 – 28.0	U=936.0	0.181
Present, n=38	23.37 ± 3.80	23.0	16.0 – 35.0		
Muscle aches					
Absent	22.90 ± 3.35	22.0	16.0 – 35.0	U=3230.5	0.980
Present	22.57± 3.18	22.0	16.0 – 29.0		
Diarrhea					
Absent, n=76	22.74 ± 3.29	22.0	16.0 – 35.0	U=172.0	0.678
Present, n=4	23.50 ± 3.11	22.50	21.0 – 28.0		
Abdominal pain					
Absent, n=63	22.79 ± 3.21	22.0	16.0 – 35.0	U=507.0	0.736
Present, n=17	22.71 ± 3.58	22.0	18.0 – 30.0		
Irregular menses					
Absent, n=47	22.74 ± 3.05	23.0	16.0 – 30.0	U=718.0	0.572
Present, n=33	22.82 ± 3.60	22.0	17.0 – 35.0		

U: Mann Whitney test. p: Comparing the different categories, *: Significant.

Table (7) shows that the side effects that showed significant associations with severity after 1 month were dry eyes. The percentage of individuals with dry eyes increased as the severity level increased, with the highest percentage observed in the very severe group (54.5%). The relationship between severity and dry eyes was statistically significant. Otherwise, no significant relationship was found between severity with local and systemic side effects after 1 month.

Table (7): Relationship between severity of acne with local and systemic side effects after 1 month.

	Severity								MC Test	p
	Mild n = 7		Moderate n = 39		Severe n = 23		Very severe n = 11			
	No.	%	No.	%	No.	%	No.	%		
Dry eyes									11.055	0.011*
Absent	7	100%	32	82.1%	13	56.5%	5	45.5%		
Present	0	0.0%	7	17.9%	10	43.5%	6	54.5%		
Mood changes										
Absent	7	100%	38	97.4%	23	100.0%	11	100%	1.065	0.786
Present	0	0.0%	1	2.6%	0	0.0%	0	0.0%		
Tiredness										
Absent	7	100%	39	100%	22	95.7%	11	100%	2.510	0.474
Present	0	0.0%	0	0.0%	1	4.3%	0	0.0%		
Headache										
Absent	7	100%	38	97.4%	23	100.0%	11	100%	1.065	0.786
Present	0	0.0%	1	2.6%	0	0.0%	0	0.0%		
Muscle aches										
Absent	7	100%	38	97.4%	23	100.0%	11	100%	1.065	0.786
Present	0	0.0%	1	2.6%	0	0.0%	0	0.0%		
Abdominal pain										
Absent	7	100%	39	100%	23	100.0%	10	90.9%	6.352	0.096
Present	0	0.0%	0	0.0%	0	0.0%	1	9.1%		
Irregular menses										
Absent	7	100%	37	94.9%	21	91.3%	11	100%	1.610	0.657
Present	0	0.0%	2	5.1%	2	8.7%	0	0.0%		

MC: Monte Carlo, *: Significant.

DISCUSSION

The mean age of our patients was 22.77±3.27 years. The age range was between 16.0 and 35.0 years. In agreement with our results, **Sallam *et al.*** [15], who investigated isotretinoin effects on free testosterone and DHEAS in fifty adult Egyptian females in Dakahlia Governorate with acne vulgaris, the mean age of their cases was 23.26±4.64 years. In the same line was a large retrospective review by **Brzezinski *et al.*** [6], the patients age ranged from 13 to 35 years.

In our study the severity of acne varied, with 8.8% of cases were classified as mild, 48.8% as moderate, 28.8% as severe, and 13.8% as very severe. The mean dose of the isotretinoin at the first month was 25.38 mg, with a range of 10.0 to 30.0 mg. At the third month, the mean dose increased to 28.62 mg, with a range of 10.0 to 40.0 mg.

In a previous study by **Feily *et al.*** [16], patients were given daily doses of 20 mg isotretinoin for three months, which was consistent with our findings. In a recent study by **Abukhalil *et al.*** [17] the most isotretinoin dose was 40 mg (60.9%), followed by 20 mg (11.1%) and 30 mg (6.4%).

Before treatment, the most common findings in our patients with acne were hair loss (5.0%), dry eyes (3.8%), followed by irregular menses (2.5%). After 1 month of treatment, the highest reported side effects were dry lips (92.5%), xerosis of skin (35.0%), dry eyes (28.8%), followed by dryness of mucous membrane (13.8%). After 3 months, the most prevalent side effects were dry lips (100%), xerosis (73.8%), dry eyes and mood changes (63.8% for each), tiredness (52.5%), dryness of mucous membrane (51.3%) and joint ache (47.5%).

Our study findings are consistent with previous studies on the side effects of isotretinoin. For example, **Bhat *et al.*** [18] observed 98% rate of occurrence for dry lips. Moreover, the most predominant side effects in study by **Abukhalil *et al.*** [17] were dry lips and xeroderma which experienced by 96.2% of participants. **Harfouch *et al.*** [14] noticed that the most frequent side effects were dry eyes and dry lips (96.3%) followed by xerosis (81.6%).

Brzezinski *et al.* [6] noted that, the most common among the adverse effects of isotretinoin was dry lips, and was seen in all participants (100%), followed by xerosis (94.97%), facial erythema (66.21%). Dryness reported in our study, together with other studies, could be connected to isotretinoin mechanism of action, as it reduces sebaceous gland size and sebum production resulting in a change in the skin lipid composition causing dryness of the skin.

In our study, the percentage of individuals with xerosis increased as the severity of acne increased, with the highest percentage observed in the severe group (56.5%). The relationship between

severity of acne and xerosis was statistically significant (p = 0.029). The relationship between severity of acne and dry eyes was statistically significant (p=0.011). **Zakrzewska *et al.*** [19] showed that dry eyes were significant predictor of the severity of acne in patients treated with isotretinoin from three to six months. Also, **Alajaji *et al.*** [20] found that the severity of dry eyes is increased in patients with increased acne severity.

In our study, the p-value for dryness of mucous membranes was lower than 0.05, suggesting a significant relationship between the dose of isotretinoin and the presence of this side effect. The p-value for dry eyes was higher than 0.05, indicating no significant relationship between dose and the presence of this side effect. In agreement, **Abd El-Raheem *et al.*** [21] reported that changes in dry eyes parameters results were higher among patients on high dose of isotretinoin, but still statistically not significant with (p >0.05).

In our study, after 1 month of treatment, hair loss was found in (8.8%) of patients. After 3 months treatment, hair loss was found in (42.5%) of patients. According to our findings, the median values for the dose administered showed no significant differences on hair loss after 3 months. **Abukhalil *et al.*** [17] reported that, hair loss is affected by dose of isotretinoin. Although the exact mechanism underlying hair loss in response to isotretinoin is unknown. **Lytvyn *et al.*** [22] have highlighted the relationship between isotretinoin dose and hair loss.

In our study, after 1 month of treatment, the least reported side effects were facial erythema (3.8%), sun sensitivity (2.5%), epistaxis (1.3%), irregular menses (5%), while mood changes, tiredness, headache, muscle ache and abdominal pain were reported at 1.3% each. After 3 months treatment, the reported side effect included irregular menses (40%), muscle ache (37.5%), facial erythema (33.8%), sun sensitivity (32.5%), itching (27.5%), epistaxis (21.3%), abdominal pain (21.3%), headache (13.8%), exfoliation (7.5%), paronychia (6.3%), diarrhoea (5%), insomnia (3.8%), urticaria (2.5%), and retinoid dermatitis (1.3%).

In a study by **Abukhalil *et al.*** [17], the least prevalent side effects were increased risk of infection (4%), and bone fractures (2.7%). **Brzezinski *et al.*** [6] noted that, the prevalence of adverse effects of isotretinoin were: epistaxis (47.26%), cheilitis (41.78%), muscle aches (38.78%), itching of the skin (38.12%) and exfoliation of the skin (30.97%). In a previous Saudi study, **Al-Harbi** [23] reported that constipation occurred in (8%) of their patients and joint pain occurred in (9%) of patients.

In our study, older age was significantly associated with higher incidence of dry eyes and vision changes, while younger age was significantly associated with higher incidence of headache. In another study, **Abukhalil *et al.*** [17] noted a statistically significant difference that based on age. They observed that participants aged ≤ 20 exhibiting a lower proportion of side effects than those aged ≥ 21 years.

In our study, there were no significant associations between severity of acne with dermatologic and systemic side effects but there was a significant relationship between severity of acne with diarrhea (p = 0.027). According to our findings after 3 months, the median values for the administered doses did not show significant differences on most side effects after 3 months. However, there was a significant relationship between higher dose and the presence of diarrhea, as indicated by a p-value lower than 0.05.

In our study, regarding CBC, there was a statistically significant decrease in hemoglobin level in 5.0% of patients after 1 month and 3 months treatment with isotretinoin. We observed a statistically significant relationship between increased age and decrease hemoglobin level (p-value 0.004). There were no significant associations between severity of acne with decrease hemoglobin level (p>0.05). In a study by **Abukhalil *et al.*** [17], anemia was the least prevalent side effect (5.5% of their cases). **Erturan *et al.*** [24], suggested that oxidative stress of isotretinoin on blood could explain these changes.

In our study findings, increase in blood cholesterol level occurred in 10% of patients after 1st month and 41.3% of patients after 3 months, with a significant increase after 3rd month treatment versus baseline and 1st month (p<0.001 for each). There was no significant relation between severity of acne and increase in blood cholesterol level (p> 0.05).

Along with our findings, **Alajaji *et al.*** [20] found that blood cholesterol level was statistically significantly increased (P<0.001) after isotretinoin treatment. **Al-Haddab *et al.*** [3] showed that cholesterol level in patients who treated with oral isotretinoin had increased and associated with severity of acne with a prevalence rate of 21.8%.

In our study, the blood triglyceride (TG) level increased in 5.0% of cases after 1 month and 8.8% of cases after 3 months. There was a significant difference (p = 0.005) among the three periods. Along with our findings, **Alajaji *et al.*** [20] found that triglyceride levels were statistically significantly increased after isotretinoin treatment. In another retrospective study, **Vieira *et al.*** [25] in Brazil reported that triglyceride levels were increased beyond the normal range in 11% of patients.

Similar to our findings, **Zane *et al.*** [26], at the University of California, reported increased TG levels in 44% of participants. This increase in TG level was associated with acne severity. Moreover, they suggested that this abnormality generally was transient and reversible. **Zakrzewska *et al.*** [19], showed that triglycerides, total cholesterol are both significant predictors of the severity of acne in patients treated with isotretinoin from three to six months.

It is unknown what specifically causes isotretinoin to elevate lipid levels. Retinoids often bind to albumin in the plasma. Albumin's rise is thought to be caused by the retinoid-albumin interaction in plasma, which removes triglyceride from albumin. Another theory that has been put up is that isotretinoin interacts with some vital proteins or lipid metabolism-related enzymes, such as hydroxymethylglutaryl reductase [(27)].

Regarding ALT and AST levels, after 1st month of treatment there was no change in both levels in comparison to the 3rd month of treatment, there were elevations in only 1.3% of patients. We found that there were no significant differences observed between the three periods. Changes in ALT and AST levels remained minimal throughout the study. There was no significant relationship between severity of acne with ALT and AST level (p>0.05 for each). **Alajaji *et al.*** [(20)] found that, 12.7% of their patients had increased ALT and 5.4% had elevated AST after three months of isotretinoin treatment. **Vieira *et al.*** [(25)] in Brazil reported that 8.6% of cases had elevated AST levels and 7.3% of cases had elevated ALT levels after three months of isotretinoin treatment.

In our study, there was no significant relationship between severity of acne with ALT and AST level (p>0.05 for each). **Kapała *et al.*** [(9)] reported that higher doses of isotretinoin were associated with liver enzyme (AST/ALT) elevation in 43 (7.8%) of participants. Although the exact mechanism causing serum aminotransferase increases caused by isotretinoin is unknown, the fact that they seem to occur more frequently with greater dosage treatment suggests that they are a direct harmful impact [(28)]. **Lamon-Fava *et al.*** [(27)]**,** suggested that elevations of liver enzymes may be due to the oxidative stress of isotretinoin on hepatocytes, which can be prevented by antioxidants.

CONCLUSION

In conclusion, our results confirm the importance of studying isotretinoin side effects and increasing the awareness of its possible complications. The most common side effects were dry lips, dry eyes, irregular menses and hair loss. There was a significant relationship between higher dose of isotretinoin and severity of acne vulgaris with the presence of diarrhea. Isotretinoin appeared to have a bigger effect on lipids than on liver enzymes, and we suggested using isotretinoin with close monitoring. However, these findings require confirmation by larger, more-powered study with larger sample size.

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