Effect of Acitretin on Semen Parameters in Psoriatic Male Patients

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ABSTRACT

Background: Acitretin belongs to a group of drugs known as retinoids which have similar activity to vitamin A. Vitamin A helps regulate the immune system, impacts cellular growth, differentiation, proliferation, and plays a role in embryonic development.

Objective: The aim of the current study was to evaluate the effect of acitretin administration on semen parameters in male psoriatic patients.

Patients and methods: This cohort study included a total of 31 male psoriatic patients, attending at Dermatology and Andrology Clinics, Mansoura University Hospitals to demonstrate the effect of Acitretin administration on semen parameters. This study was conducted between June 2019 to September 2020.

Results: The average Psoriasis Area and Severity Index (PASI) score of the studied cases was 17.96 ± 4.55. Most of the studied cases has moderate to severe activity, while only 25.8% of which had severe disease. Positive family history and associated skin diseases were demonstrated in 22.6% and 16.1% of cases respectively. There was no statistically significant differences were detected after treatment as compared with before treatment as regards mean semen volume, semen PH, mean total sperm motility, mean ratio of live sperms, mean sperm concentration, mean pus cells count and mean ratio of sperm with normal morphology.

Conclusion: It could be concluded that retinoids seem to have no adverse effects in the context of semen parameters in male psoriatic patients.

Keywords: Acitretin, Semen Parameters, Psoriatic Male Patients

INTRODUCTION

Psoriasis is a common, chronic inflammatory disease of the skin having worldwide prevalence of 2% [(1)]. Psoriasis is generally thought to be a genetic disease that is triggered by environmental factors [(2)].

Most patients (80-90%) present with plaque psoriasis, characterized by a chronic remitting and relapsing course. Other types include guttate, pustular, erythrodermic and inverse psoriasis [(3)].

Psoriasis may be considered severe if there is associated functional impairment (e.g., genital affection, palmoplantar disease, or psoriatic arthritis). Psoriasis is known to have a negative impact on the patient's health and quality of life of both the affected person and the individual's family members [(4)].

There is no cure for psoriasis; however, various treatments can help to control the symptoms [(5)]. Many treatment options exist topical agents are typically used for the mild disease, phototherapy for moderate disease, and systemic agents for severe disease [(6)].

The majority of therapeutic options in psoriasis carry significant adverse effects and toxicity profile. However, retinoids in general and acitretin in particular offer the advantage of being a non-immunosuppressive drug with a better safety profile [(7)].

Acitretin is one of the treatments of choice for pustular psoriasis. Even though acitretin is less effective as monotherapy for chronic plaque psoriasis, combination therapy with other agents, especially UVB or psoralen plus UVA phototherapy, can enhance efficacy [(8)].

Acitretin belongs to a group of drugs known as retinoids. Retinoids include natural and synthetic compounds that have similar activity to vitamin A. Vitamin A helps regulate the immune system, impacts cellular growth, differentiation, proliferation, and plays a role in embryonic development. Other effects of retinoids include immunologic anti-inflammatory effects, induction of apoptosis, and inhibition of tumor promotion [(9)].

Currently, there are few studies on the effects of retinoids on the male reproductive system, oral retinoid treatment was considered to be safe. Given the wide clinical usage of retinoids, clarification of whether retinoids affect the reproductive system in male patients is urgently needed, a recent study done by **Liu *et al.*** [(10)] found that different doses of acitretin did not significantly affect semen quality in psoriatic patients at different treatment stages**.**

The aim of the present study was to evaluate the effect of acitretin administration on semen parameters in male psoriatic patients.

PATIENTS AND METHODS

This cohort study included a total of 31 male psoriatic patients, attending at Dermatology and Andrology Clinics, Mansoura University Hospitals to demonstrate the effect of Acitretin administration on semen parameters. This study was conducted between June 2019 to September 2020.

Inclusion criteria: Psoriatic male patients in whom acitretin is indicated, patient taking acitretin at least 3 months, and patients aged from 18 to 50 years.

Exclusion criteria: Systemic diseases, endocrinal diseases, autoimmune diseases, hormonal treatment in the last 3 months, genetic diseases, varicocele, orchitis, and prostatitis.

***Ethical Consideration*:**

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The whole study design was approved by the institutional review board (IRB), Faculty of Medicine, Mansoura University (IRB approval: MS.19.06.684.R1- 2019/6/18). Every patient signed an informed written consent for acceptance of participation in the study. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

All patients were subjected to:

1. **Full history taking:**
   - Personal history.
   - History of the present illness: onset, course, duration of psoriasis, precipitating and relieving factors.
   - History of medications: nature, route, dose, compliance, duration, effects, and side effects.
   - Family history of psoriasis or other dermatoses.
   - Past history of any associated systemic, dermatological diseases or major surgical operations.
2. **Through general examination:** to exclude any systemic diseases.
3. **Hormonal profile** (prolactin, free testosterone, FSH, LH).
4. **Doppler ultrasound** to exclude varicocele.
5. **Full dermatological examination:**
   A. Skin, hair, nails, and mucous membranes examination to assess the clinical type of psoriasis, distribution and severity and to exclude autoimmune skin diseases.
   B. Lesions were scored according to psoriasis area and severity index (PASI) score: The Psoriasis Area and Severity Index (PASI) is the most used tool to assess disease severity in patients with psoriasis in clinical trials. The PASI measures erythema, scaling and thickness of lesions and is weighted by the area of involvement. It is an important tool in measuring the impact of disease on quality of life **[(11)].** Psoriasis area severity index score classifies patients with psoriasis into mild psoriasis (PASI ≤10), moderate to severe psoriasis (PASI >10 - <20), severe psoriasis (PASI ≥20) **[(12)].**

Semen analysis:

Semen analysis was done before and 3 months after starting acitretin. Semen specimens were collected after a sexual abstinence period of at least 2 days but not more than 7 days. Semen was obtained by masturbation into a sterile plastic container. Samples were left to liquefy at 37°C and were analyzed just after liquefaction (within an hour) and all samples were examined according to the WHO 2010 criteria **[(13)]**.

The Treatment Course: (1) Dose of acitretin: 0.5 mg/kg/day. (2) Form of the drug: Tablets. (3) Route of administration: Oral. (4) Duration of administration: 3 months.

Follow up visits: After three months to assess the semen parameters after the treatment course of acitretin.

Statistical analysis:

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA). Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test (χ^2) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation). Independent samples t-test was used to compare between two independent groups of normally distributed variables (parametric data) while Mann Whitney U test was used for non-normally distributed Data (non-parametric data). Paired samples t-test was used to compare between two dependant groups of normally distributed variables (parametric data) while Wilcoxon Signed rank test was used for non-normally distributed Data (non-parametric data). P value < 0.05 was considered significant.

RESULTS

This is a cohort (pre-post) study. It was carried out on 31 psoriatic male patients. The mean ages of psoriasis patients were 39.74 ± 8.84 years. There were 14 cases (45.2%) with age ≤ 40 years and 17 cases (54.8%) with age > 40 years. There were 15 cases (51.6%) from urban areas and 16 cases (48.4%) from rural areas. Among the included cases, there were 17 cases (54.8%) smokers (Table 1).

Table (1): Sociodemographic data in the cases of the study:

Items		Study cases n=31
Age (years)	Mean ± SD	39.74 ±8.84
	Median (min-max)	42 (18 -50)
Age group		
≤ 40 years		14 (45.2%)
> 40 years		17 (54.8%)
Residence		
Urban		15 (51.6%)
Rural		16 (48.4%)
Smoking		
Yes		17 (54.8%)
No		14 (45.2%)

Continuous data expressed as mean ± SD and median (range)
Categorical data expressed as Number (%)

The type of psoriasis in the cases included psoriasis vulgaris in 24 cases (77.4%), erythrodermic psoriasis in 3 cases (9.7%) and pustular psoriasis in 4 cases (12.9%). The mean duration of the disease was

10.06 ± 5.29 years with range between 1 and 23 years. There were 19 cases (61.3%) with disease duration ≤ 10 years and 12 cases (38.7%) with disease duration > 10 years. Regarding the disease activity, the mean PASI score of the cases was 17.96 ± 4.55 with range between 10 and 26.5. There were 23 cases (74.2%) with moderate to severe activity and 8 cases (25.8%) with severe disease (Table 2).

Table (2): Analysis of the disease characters of the study group:

Items		Study cases n=31
Type of psoriasis		
Psoriasis	24 (77.4%)	
Erythrodermic	3 (9.7%)	
Pustular	4 (12.9%)	
Duration of the disease (years)	Mean ±	10.06 ± 5.29
	Median	8 (1-23)
Disease duration		
≤ 10 years	19 (61.3%)	
> 10 years	12 (38.7%)	
PASI	Mean ±	17.96 ± 4.55
	Median	17 (10 - 26.5)
Classification of disease severity according to		
Moderate to severe	23 (74.2%)	
Severe (PASI >	8 (25.8%)	

Continuous data expressed as mean ± SD and median (range)
Categorical data expressed as Number (%)

There were 7 cases (22.6%) with positive family history and there were 5 cases with associated skin diseases (16.1%) (Table 3).

Table (3): Analysis of family history and associated skin diseases in the cases of the study:

Items	Study cases n=31
Family history	
Negative	24 (77.4%)
Positive	7 (22.6%)
Associated skin diseases	
No	26 (83.9%)
Yes	5 (16.1%)

Continuous data expressed as mean ± SD and median (range)
Categorical data expressed as Number (%)

The mean semen volume before treatment was 3.37 ± 0.30 ml and after treatment the mean semen volume was 3.38 ± 0.17 ml with no statistically significant difference after treatment as compared with before treatment. The mean semen PH in the included cases before treatment was 7.46 ± 0.21 and after treatment the mean semen PH was 7.66 ± 0.19 with no statistically significant difference after treatment as compared with before treatment. The mean total sperm motility in the included cases before treatment was 62.94 ± 4.59 % and after treatment the mean total sperm motility was 64.89 ± 2.99% with no statistically significant difference after treatment as compared with before treatment.

The mean ratio of live sperms in the included cases before treatment was 79.51 ± 13.33% and after treatment the mean ratio of live sperms was 81.17 ± 12.59 % with no statistically significant difference after treatment as compared with before treatment. The mean sperm concentration in the included cases before treatment was 46.90 ± 8.02 and after treatment the mean sperm concentration was 49.53 ± 9.23 with no statistically significant difference after treatment as compared with before treatment. The mean pus cells count in the included cases before treatment was 3.72 ± 0.51 % and after treatment the mean sperm concentration was 3.98 ± 0.38 % with no statistically significant difference after treatment as compared with before treatment. The mean ratio of sperm with normal morphology in the included cases before treatment was 2.74 ± 1.61 and after treatment the mean pus cells count was 2.42 ± 1.59 with no statistically significant difference after treatment as compared with before treatment (Table 4).

Table (4): Analysis of semen parameters changes level before and after treatment:

	Before treatment (N=31)	After treatment (N=31)	Test of Significance
Semen volume (ml)	3.37 ± 0.30	3.38 ± 0.17	t= - 0.045 P= 0.946
PH	7.46 ± 0.21	7.66 ± 0.19	t= - 1.246 P= 0.256
Total motility (%)	62.94 ± 4.59	64.89 ± 2.99	t= - 1.948 P= 0.108
Ratio of live sperms (%)	79.51 ± 13.33	81.17 ± 12.59	t= - 1.418 P= 0.192
Sperm concentration (x 10^6/L)	**46.90 ± 8.02**	**49.53 ± 9.23**	t= - 1.760 P= 0.142
Ratio of sperm with normal morphology (%)	3.72 ± 0.51	3.98 ± 0.38	t= - 2.236 P= 0.078
Pus cells (/ml)	2.74 ± 1.61	2.42 ± 1.59	z= 2.301 P= 0.054

P: probability. Continuous data expressed as mean ± SD
T: Independent samples t test, z= Mann-Whitney U test

DISCUSSION

This study was carried out on a total of 31 male psoriatic patients who were recruited from the

outpatient clinic of Dermatology and Andrology Clinics of Mansoura University Hospital.

The mean ages of psoriasis patients were 39.74 ± 8.84 years. There were 14 cases (45.2%) with age ≤ 40 years and 17 cases (54.8%) with age > 40 years. There were 15 cases (51.6%) from urban areas and 16 cases (48.4%) from rural areas. There were 17 cases (54.8%) smokers and 14 (45.2%) cases.

Similarly, **Mahil *et al.*** [14] have found that mean age of psoriasis patients was 44·9 years and 91% of which had white ethnicity

In accordance to some extent **Icen *et al.*** [15], have demonstrated that; the mean age at diagnosis (± standard deviation) of psoriasis was 43.2 ± 17.0 years. Average age at incidence increased across the three decades from 39.8 years in 1970–1979, to 41.9 years in 1980–1989 and 45.5 years in 1990–1999 ($p<0.001$).

Mohd Affandi *et al.* [16] have found that; females patients had an earlier age of onset of psoriasis, with a mean age of 32.59 ± 16.64, compared to male, with a mean age of 37.09 ± 15.51 .

The current study displayed that; the mean duration of the disease was 10.06 ± 5.29 years with range between 1 and 23 years. There were 19 cases (61.3%) with disease duration ≤ 10 years and 12 cases (38.7%) with disease duration > 10 years.

While **Truong *et al.*** [17] have displayed that; mean age of psoriasis onset was 28 years and mean disease duration was 18 years. While, **Hägg *et al.*** [18] have demonstrated that, the mean psoriasis duration was longer for women (20 years) compared to men (18 years) with a statistically significant difference ($p = 0.002$).

El Zayat *et al.* [19] have reported that; the median duration of psoriasis was 3.5 years ranging from 0.67 to 35 years among males and 3.0 ranging from 0.17 to 35 years among females.

Regarding the type of psoriasis in the cases included psoriasis vulgaris in 24 cases (77.4%), erythrodermic psoriasis in 3 cases (9.7%) and pustular psoriasis in 4 cases (12.9%).

Regarding the disease activity, the mean PASI score of the cases was 17.96 ± 4.55 with range between 10 and 26.5. There were 23 cases (74.2%) with moderate to severe activity and 8 cases (25.8%) with severe disease.

This came in agreement with recent Egyptian study conducted by **El Zayat *et al.*** [19] who have reported that; the median PASI score was 13.4 (57.8% were moderate , 24.4% mild and 17.8% severe) .

Also **Ljosaa *et al.*** [20] have demonstrated that; the mean PASI score was 5.5 (SD 4.9), and the mean worst pain intensity of those who reported skin pain was 5.7 (SD 2.3).

The present study revealed that; there were seven cases (22.6%) with positive family history and there were five cases with associated skin diseases (16.1%).

Comparable incidence in positive family history was reported in a Malaysian study conducted by **Mohd Affandi *et al.*** [16] in which positive family history was reported in 23.1% of patients, and female patients had a higher percentage of family members with psoriasis, compared to male patients.

Higher incidence was recorded by **Solmaz *et al.*** [21] who have reported that; approximately 40% of patients have a family history of psoriasis or PsA, which may affect disease features.

As regards, analysis of semen parameters before and after treatment, the current study demonstrated that, no significant differences were recorded before and after treatment in terms of semen volume, PH, total motility, sperm concentration, ratio of sperm with normal morphology and Pus cells.

In accordance, **Liu *et al.*** [11] conducted their study to assess the main parameters of semen and the sperm morphology of 31 psoriatic patients before and after treatment with different doses of ACI, and the changes in reproductive hormone levels were measured and compared with those of 14 healthy control individuals.

They have demonstrated in their results that; ACI can improve the clinical symptoms of psoriatic patients, but different doses of ACI did not cause significant changes in sperm concentration, sperm morphology, total sperm count, sperm motility, or reproductive hormone levels 1 month or 3 months after treatment.

Similarly, **Parsch *et al.*** [22] conducted their study on a total of 10 subjects treated orally with acitretin (Ro 10–1670) over a period of 3 months. Before, during and after treatment, semen and blood analyses were performed to investigate drug-induced impairment of spermatogenesis and the hypothalamic - pituitary-gonadal axis. Therefore, they concluded that acitretin in therapeutically effective doses does not influence spermatogenesis, sperm morphology, sperm motility and the hypothalamic pituitary gonadal axis.

In agreement**, Geiger and Walker** [23] have demonstrated that; acitretin does not cause any alteration in sperm parameters.

This came in the same line with animal researches in which **Sengör *et al.*** [24] conducted their study on a total of 31 male adult Wistar albino rats divided into 3 groups as two experimental groups and one control group. The first group consisting 14 rats were applied orally standard dose (0.75 mg/kg/day) acitretin and the second group consisting 16 rats were applied high dose (1.5 mg/kg/day) acitretin. Acitretin was given within dimethyl sulphoxide (DMSO), which was diluted with saline solution as a ratio of 1/10, in order to increase its solubility. The control group consisting of 9 rats were given only saline solution including DMSO for 8 weeks. After 8 weeks of the administration, half of the rats in the first and second groups and the entire control group were sacrificed under deep ether anesthesia and bilateral orchiectomy

was made. The remaining rats were compared with the control group using a similar method at the end of 8 weeks of wash-off period.

The orchiectomy materials were histopathologically evaluated under the light microscope for spermatogenesis according to parameters including spermatogenetic activity, spermatogenetic organization, seminiferous tubular diameter, interstitial Leydig cells and fibroblasts. The groups, which were evaluated at the end of the 8th and 16th weeks, were compared with the control group regarding the mentioned parameters and no statistical significance was observed among the groups. In their study it was concluded that the standard and high doses of acitretin do not have any effect on the spermatogenesis of the rats[24].

On the contrary, one study conducted by **Rossi and Pellegrino** [25] have demonstrated that; retinoids have been associated with male reproductive system dysfunctions in human and animal studies as they have demonstrated that; acitretin was associated with erectile dysfunction.

However, **Rossi and Pellegrino** [25] have concluded such fact based on a case record only, in other words not evident outcome that could be generalized to overall populations.

Limitations: Despite the promising outcomes of the current study, small sample size remains the main limitation. In addition, no comment on the effect of different doses of retinoids was recorded.

CONCLUSION

It could be concluded that retinoids seem to have no adverse effects in the context of semen parameters in male psoriatic patients.

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