

Study of Levels of Free Testosterone in Patients with Acne Vulgaris before and after Treatment

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ABSTRACT

Background: Acne vulgaris is one of the most common diseases afflicting humans and it is the skin disease most commonly treated by physicians. The prevalence of acne is about 15% in all age-groups and it is seen more frequently in women than men. Abnormal follicular differentiation, increased cornification, enhanced sebaceous gland activity, hyperseborrhea, bacterial hypercolonization, as well as inflammation and immunological host reaction are the major contributors to acne formation. Other factors such as diet, exposure to the sun, poor hygiene, stress, and genetics are believed to cause or worsen acne symptoms. Hormonal imbalance also plays a role in acnegenesis. Out of all the hormones, androgens are thought to be most important due to its association with the follicular and sebaceous glands.

Aim and objective: Our aim of the study is to compare the severity of acne vulgaris with free testosterone levels and to correlate its level before and after treatment. Ninety-three patients attending OPD of the Department of Dermatology, Venereology and Leprosy of Dayanand Medical College and Hospital, Ludhiana, were enrolled in the study period of 1 year.

Results: The mean free testosterone levels before treatment were 1.58 ± 1.50 pg/mL and after treatment were 1.34 ± 0.90 pg/mL. These values were statistically significant ($p = 0.006$). The mean free testosterone levels in the age-group of <20 years before treatment were 1.93 ± 1.65 pg/mL and after treatment were 1.61 ± 1.06 pg/mL. These values were statistically significant ($p = 0.016$).

Conclusion: The increase in free testosterone levels may be responsible as one of the factors for the development of acne vulgaris.

Clinical significance: As free testosterone is associated with acne vulgaris, free testosterone levels should be measured in patients presenting with acne vulgaris, especially in the age-group 15–30 years and treatment-resistant cases and anti-androgen treatment may be indicated in cases with elevated free testosterone levels.

Keywords: Acne, anti-androgen therapy, Free testosterone.

Indian Journal of Medical Biochemistry (2021): 10.5005/jp-journals-10054-0175

INTRODUCTION

Acne vulgaris remains one of the most common diseases afflicting humans and is a skin disease most commonly treated by physicians.¹ The prevalence of acne is about 15% in all age-groups and is seen more frequently in women than men.^{2,3} The majority of adult cases can be classified as persistent, occurring especially in women, while in boys, acne usually disappears after adolescence. However, there are cases of truly late-onset acne (occurring after 25 years of age),⁴ and in the last decade, there has been an increase in the age of onset, mainly in women aged 20.5–26.5 years.⁵

Acne is a disease of the pilosebaceous unit, clinically characterized by seborrhea, comedones, papules, pustules, nodules, and, in some cases, scarring.⁶ It is mainly a non-inflammatory lesion that occurs due to continuous production of sebum and keratin in the obstructed sebaceous follicle, along with the formation of microcomedone (closed comedones—whiteheads and open comedones—blackheads). Inflammatory acne is due to the rupture of contents of comedones into the dermis.⁶

Abnormal follicular differentiation, increased cornification, enhanced sebaceous gland activity, hyperseborrhea, bacterial hypercolonization, as well as inflammation and immunological host reaction are the major contributors to acne formation. Other factors such as diet, exposure to the sun, poor hygiene, stress, and genetics are believed to cause or worsen acne symptoms.

Out of all the hormones that can affect acnegenesis, androgens are the most important. Androgen receptors have been localized on the basal layer of the sebaceous gland and the outer root sheath of keratinocytes of the hair follicle. Major

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How to cite this article: Kaur P, Bajwa N, Gupta SK, *et al.* Study of Levels of Free Testosterone in Patients with Acne Vulgaris before and after Treatment. *Indian J Med Biochem* 2021;25(2):47–50.

Source of support: Nil

Conflict of interest: None

androgens that interact with androgen receptors are testosterone and dihydrotestosterone.⁷

Therefore, a detailed understanding of androgen synthesis and the pathology behind hyperandrogenism is a must for dermatologists to formulate a tailored therapy for individual patient's needs.

In this scenario, our aim of the study is to compare the severity of acne vulgaris with free testosterone levels and to correlate its level before and after treatment.

MATERIALS AND METHODS

One hundred female patients of acne vulgaris who came to OPD of the Department of Dermatology, Venereology and Leprosy of

Dayanand Medical College and Hospital, Ludhiana, were enrolled in the study period of 1 year. Patients were graded on a scale of I–IV according to Pillsbury Classification.⁸ Out of these, 93 female patients came for follow-up and data of 93 patients were finally included in the study.

Inclusion Criteria

Only female patients aged 15–40 years with grade III and IV (Pillsbury classification⁸) acne were included in this study.

Exclusion Criteria

Patients with BMI >30 kg/m², previously diagnosed thyroid or pituitary disease, coronary artery disease, diabetes mellitus, chronic renal failure, rheumatic disease, pregnancy, history of mood and depressive disorders, and patients taking any vitamin supplementation were excluded from the study.

During the first visit, detailed history and clinical examinations were done along with baseline free testosterone levels (group I). Patients were called for follow-up after 12 weeks of treatment and free testosterone levels were estimated (group II) to compare the levels before and after treatment.

Free testosterone levels were measured manually by a kit method using the competitive ELISA principle.

Statistical Analysis

Results were analyzed using SPSS 21 software using Chi-square. Paired “t” test and Pearson correlation test were used for statistical analysis. In this study, $p < 0.05$ has been taken as statistically significant.

RESULTS

31.2% of patients were in the age-group of 15–20 years, 53.8% of patients were in the age-group of 21–30 years, and 15.1% of patients were in the age-group of 31–40 years. So maximum number of patients was in the age range of 21–30 years (Table 1).

The mean free testosterone levels before treatment were 1.58 ± 1.50 pg/mL and after treatment were 1.34 ± 0.90 pg/mL. These values were statistically significant ($p = 0.006$, Table 2 and Fig. 1).

59.13% of patients were suffering from grade III acne and 40.87% of patients were suffering from grade IV.

The mean free testosterone levels before treatment in patients from grade III were 1.45 ± 1.44 pg/mL and after treatment were 1.22 ± 0.83 pg/mL. These values were statistically insignificant.

The mean free testosterone levels before treatment in patients from grade IV were 1.76 ± 1.56 pg/mL and after treatment were

1.39 ± 0.97 pg/mL. These values were statistically significant ($p = 0.007$).

The mean free testosterone levels in the age-group of <20 years before treatment were 1.93 ± 1.65 pg/mL and after treatment were 1.61 ± 1.06 pg/mL. These values were statistically significant ($p = 0.016$, Table 3 and Fig. 2).

The mean free testosterone levels in the age-group of 21–30 years before treatment were 1.44 ± 1.45 pg/mL and after treatment were 1.21 ± 0.74 pg/mL. These values were statistically insignificant ($p = 0.107$, Table 3).

The mean free testosterone levels in the age-group of 31–40 years before treatment were 1.36 ± 1.27 pg/mL and after treatment were 1.24 ± 0.98 pg/mL. These values were statistically insignificant ($p = 0.212$, Table 3).

The patients have been classified into three groups based on the treatment received. The mean testosterone level in patients before treatment who have received doxycycline and benzoyl peroxide ointment were 1.37 ± 1.47 pg/mL and after treatment were 1.12 ± 0.7 pg/mL. The difference in testosterone level was statistically significant ($p = 0.04$). The mean testosterone level in patients before treatment who have received azithromycin and isotretinoin were 1.28 ± 0.95 pg/mL and after treatment were 1.33 ± 1.19 pg/mL. The difference in testosterone level was statistically significant ($p = 0.327$). The mean testosterone level in patients before treatment who have received salicylic acid and doxycycline

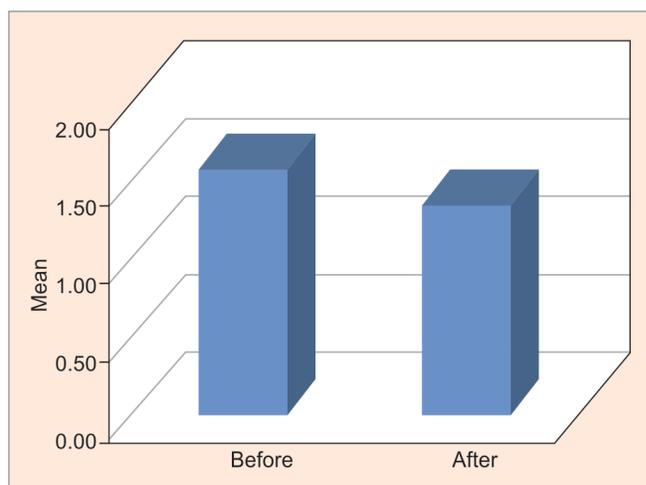


Fig. 1: Comparison of free testosterone before and after treatment

Table 1: Age distribution of females with acne vulgaris

Age-group	No. of patients	Percentage
15–20	29	31.2
21–30	50	53.8
31–40	14	15.1
Total	93	100.0

Table 2: Comparison of free testosterone before and after treatment

	Before	After	<i>p</i> value
	Mean \pm SD	Mean \pm SD	
Free testosterone	1.58 ± 1.50	1.34 ± 0.90	0.006
Range (pg/mL)	0.08–9	0.2–5	

$p < 0.05$ is taken as statistically significant

Table 3: Comparison of free testosterone before and after treatment in relation to age

	Before (mean \pm SD)	After (mean \pm SD)	<i>p</i> value
Age < 20			
Free testosterone	1.93 ± 1.65	1.61 ± 1.06	0.016
Range (pg/mL)	0.10–8.0	0.20–5.0	
Age 21–30			
Free testosterone	1.44 ± 1.45	1.21 ± 0.74	0.107
Range (pg/mL)	0.08–9.0	0.20–3.20	
Age 31–40			
Free testosterone	1.36 ± 1.27	1.24 ± 0.98	0.212
Range (pg/mL)	0.25–5.0	0.20–4.0	

$p < 0.05$ is taken as statistically significant

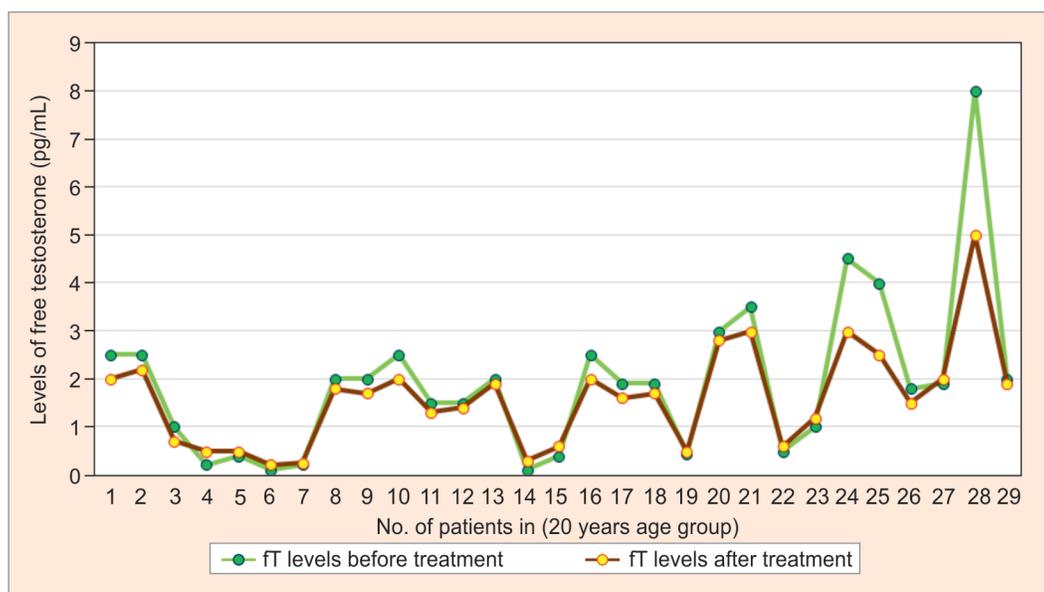


Fig. 2: Comparison of levels of free testosterone before and after treatment in patients of <20 years of age

was 2.35 ± 1.77 pg/mL and after treatment was 1.89 ± 0.98 pg/mL. These values were statistically significant ($p = 0.007$).

DISCUSSION

Acne is the most common disease of the skin and may not only cause a cosmetic problem but may also be a sign of an underlying disease. Acne vulgaris is a disease of the young usually starting at adolescence and rarely going beyond the third decade. Literature brings out quite clearly the controversies that exist as far as the androgen status of a patient with acne vulgaris is concerned.

In the present study, 31.2% of patients were in the age-group of 15–20 years, 53.8% of patients were in the age-group of 21–30 years, and 15.1% of patients were in the age-group of 31–40 years. So the maximum number of patients was in the age range of 21–30 years (Table 1). The mean age of the patients was 24.52 ± 6.54 years.

This finding is in association with the findings of a case-control study by Slayden et al. where the age of the women ranged from 12 to 43 years and the mean age was 26.5 ± 6.32 years.⁹ Rahman et al. reported similar results with mean age 22.43 ± 5.2 years.¹⁰ Whereas Hamilton et al., in 1964, found a sharp rise in prevalence of acne around 10 years, coming to a peak at 15 years of age.¹¹

Literature review suggests that acne is more persistent in female patients, though the reason for this is not known. The prevalence of acne in the age-group of 11–20 years was found in the study of Burton et al. that reported a peak prevalence and severity of acne between the age-group of 14 and 19 years when 75% of subjects were affected.¹²

Adolescent acne usually begins before the onset of puberty, when the adrenal gland begins to produce and release more androgen hormone and the sebaceous activity is predominantly dependent on androgenic sex hormones. Therefore, the prevalence of acne in the present study is consistent with the concept of occurrence of adolescent acne.

It has been seen that free testosterone levels in patients suffering from both grade III and grade IV acne get decreased. During the follow-up, it has been found out that 71% of patients suffering from grade III acne showed clinical improvement, whereas

44.7% of patients suffering from grade IV acne showed clinical improvement.

The mean free testosterone levels before treatment were 1.58 ± 1.50 pg/mL and after treatment were 1.34 ± 0.90 pg/mL. These values were statistically significant ($p = 0.006$). In the age-group <20 years, free testosterone levels were significantly higher than other age-groups (Tables 2 and 3).

Variation in the binding capacity and percentage of total testosterone bound to serum proteins measure free testosterone a more reliable reflection of its' biologic activity.^{13,14} Few studies have shown the association of DHEAS and testosterone with acne severity.^{15,16} In a study by Lawrence et al., free and total testosterone levels in plasma were significantly increased in females with acne vulgaris and this finding was in agreement with the results of this study.¹⁷ Testosterone is the major androgen in human blood that encourages many metabolic processes in the epithelium of the sebaceous gland,¹⁸ since androgen promotes sebum production and its excretion ability will result in amassing of sebum in the definite sites of the body.^{19,20}

The findings of our study are supported by the finding of the studies by Hatwal et al. and Held et al., who concluded that females with acne had a significantly higher level of serum testosterone than controls.^{21,22} Whereas studies by Sultan et al.,²³ Förström et al.,²⁴ and Clibula et al.²⁵ found that testosterone levels in acne patients were found to be within the normal limits.

In our study, it has been found out that, patients receiving isotretinoin as therapy showed an increase in free testosterone level though it was not significant. Our results are relatively concordant with those of Lookingbill et al. and Karadag et al., these reports suggest that isotretinoin therapy decreases total testosterone, prolactin, and DHT while increasing free testosterone and DHEA. Although the mechanism of these changes is not well understood, we hypothesize that isotretinoin induces the separation of testosterone from sex hormone-binding globulin, thereby increasing free testosterone levels and inhibiting the transformation of testosterone to DHT.²⁶

A reduction in the level of SHBG results in an increase in the free testosterone fraction, even in the presence of normal

total testosterone levels. Recent studies have shown a much higher correlation between hirsutism and circulating levels of free testosterone than with total testosterone.^{27,28} Reductions in plasma SHBG concentrations have been demonstrated in women with hirsutism,^{16,29} in young women with diffuse hair loss, and in women with late-onset and persistent acne.³⁰ It has been postulated that free testosterone enters the cells of the target organ by diffusion. However, skin is not the only receptor of androgenic stimuli since it can metabolize testosterone to its biologically more potent form. In this step, testosterone is converted to dihydrotestosterone in the cytoplasm by the enzyme 5 α reductase.

CONCLUSION

Thus, the increase in free testosterone levels may be responsible as one of the factors for the development of acne vulgaris. Our data suggest that not all but in the majority of the patients, acne is not solely a cosmetic problem and the presence of androgen excess disorders should be evaluated in patients presenting with acne. Changes in hormone levels should be considered in disease pathogenesis and treatment prescription to female patients with moderate to severe acne vulgaris even if they are non-obese and with no apparent signs of androgen excess. There is a dermatological dogma that states that acne regresses with adulthood; however, this is not true for many patients, especially women. As free testosterone is associated with acne vulgaris, free testosterone levels should be measured in patients presenting with acne vulgaris, especially in the age-group of 15–30 years and treatment-resistant cases and anti-androgen treatment may be indicated in cases with elevated free testosterone levels.

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