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Testosterone to estrogen ratio to assess hormonal imbalance in females with severe acne vulgaris

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ABSTRACT

Objective: Acne vulgaris is one of the commonest skin condition affecting young adults. Androgens are thought to play a crucial role in the pathogenesis of acne but the levels are usually within normal limits so it is difficult to decide when to start hormonal treatment in these patients. So, we planned to calculate testosterone to estrogen ratio in these patients. **Design and Methods:** Case control study was performed in the 90 females with severe acne vulgaris with mean ± S.D of age 21.93 ± 0.46 years. Patients attending dermatology OPD were randomly selected. Serum testosterone and estrogen were measured and testosterone/ estrogen ratio was calculated. Their results were compared with a group of 90 age matched healthy controls. **Results:** Mean ± SD of testosterone/ estrogen in the patients was significantly high as compared to controls. Area under receiver operating characteristic curve was 0.899 which suggests that this ratio can be used to evaluate risk of hormone imbalance in patients with severe acne vulgaris. At testosterone to estrogen ratio of 0.32 specificity was 0.889 and sensitivity was 0.891. **Conclusion:** The ratio can be used as a screening test to assess hormonal imbalance in females with severe acne vulgaris.

KEYWORDS

Acne vulgaris;
Androgen, estrogen;
Hormonal imbalance;
Hormone treatment;
Immunoassay.

INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous unit, characterized by seborrhea, formation of comedones, erythematous papules and pustules, less frequently by nodules, deep pustules, or pseudocysts and, in some cases, it is accompanied by scarring[1].

The link between sebaceous gland activity and puberty has been recognized for many years[1].

With the onset of puberty, androgen mediated stimulation of the sebaceous gland results in increased sebum production in both sexes. They are without doubt the most important hormones controlling sebaceous gland activity[2]. Androgens are thought to play a crucial role in the pathogenesis of acne[3]. The relevance of hyperandrogenism in male acne patients is often not considered, whereas in women or prepubertal children suffering from acne, disorders of androgen metabolism are readily suspected. Extensive investigations have documented that in women, acne is accompanied by hyperandrogenemia[4].

It is well known that exogenous estrogens in the form of oral contraceptive pill given in sufficient amounts suppresses sebum production and decrease acne lesions by increasing sex hormone binding globulin and decreasing circulating free testosterone, but the role of endogenous estrogens in the pathophysiology of acne is not very well defined[1].

In our previous study, we found that though serum testosterone levels were significantly high in females with severe acne vulgaris as compared to healthy controls but its circulating levels were within normal range. Similarly, we found that serum estrogen levels though were significantly low in females with severe acne vulgaris as compared to age matched healthy controls but the circulating levels of estrogen were within normal range in patients[5].

This observation leads to a problem in clinical setting as it becomes difficult to decide whether patients should be put on any hormone treatment if levels of circulating hormones are within normal range and what should be the cutoff point beyond which treatment should be started in these patients. So we planned to evaluate testosterone to estrogen ratio in females with severe acne vulgaris to find a cutoff point beyond which treatment might be started.

MATERIALS AND METHODS

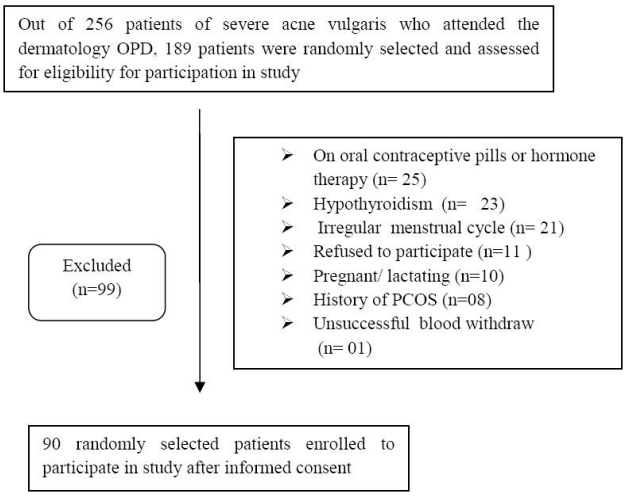
This cross-sectional study was performed in the 90 female patients of severe acne vulgaris (Group A) attending the Dermatology outpatient clinic of Pt. B.D. Sharma UHS, Rohtak. Presence of any one of the parameters classifies the patient under category of severe acne vulgaris as defined by Lehman and Associates: > 5 cysts, or total comedone count > 100, or total inflammatory lesion count > 50, or total lesion count > 125[6]. Serum testosterone, estrogen were measured in these patients during luteal phase (19^{th}-21^{st} day)[2]. Their results were compared with a group of 90 age and sex matched healthy controls (Group B). All the patients were ruled out for any systemic or dermatological ailment. The research protocol was approved by ethical committee of UHS, Rohtak and informed consent was taken from all patients and healthy females prior to inclusion in the study.

41.1% patients were on oral antibiotic with topical retinoid and benzoyl peroxide; 31.1% patients were on oral antibiotic with topical retinoid, 27.78 % on oral antibiotic with topical retinoid, topical antibiotic and benzoyl peroxide.

METHODOLOGY

Venous blood was collected aseptically from antecubital vein. Serum was separated by centrifugation (2000 rpm for 15 minutes) and subjected to analysis of: Hormone levels were measured using direct chemiluminescent technology by ADVIA Centaur CP.

Standard curves for hormones were plotted using increasing concentration of hormone on X-axis and relative light units (RLU) on Y-axis. Two levels of controls were used for all the hormones and samples were run only when levels were within range.



Flow chart of participants

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Quality control charts were prepared by plotting observed values on Y-axis and time when the observations were made on X-axis. The control limits were calculated from the mean (x) and standard deviations (s). 95% to 99.7% control values correspond to mean ± 2 or 3 SD.

TESTOSTERONE (TSTO)

Testosterone assay is a competitive immunoassay using direct chemiluminescent technology. Testosterone in the patient sample competes with acridinium ester-labeled testosterone in the Lite Reagent for a limited amount of polyclonal rabbit antitestosterone antibody bound to monoclonal mouse anti-rabbit antibody, which is coupled to paramagnetic particles in the Solid Phase. The assay uses Testosterone Releasing Agent to release bound testosterone from the endogenous binding proteins in the sample. An inverse relationship exists between the amount of testosterone present in the patient sample and the amount of RLUs detected by the system.

ESTRADIOL-6 III (E2-6 III)

Estradiol-6 III assay is a competitive immunoassay using direct chemiluminescent technology that derives its name from the coupling of the estradiol immunogen at the specificity-enhancing sixth position, allowing for the production of a highly specific antibody. This 17β-estradiol-6-antibody allows the ADVIA Centaur CP Estradiol -6 III assay to be used across a wide range of applications. Estradiol in the patient sample competes with acridinium ester-labeled estradiol in the Lite Reagent for a limited amount of rabbit antiestradiol antibody in the Antibody Reagent. Rabbit anti-estradiol is captured by mouse antirabbit IgG, which is coupled to paramagnetic particles in the Solid Phase. An inverse relationship exists between the amount of estradiol present in the patient sample and the amount of RLUs detected by the system.

STATISTICAL ANALYSES

Values are expressed as mean ± SD. Statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, Illinois). We used unpaired`t' test to compare individual lipid ratio's between patients and controls. Area under operating characteristic curve was calculated; which is an effective method to evaluate the performance of each individual diagnostic test. Sensitivity and specificity were calculated at a particular cut off point to predict the usefulness of each individual ratio in females with severe acne vulgaris.

RESULTS

The p value was calculated using unpaired`t' test with equal variance. The mean age of patients was 21.93 ± 0.46 years while the mean age of controls was 21.97 ± 0.49 years. Testosterone/ estrogen levels were significantly high in the patients (0.39 ± 0.05) when compared to controls (0.22 ± 0.04) ($p < 0.000$) (Table 1). Area under receiver operating characteristic curve (AUC) was 0.899 for testosterone to estrogen ratio which suggests that this ratio can be used to evaluate risk of hormone imbalance in patients with severe acne vulgaris. At testosterone to estrogen ratio of 0.32 specificity was 0.889 and sensitivity was 0.891.

DISCUSSION

The relationship of testosterone to estrogen ratio with acne vulgaris has not been widely reported. Androgens are thought to play a crucial role in the pathogenesis of acne. The exact mechanisms by which androgens increase the size and secretion of sebaceous glands are unknown. Testosterone and dihydrotestosterone form complexes with nuclear androgen receptors. The androgen– receptor complex then interacts with DNA in the nuclei of sebaceous cells to regulate genes involved in cell growth and lipid production. Androgens may act directly, indirectly, or both on epithelial cells within the pilosebaceous unit by regulating the production of growth factors by dermal fibroblasts. The stromal–epithelial interaction of sex steroid hormones and growth factors is an important phenomenon in the local regulation of other endocrine-responsive tissues. Evidence exists for the importance of these autocrine and paracrine effects of androgens and growth factors in the regulation of sebaceous

glands[1,2]. It has been hypothesized that estrogens may act by reducing endogenous androgen production in acne vulgaris lesions by one of several mechanisms, including direct opposition of androgens within the sebaceous gland, inhibition of androgen production by the gonads through a negative feedback loop on gonadotrophin release, or regulation of genes involved in sebaceous gland growth or lipid production[1,2,7]. The problem in evaluating serum testosterone and estrogen is that the parameters though significantly high as compared to healthy controls but levels are usually within normal range so clinically it gets difficult to decide the levels of these hormones beyond which patient should be put on treatment[5]. So we calculated testosterone to estrogen ratio in females with severe acne vulgaris which would give a better and integrated method to assess risk of diseases due to imbalance of hormone levels. We found that testosterone to estrogen ratio was high in females. It has also been shown that target tissues for androgens contain not only an androgen receptor but in most instances also the receptor for estradiol. Local modulation of the balance of androgen/estrogen action could be envisioned to regulate target cell function[8,9]. Moreover, Estrogen receptor (ER) α and β is localized in sebocytes and either androgens or estrogens can activate the non-genomic signaling pathways of ERα, ERβ and the androgen receptor located in basal layer of sebaceous gland[10]. Strength of our study was that all the patients were of severe acne vulgaris and we could calculate cut off value for testosterone to estrogen ratio above which putting patients on hormone therapy may help in alleviating acne lesions. No study to the best of our knowledge has calculated testosterone to estrogen ratio in females with severe acne vulgaris. This was a case control study; further prospective research is required to reach a final conclusion but till then we suggest routine screening of serum testosterone and estrogen in females with severe acne vulgaris and to calculate testosterone to estrogen ratio. We also recommend future studies to look at the effect of treating females with severe acne vulgaris with hormone therapy to decrease the ratio.

CONCLUSION

These ratios represent integrated and simple method to assess hormonal imbalance in females with severe acne vulgaris but further long-term prospective research is needed to reveal the predictive value of the testosterone to estrogen ratio in assessing the risk in patients with severe acne vulgaris but till further research testosterone to estrogen ratio may be used as a routine screening measure.

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