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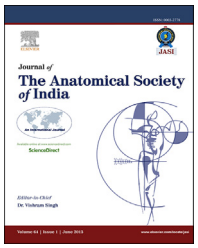

Original Article

Epidermal androgen receptors in acne vulgaris patients before and following oral isotretinoin

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ABSTRACT

Introduction: The role of androgens and androgen receptors (AR) in the pathophysiology of acne vulgaris appears to be a complex phenomenon. It has been suggested earlier that oral administration of isotretinoin, the drug of choice for severe cases of acne, exerts its action through ARs, which is quite debatable. The aim is to study the response of androgen receptor (AR) in the skin of acne vulgaris patients by administrating isotretinoin orally.

Methods: Skin biopsy was procured from untreated patients of severe cases of acne vulgaris. Out of these, twenty histopathologically confirmed patients were included in the study. They were treated with oral isotretinoin in the dose of 0.5 mg/kg/day for 12 weeks, following which their skin biopsies were repeated. Immunostaining for androgen receptor was performed using mouse monoclonal antibodies. Androgen receptor index (AR index) was calculated for the acne patients before and following treatment with oral isotretinoin. Statistical analysis was done using paired t-test.

Result: The AR indices in skin of untreated acne patients were higher in male patients (26.62 ± 20.74) as compared to the female patients (7.5 ± 10.61). AR indices after 12 weeks of oral isotretinoin treatment showed a reduction in both males and female patients (20.55 ± 16 and 4.71 ± 6.75 respectively). However, the post treatment reduction in AR index was statistically significant in male patients only.

Discussion: Determination of AR status can be helpful in planning the treatment methodology of severe cases of acne. Our study also implicates the effectiveness of oral isotretinoin on acne patients through its interaction with androgen receptor.

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1. Introduction

Acne vulgaris is a multifactorial disease seen primarily in adolescents, involving the pilosebaceous unit. It is characterized by hypersecretion of androgens, abnormal cornification of the pilosebaceous duct and secondary bacterial invasion of the blocked glands. Although, superficial and not life threatening, acne is a disease that, if untreated, can have serious physical and psychological consequences. Severe acne can result in permanent physical scarring, that has been implicated as a risk factor for suicide, particularly in men. Other psychological stigmas associated with acne include, lowered self esteem and professional expectations, social inhibition, depression and anxiety.[1] Acne vulgaris is the single most common skin disease, which affects 85% of teenage boys and 80% of teenage girls.[1] The condition usually starts in adolescence and frequently resolves by the mid twenties.[2] However, there are differences in the presentation of acne in different gender, race and ethnic groups.[3]

The primary site of acne is the face and to a lesser extent, the back, chest, and shoulders. The lesions may be either non inflammatory or inflammatory.[4] Severe cases of inflammatory acne with large nodule are termed as Nodulocystic or severe nodular acne. Patients may have hypertrophic scars especially on trunk.[5]

Androgens play a role in the keratinocyte proliferation and follicular hyperkeratinisation of sebaceous follicles that is seen in acne vulgaris[6]. Androgens exert their effect through androgen receptors. Androgen receptors (AR) have been localized in the pilosebaceous unit and it has been observed clinically that antiandrogens may reduce follicular casts in these regions.[7] Androgen receptors are present in normal skin, being localized in the basal and suprabasal layer of epidermis and differentiating cells of the sebaceous glands.[8,9] Studies suggest significant association between testosterone and acne vulgaris.[10] The most potent androgen is Dihydrotestosterone (DHT), which is formed in the sebaceous glands, by a 5α reduction of testosterone. Local tissue conversion of testosterone to the more androgenic Dihydrotestosterone, by the enzyme 5α-reductase, has been shown to be increased in the affected skin of acne patients.[11,12]

At the cellular level, the androgens act by intracellular conversion of testosterone to Dihydrotestosterone (DHT) by the enzyme 5α-reductase and subsequently bind to its androgen cytosol and nuclear receptor. The binding of the nuclear hormone receptor complex to the nuclear chromatin promotes gene expression as a direct response to hormone stimuli. The extent of hormone stimulation correlates with the number of androgen receptor binding sites.[13] Androgen receptors on keratinocytes and sebocytes mediate hyperkeratinisation, sebaceous gland development and the production of sebum.[14] It is also suggested that the whole skin of acne patients, have higher target organ sensitivity than the skin of normal controls of the same age.[15]

Based on the earlier studies, it has been suggested that AR and Androgens play distinct roles in the skin pathogenesis and AR seems to be a better target than androgens for the treatment of acne vulgaris and other skin diseases.[16] Androgen receptors have affinities for a wide variety of steroid and non-steroid drugs, therefore androgen receptor expression has been used to predict clinical response to antiandrogenic treatment.[17]

Isotretinoin is becoming the drug of choice for severe recalcitrant nodulocystic acne.[18,19] A study indicates that the skin androgen receptors are sensitive to oral isotretinoin administration in acne patients.[20] It has been observed that isotretinoin causes a significant decrease in androgen receptor binding capacity without an alteration in its affinity.[20]

Extensive review of literature indicates the complexity of the role of androgens and androgen receptors in the pathophysiology of acne vulgaris. The mechanism by which isotretinoin exerts its response on acneic skin is equally debatable. Additionally, ethnic and racial differences have been seen in the presentation of acne vulgaris. Most of the published work on androgen receptor in patients with acne refers to western population. To the best of our knowledge no literature is available on AR expression in the skin of acne patients in Indian population. To the best of our knowledge, there is hardly any data on the effect of isotretinoin on androgen receptors in acne patients in Indian population. Therefore, the present study was an attempt to determine the status of epidermal androgen receptors in the skin of acne vulgaris patients before and following treatment with oral isotretinoin in Indian population.

2. Materials and methods

2.1. *Sample collection*

The study was conducted on patients between 16 and 25 years of age who presented in dermatology OPD with acne vulgaris in LN Hospital, New Delhi, India. A detailed history of patients presenting with acne was taken. Their lesions were examined thoroughly.

Their lesions were graded as follows:

- Grade I – < 25 comedones without pustules.
- Grade II – 25 – 50 comedones with pustules.
- Grade III – > 50 comedones with pustules and truncal involvement.
- Grade IV – nodular and cystic lesions truncal involvement.

We included twenty histopathologically confirmed patients (twelve males and eight females) with grade III and IV acne vulgaris in our study. A written and informed consent was taken from the patients for the investigations, biopsy and subsequent oral isotretinoin treatment. Before starting the treatment, each patient underwent the following investigations: Complete haemogram, Liver function tests, Kidney function tests, Lipid profile and Serum calcium levels. Patients having normal blood investigations were included in the study. Pregnant patients and patients with past history of hepatitis were excluded from the study.

After taking due approval from Institutional ethical committee, the patients were subjected to punch biopsy from the affected skin before starting the treatment. Oral isotretinoin in the dose of 0.5 mg/kg/day was administered to the patients