**ACNE VULGARIS: A REVIEW ON PATHOPHYSIOLOGY AND TREATMENT**

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**ABSTRACT**

*Acne vulgaris* is a disease associated with sebaceous follicle. It starts appearing after the onset of puberty and can extend up to 40-50 years of age. As far as the pathogenesis of acne is concerned, it is not fully understood up till now. Treatment of acne is very frustrating and involves an understanding of etiopathological factors. This review focuses on various factors accountable, pathogenesis, and therapy of acne.

**Keywords:** Acne, Skin diseases, Acne therapy, Propionibacterium acnes, Acne vulgaris

**INTRODUCTION**

Acne is considered as one of the most widespread skin diseases [1]. When extreme disfiguration occurs, it results in the development of severe consequences among the young people and may result in depression and suicide. *Acne vulgaris* is the second uppermost reason of suicide among skin diseases. When a person suffering from acne is compared with an individual who is not suffering from acne than it is found that the former has higher level of anxiety, more socio inhibition and has more aggressiveness [2].

Acne is an exclusive disease associated with skin occurs when sebaceous glands (SGs) attain special conditions. This disease occurs in both male and female; there is no preference among them, but the course is more severe in males [3].

**ETIOLOGY OF ACNE**

Factors that can lead to acne are as follow: SG produces more sebum, hypercornification of the sebaceous ducts, colonization of *Propionibacterium acnes* in the pilosebaceous ducts and inflammation.

Severity of acne is connected with seborrhea which is associated with follicular infundibulum. In case of milder acne, there occur hypercornification, hyperkeratinization, and hypodesquamation of keratinocytes of the infundibulum which lead to the production of comedones. In severe acne, infundibulum breaks and releases sebum into the dermis which produces inflammatory responses.

**INCREASED ANDROGENS AND SEBUM PRODUCTION**

As far production of sebum in the body is concerned, it is produced by the sebocytes dissolution in sebaceous lobules than they are passed to the follicle via sebaceous ducts, and finally, reach to skin surface by means of infundibulum. SG is mainly found in face and truck, i.e., the regions where acne generally forms [4-6].

After the onset of puberty androgen, production increases within the body and SG are the main target organ for the same because they have higher androgen receptor in skin [7,8]. Testosterone is the main androgen responsible for acne. One of its derivative dihydrotestosterone formed in the body by the action of enzyme 5α-reductase (type-1). Type-1 of 5α- reductase is the foremost isotype found in human skin, specifically in SG rich area [9-12]. As sebum content rises in acne patients due to rise androgen level and also regulated by them [13].

**METABOLISM OF ANDROGENS IN SEBOCYTES**

Sebum production is mainly regulated by dehydroepiandrosterone sulfate (DHEA-S). This androgen has highest sebum concentration and is present in an equal amount in both male and female. DHEA-S is a considered as weak androgen, but the sebocytes have required enzymes to convert it into strong androgens (androstenedione, testosterone, and dihydrotestosterone). Despite there formation within the sebocytes, these androgens can also be re-up taken by the sebocytes. After the reuptake, testosterone and dihydrotestosterone binds to the receptor of cytoplasmic androgen to form complex of androgen and receptor which enters the nucleus via nucleopore and bind to specific gene sequences in the nucleus (Fig. 1) [14].

In most of the patients of seborrhea, despite normal levels of androgens sebum production is high because of increased sensitivity of sebocytes toward androgen (it may be the cause) [15]. Hence, seborrhea and acne can occur both at normal as well as higher levels of androgens [16,17].

**Fatty acids**

It was hypothesized by Weeks et al. that free fatty acid formed by action of lipase enzyme of *P. acnes* on the triglycerides of sebocytes is highly inflammatory and chemotactic. They also showed that inhibition of lipase cause the reduction in the free fatty acid amount in the skin, but it does not suppress the acne because of the formation of pro-inflammatory fraction of lipid by other mechanisms than the bacterial lipase and are responsible for inflammation in acne [18].

**Linoleic acid deficiency**

Linoleic acid plays an important role in the creation of intracellular lipid lamellae after incorporation with sphingolipids in follicular epithelium. Linoleic acid deficiency is very important in the etiology of acne as such condition causes impairment in the follicular epithelium barrier which allows the other free fatty acids produced by bacterial lipase activity or/ and by the metabolism of sebocytes to enter the epithelium and cause localized deficiency of essential lipids. Zouboulis showed that linoleic acid can regulate the interleukin (IL)-8 secretion as well as the inflammatory responses [19,20].

**Ductal hypercornification**

It is known that during the formation of acne infundibulum changes occurs but the mechanism behind the changes yet clearly not known. One of the hypotheses said that local follicular insufficiency of linoleic acid effects IL-1α and androgens which cause apparent early cornification of keratinocytes [21-23].
Acne is neither a contagious disease nor infectious. Those bacterial species that exist in human skin as residential flora can colonize in the follicular ducts of the SG. Only three form of microorganism thus results in local follicular hyperkeratosis deficiency. Further analysis showed that there are also other comedogenic sebum components that contribute toward acne development. These include fatty acid peroxides and squalene peroxides, which are created by the action of ultraviolet radiations on sebum lipid squalene. Androgens are also thought to contribute toward it because antiandrogens are found to reduce comedone formation irrespective of increased sebum production in some patients. Body’s inflammatory mediators are also contributing toward it. IL-1α increases the keratinocyte proliferation [24].

Oxygen stress and free radicals
One of the hypotheses also said that in response to the invading microorganism the phagocytes of the body such as neutrophils release reactive oxygen species (ROS) to cause lysis of the invading cell. These ROS are involved in inflammation [25].

Microorganism
Acne is neither a contagious disease nor infectious. Those bacterial species that exist in human skin as residential flora can colonize in the follicular ducts of the SG. Only three form of microorganism thus contributes toward the development of acne lesions. These are: Bacteria (P. acnes and Staphylococcus epidermidus) and yeasts (Malassezia furfur).

However, it is found that acne does not improve after treatment with antifungal drugs. Therefore, yeast cannot be involved in pathogenesis of acne. Staphylococci can also be excluded because during first weeks of treatment in most of the patients it develops resistance [26]. Hence, scientific data mainly concentrated toward P. acnes. P. acnes is a Gram-positive having characters such as non-motility and pleomorphism. They are rod-shaped cells which cause the fermentation of sugars so as to yield propionic acid as one of their metabolic end products.

This bacteria predominantly found in SG rich area of the skin in adults [27]. In the human skin, it exists from the birth till the death of the person [28-34].

P. acnes and its metabolite possibly interact with sebocytes or keratinocytes via cell-mediated immunity and then produce cytokines. These than non-specifically attract the lymphocytes. According to the primary data, both T-helper 1 and T-helper 2 play a very important role in the inflammation process. P. acnes is also found to have mitogenic activity. Hence, there are two mechanisms via which P. acnes cause lymphocytic activation, i.e., antigen-driven and mitogen-driven [35].

Genetic factors
Predisposition of acne can also occur genetically. Very slight knowledge is obtained about the hereditary mechanisms. Numerous genes are responsible for it. Among them, the main are cyp-P450-1A1 and steroid 21-hydrolase which controls adrenal glands androgen production. People having XXY karyotype shows severe type of acne usually [36].

Immunological factors and inflammation
The development and course of acne are influenced by immunological and inflammatory factors in various ways. Earlier it was thought that inflammation is produced as the result of other factors responsible for acne, especially bacterial metabolites but from the new data, it was found that the patients of acne have a leaning of follicular inflammation from the outset [37]. It is accepted that follicles are surrounded by leukocytes, especially T-lymphocytes. They initiate the comedone formation by the production of IL-1, which is the way to the development of acne. Inflammation triggers sebum production. Leukotriene B4 binds to peroxisome proliferator-activated receptor-α on the sebocyte and thus regulates the lipid metabolism. Further support for the above observation is that there occurs a decline in sebum lipid production when leukotriene antagonist zileuton was used [38].

Pathogenesis of acne
The various factors mentioned in the etiology contribute to the pathogenesis of acne in the following way (Fig. 2).

Seborrhea increase androgen concentration due to genetic factors as well as because of attainment of puberty all ultimately leads to the increased sebum production. On puberty, body’s androgen production increases. In the sebocyte, androgens are synthesized as well as androgen-receptor complex within the cytoplasm. These then enter nucleus via nucleopore and alter the specific gene sequence and thus affect the reading rate in the follicular wall can also occur because of oxygen stress or by generation of free radicals by phagocytes in response to invading micro organism. The entered free fatty acids are highly chemotactic and lead to the production of various cytokines such as IL-8 and IL-1α which lead to inflammation and upward regulation of keratinocyte proliferation. This leads to ducal hyperkeratosis and formation of dense horny lamellae. Retention-proliferation hyperkeratosis results because of it. Retention-proliferation hyperkeratosis first form microcomedone, which further grow and convert into comedone and this comedone further develop and form acne [6-36,39].

Treatment of acne
Aim of acne treatment
The main goal of treatment of acne is to stop scarring and minimize the duration of disease. It also focused to decrease the psychological stress that affects at least half of sufferers [40-43]. So, clinical trial evidence of
Treatment of different types of acne

Treatment of mild acne

The topical preparation usage is the main way to treat it, and preparations that can be used for the treatment of mild acne are shown in Fig. 3.

The above-mentioned treatments are most popular among the patients, but they require good explanation regarding the use for their good compliance among the patients. Moreover, they are slow beneficial drugs [43].

Benzoyl peroxide

It is a powerful oxidizing agent with keratolytic and antibacterial properties. Benzoyl peroxide does not lead to the induction of any type of altered in the resistance pattern of aerobic bacteria toward antibiotics, but benzoyl peroxide can check such resistance when used along with topical formulation of erythromycin.

It is available in the form of lotions and creams in the market in a concentration of 2.5-10%. They can be used once in a day. There is no available dose-response profile which can show the increase in efficacy with higher doses. The main adverse effects associated with benzoyl peroxide are transient irritation of skin, occasional allergic contact dermatitis and bleaching of clothes. In long-term or in conjunction with oral antibiotics they can be used in the cure of moderate type of A. vulgaris [44].

Azelaic acid

It is keratolytic in nature and may lead to change in the composition of free fatty acid of skin surface lipids, and it can significantly reduce the follicular bacterial density, but it can cause local irritation and photosensitization. Its treatment generally limits to 6 months. It is used in a concentration of 20% and can be used twice a day [45].
Topical retinoid formulation

They are valuable for the treatment of mild as well as moderate acne. It can be applied once or twice a day. Tretinoin is available as cream and lotion. Isotretinoin is used in a gel preparation. Both formulations have comedolytic activity. They have untoward effects such as desquamation, occasional hyperpigmentation or hypopigmentation, erythema, and sensitization of the skin to sunlight. It shows malformation in infants born to women who have used topical retinoids during early pregnancy [46,47].

Topical antibiotics

They are particularly used in the treatment of mild to moderate acne and in acne which shows resistance to benzoyl peroxide. These antibiotics affect the metabolic pathways of P. acnes. Topical preparations of clindamycin and erythromycin are similar in terms of efficiency. These topical preparations are suitable for greasy skins because of their alcoholic base. Clindamycin in a lotion base is less irritating to dry or scaly skin and is preferred by women. Topical tetracycline is less effective and leaves a residue that may fluoresce under ultraviolet light. The development of antibiotic resistance in P. acnes limits the use of these topical antibiotics now [48].

Treatment for moderate acne

Treatment of moderate type of acne can be done in following ways [48] as shown in Fig. 4.

Oral antibiotics

Systemic antibiotics administration remains the main way to treat the disease, and tetracycline remains the first choice for treatment. To make sure satisfactory absorption, oral antibiotics should be ingested half an hour before meal and patients must avoid simultaneous use of iron supplements or milk. Development of resistance by P. acnes and Staphylococcus epidermidis for erythromycin is the limiting factor for its use in treatment. Minocycline is the main suggested systemic antibiotic for the treatment of acne. There is slight differentiation between minocycline and tetracycline clinically as there is less dietary restriction in case of minocycline. Doxycycline or trimethoprim can be used further as an alternative. Adverse drug reaction associated with oral antibiotics involve gastrointestinal tract disturbance upset, vaginal candidiasis, and hyperpigmentation when elevated dose of minocycline are used [49].

Hormonal therapy

The SGs inflammation results in the formation of acne. There is a few evidence which shows support to any hormonal disturbances in girls with acne, but 46% of women population with acne between the ages of 18 and 32 has little increase in the level of testosterone and also there is inhibition of sex hormone binding globulin [50]. Cure can be done with antiandrogens like cyproterone acetate 2 mg along with ethinyl estradiol 35 mg which is similarly effective as oral tetracycline but duration of treatment is 3-6 months when used alone [51]. Cyproterone acetate (50 or 100 mg) from days 5-15 of the menstrual cycle beside 35 mg of ethinyl estradiol from days 5-26 had reported to show more beneficial effects [52].

Combined contraceptive pills may aggravate acne, for example, that contains norethisterone or levonorgestrel, but this is not the same for the entire cases, for example, those which contain desogestrel or gestodene [53].

Treatment of severe acne

Treatment of severe type of acne can be done in following ways [48] as shown in Fig. 5.

Isotretinoin

Isotretinoin decreases activity of SG, which may lead to decrease in sebum production that results into a noteworthy decline in the population of P. acnes. Retinol concentration is increased in the cutaneous region and may reflect a metabolic interference with endogenous vitamin A [54-56].
Most of the patients require a therapy of 4 months at least but in 15% of the cases even more time period is required [57]. Out of all, 40% of patients are cured and need no further treatment, and a further 21% need topical treatment alone. In left, behind 39% relapse occurs within 3 years. Out of all, 16% require oral antibiotics and 23% require further courses of isotretinoin [58]. Irrespective to high cost of isotretinoin in it is comparatively cheap to treat moderate or severe type of acne with it as compared to other available antibiotics [59].

**CONCLUSION**

On the basis of above literature, it is clear that the pathophysiology as well as treatment of acne is not simple. The major problem associated with available therapeutics is the adverse effect and resistance. Moreover, treatment criteria can vary as per the situation.

**REFERENCES**


