

Research Journal of Pharmaceutical, Biological and Chemical Sciences

REVIEW ARTICLE

Review on Pathophysiology and Treatment of Acne

L Chandrasekar

Research Scholar, Shri Jagdishprasad Jhabarmal Tibrewala University, Dist-Jhunjhunu, Rajasthan, India

ABSTRACT

Acne vulgaris is one of the most common skin diseases, which is observed in about 90% of young adults sometime or the other in their life. The present review article describes the pathophysiology and topical therapy for acne. The pathophysiological factors that cause the development of acne are : [1] Abnormal keratinization and desquamation of pilosebaceous follicular epithelium [comedogenesis], [2] Increased sebum production, [3] Follicular proliferation of *Propionibacterium acnes* and [4] Inflammation. No topical therapies influence the production of sebum. Topical tretinoin [all-trans-retinoic acid] slows the desquamation process, thereby reducing the number of microcomedones & comedones. Adapalene- a naphthoic acid derivative a far more stable molecule than tretinoin offers comparable efficacy and also less irritating. Salicylic acid is effective against comedones and inflammatory lesions in acne vulgaris. Topical isotretinoin is effective against both non-inflammatory and inflammatory lesions. Benzoyl peroxide [BP] for topical therapy is an oxidizing agent that is bactericidal for *P.acnes*. Azelaic acid is effective against mild to moderate inflammatory and non-inflammatory acne. Topical antibiotics like erythromycin, clindamycin and metronidazole also cause a decrease in the production of chemotactic factors by *P.acnes*, reducing the tendency towards inflammation. Use of intralesional corticosteroids is popular in severe nodular or cystic forms of acne. Other modes of treatments also discussed.

Keywords : Acne, Sebum, Inflammation, *P.acne*, Topical therapy.

**Corresponding author*



INTRODUCTION

Acne vulgaris is a very common inflammatory disease of the Pilosebaceous follicle [1]. It affects nearly all adolescents and adults at some time in their lives. Although overall health is not impaired, acne is not a trivial disease. It can produce cutaneous and emotional scars that last a lifetime. It is common enough to be called a physiological process, but regarded as a disease due to its inflammatory component and the disfigurement it produces on the socially and psychologically most important body region, namely the face. Millions of people around the globe are affected with this skin problem and hence treatment of acne is of critical importance to the practice of dermatology.

Over the last 40 years, basic science & clinical research have shed much light on the pathogenesis of acne vulgaris. A disease that was once largely a mystery fought with many myths and misunderstanding is now beginning to be characterized at the histological and biological level. Science has clarified many of the physiological processes and immunological reactions that result in the development of acne lesions at all stages in the disease process.

ACNE VULGARIS

Acne can be defined as any disease whose initial pathology is the microcomedone and includes acne vulgaris, neonatal acne, infantile acne and pomade acne. Excluded from this group are a variety of diseases that resemble acne, but have fundamentally different pathogenesis e.g Rosacea, Steroid folliculitis, Periorificial dermatitis etc.,

Epidemiology

Acne occurs in all races worldwide, affecting 90% of people sometime or the other in their life. The age of onset is at puberty or just before that. The peak incidence is between 14-17 years in women and 16-19 years in men. Studies have shown that acne severity correlates better with pubertal stage than with chronological age [2].

Usually the severity and incidence of the disease declines in about 80% patients by mid 20's, but in some it may persist even in the 30's. Though acne is common and more severe in males during the teenage years, acne in adults [Clinical acne] seems to be more prevalent among women.

Acne may be present at birth[Neonatal acne] or may appear in the first six months of life[Infantile acne] as a result of circulating maternal hormones[3].

Etiology & Pathogenesis

The basic cause of acne is still unknown. It is now believed that acne vulgaris is multifactorial in origin and several factors affect the severity and clinical expression of the disease. The four principal pathologic events in acne are:

- (a) Abnormal follicular keratinization leading to comedo formation.
- (b) Increased Sebum Production
- (c) Colonization & Proliferation of Propionibacterium acnes in sebum, &
- (d) Inflammatory response by host.

Alteration in Follicular Keratinization

Current thinking holds that the microcomedone is the initial lesion of acne [4]. Microcomedones form, at least in part, before puberty as a result of unknown stimuli. Normally keratinous material is loosely arranged in sebaceous follicle but in acne it becomes dense. Increased production of keratinocytes and their increased adhesion due to persistence of desmosomes leads to 'retention hyperkeratosis'. These initial changes occur in the follicular infundibulum leading to the formation of microcomedones, thereby initiating the process of acne.

Infra-infundibular keratinocytes from acne prone regions of skin have been found to have increased capacity to produce type 1 isozyme of 5- α reductase which can cause increased conversion of testosterone to more potent dehydrotestosterone [DHT] which is responsible for hirsutism, male pattern baldness and sebum production [5].

Dehydroepiandrosterone[DHEAS] levels are significantly higher in prepubertal girls with comedonal or inflammatory acne[6]. In adolescents and adults apart from DHEA and DHT, free testosterone also contributes to the androgenic stimulation of sebaceous activity[7].

The acceleration in the rate of sebum secretion or its composition may irritate the infundibular keratinocytes leading to the release of inflammatory substances like 1L-1 α [8,9]. This adds to the induction of follicular hyperkeratosis. Hyperkeratinization of follicular epithelium causes decreased barrier function which is caused by decreased amount of ceramides[sphingolipids]. This makes the comedone wall more permeable to inflammatory substances. This horny plug debris becomes inflammatory and is the real trigger mechanism of acne.

The microcomedone can progress to 2 types of mature comedone [10]. The *open comedone* [blackhead] is filled with keratin, lipids and organisms and has a widely dilated orifice, which allows its contents to escape. The black surface is due to melanin deposition. The *closed comedone* [whitehead] is small, usually flesh colored papule that has a microscopic opening, which keeps its contents from escaping. Its continual production of keratin and sebum leads to thinning of follicular wall. This, plus the action of hydrolytic enzymes induced by the ingestion of *P.acnes* by leukocytes, result in the rupture of the follicular wall and release of its contents into the dermis, starting the inflammatory process.

Increased Sebum Production

A spurt in the level of hormones during puberty correlates well with the onset of acne vulgaris. Androgenic stimulation at the time of puberty causes enlarged sebaceous glands and increased sebum production in both sexes [11]. Acne results from hormonal imbalance increasing in severity with an increase in androgen:estrogen ratio .

Although patients with acne, especially women, may have increased circulating androgens, but most patients do not have levels of circulating androgens that are in the pathologic range . It may be that there is an end organ sensitivity of the sebaceous gland to androgen stimulation or even that the circulating androgens are converted to more potent androgen within the sebaceous gland[12].

The severity of acne is not solely related to sebaceous gland activity. Qualitative differences in sebum , viz the FFA fraction is considered more important in the causation of inflammation [13]. The role of individual components of sebum in the causation of irritation is not known. However, it is found that high levels of squalene and wax esters were found in sebum of acne patients[14]. It is also postulated that lowered levels of linoleic acid in sebum can lead to acne vulgaris by promoting the accumulation of cornified cells [15]. It is therefore be concluded that in the pathogenesis of acne, sebum is not only an important factor, but probably an essential one.

Follicular Microbial Flora

If the microbial flora is significant in the pathogenesis of acne, the most likely organism to blame is *P.acnes*, a strict anaerobe. *P.acnes* is a non-spore forming, pleomorphic, anaerobic, gram positive rod. *P.acnes* is overwhelmingly the predominant microorganism in the normal pilosebaceous follicle, as well as in the acne state[16].

There is a considerable evidence that [*P.acnes*] participate in the pathogenesis to some extent, even though their effects are indirect. They can be implicated on the following grounds:

- (a) Large number of diphtheroids accumulate in follicles at the onset of comedo formation.
- (b) Lipids secreted by the organism are strongly comedogenic. Also, lipases produced by the organism cleaves triglycerides to form free fatty acids. This is both comedogenic and inflammatory.
- (c) The intense colonization of comedones is responsible for rupture and the incitation of inflammatory lesions. *P.acnes* elaborates variety of enzymes like hyaluronidase, proteases, lipases, and chemotactic factors of neutrophils, lymphocytes and macrophages which could attach the epithelial capsules of comedones.
- (d) Finally, antibiotics capable of suppressing *P.acnes* or reducing free fatty acids are the very drugs that appreciably moderate the disease.

Inflammation

Inflammation is a direct or indirect result of the proliferation of *P.acnes*. Several lines of evidence point to its involvement in the inflammatory component of acne vulgaris. Circulating anti *P.acnes* antibody titres are elevated proportionately to the extent of inflammatory involvement of the acne patient[17].

When *P.acnes* is injected into normally sterile sebaceous cysts , rapid rupture of the cyst occurs with the subsequent development of acneiform inflammation. Inflammatory capacity of purified comedonal components were studied and found that keratinous material and live or killed *P.acnes* induced significant erythema and induration while free fatty acids and other comedonal lipids had little effect.[18].

Other factors:

1. Hot humid climate aggravates acne due ti increased sweating causing ductal hydration
2. Emotional stress aggravates preexisting acne.
3. External application of oils,pomades and comedogenic chemicals can cause acneiform eruptions.
4. Diet has no significant role in the production or aggravation of acne .

Clinical Feature

Lesions of acne vulgaris are seen on the sebaceous gland rich body regions viz., face, mid-chest, back, shoulders and upper arms. Acne lesions generally occur in the sebaceous gland connected with villous hair. Those connected with large piliary canal do not get blocked. There are two types of clinical features- Inflammatory & Non-inflammatory lesions; cysts and nodules and occasionally deep papules make up the deep lesions.

Inflammatory lesions, especially large papules, pustules and cysts often heal with altered pigmentation, even though residual scarring may not develop. Post-inflammatory hypo and hyper pigmentation are mor noticeable in brown or swarthy skin.

The severity of acne can be graded on clinical grounds as [19]

- Grade I [Mild] : Comedones, occasional papules
- Grade II [Moderate] : Papules, comedone , few pustules
- Grade III[Severe] : Predominantly pustules, nodules, abscesses
- Grade IV [Cystic] : Mainly cysts, abscesses,widespread scarring

Aims of treatment to Acne

1. To reduce follicular bacterial population and reduce lipases.
2. Remove follicular obstruction
3. Reduce Inflammation

4. Decrease sebaceous gland activity by blocking androgen stimulation.

Drugs that affect major pathophysiological features of Acne:

1. Reduction of Sebum Production

Skin Cleaning : No topical therapies influence the production of sebum. Soaps, detergents and astringents can remove sebum from the surface of the skin, but not alter sebum production & are of no therapeutic value. Infact vigorous scrubbing of the skin can aggravate acne by promoting the development of inflammatory lesions and under some circumstances causes “detergent acne”[20].

Ample evidence is not available to show that diet has any role in the cause and severity of acne. Dietary factors,short of starvation,do not influence sebum production and dietary restrictions have no role to play in the therapy of acne[21].

2. Reduction of Epithelial Desquamation in Sebaceous follicle

Excessive desquamation of follicular epithelium in sebaceous follicles, in conjunction with excessive sebum production results in the formation of microcomedones.

Topical Agents: Topical tretinoin [all-trans-retinoic acid] slows the desquamation process, thereby reducing the number of microcomedones & comedones [21]. Topical application of tretinoin can lead to local irritation [erythema, peeling,burning]. It also has a photo irritant effect.

Adapalene- a naphthoic acid derivative represents the 3rd generation retinoid. It emerged from the recognition that the irritancy of tretinoin is due to its molecular instability;when exposed to light and oxidizing agents, tretinoin becomes fragmented. Adapalene , with strong binding affinity for β and γ retinoic acid receptors, is a far more stable molecule that retains its structure regardless of light exposure or oxidants [22]. Adapalene, offers comparable efficacy to tretinoin but less irritating. It represents a good alternative to tretinoin.[23].

Salicylic acid is effective against comedones and inflammatory lesions in acne vulgaris .Topical isotretinoin is effective against both non-inflammatory and inflammatory lesions. It probably affects abnormal follicular keratinization, and does not affect sebum production.

Tazarotene is the newest retinoid introduced to treat acne. It’s a novel acetylenic retinoid in a gel formulation. The effect of Tazarotene gel is greater for non-inflammatory lesions than inflammatory lesions [24].

3. Prevention of propionibacterium acnes proliferation

P.acnes produce proinflammatory mediators that cause the formation of inflammatory lesions. *P.acnes* is highly sensitive in vitro to many antibiotics, but many of them do not gain access to the lipid rich environment of the sebaceous follicle where the organism is proliferating.

Benzoyl peroxide[BP] for topical therapy is an oxidizing agent that is bactericidal for *P.acnes*. It is lipophilic and suppresses the growth of *P.acnes* most effectively. But, similar to tretinoin, it can also cause irritation of the skin.

Topical antibiotics are almost used universally by dermatologists. Topical antibiotics are effective in the treatment of inflammatory acne. Choices for topical therapy include formulations of Erythromycin, Clindamycin and Metronidazole. Topical antibiotics also cause a decrease in the production of chemotactic factors by *P.acnes*, reducing the tendency towards inflammation.

Azelaic acid[10% cream] is effective against mild to moderate inflammatory and non-inflammatory acne. It is naturally occurring dicarboxylic acid with both comedolytic & antibacterial effects. [25].

4. Anti-Inflammatory

The goal of therapy is to neutralize the pathophysiological events. Variations in severity of acne may best be explained by variations in antibody response and cellular immune response to this pathogen; the more intense the immune response, the more severe the acne. Use of intralesional corticosteroids is popular in severe nodular or cystic forms of acne. Rapid regression of lesions is achieved.

Other Modes of Treatment

1. Cryoslush Therapy : Solid Carbon-di-oxide is mixed with acetone and this slush like mixture is brushed lightly over the skin. The degree of erythema and peeling is determined by the amount of time the slush is in contact with the skin.
2. UV Light : UV light produces erythema and desquamation. Enough light must be given to produce moderate erythema and some desquamation. Patients must be properly shielded.
3. Radiation Therapy : Superficial radiation therapy is effective in reducing the size of sebaceous gland. This is only temporary and regeneration occurs in 3-4 months.
4. Acne Surgery : The mechanical removal of comedones and the incision and drainage of pustules and cysts aid in the involution of these lesions. If properly performed, the procedure causes no scarring and more rapid resolution of lesion.



CONCLUSION

More grey areas needs to be investigated, to explore research in:

1. Looking for safe topical sebaceous gland inhibitors.
2. Efficacious techniques to measure sebum production and follicular turnover.
3. Finding new agents that might interfere with metabolic pathway that are involved in the synthesis of sebaceous lipids or proteins in the follicles like anti-androgens,5- α reductase inhibitors, local antibacterial agents and inhibitors of follicular keratinization.
4. Finding novel delivery methods so that these agents may be delivered locally to the specific sites of involvement.

REFERENCES

- [1] Launey WE & land WA. In Principles and Practice of Dermatology 1984; 2: 84-91.
- [2] White GM. Acne Therapy. Adv Dermatol 1999; 14:29-59.
- [3] Tutakne MA, Chari KVR, Valia RG. Textbook and color Atlas Dermatology 2001; 2:689-710.
- [4] Webster GF. State of Science 1999; 135(9).
- [5] Thiboutot D, Knaggs H, Gilliland K, Hagari S. Br J Dermatol 1997; 136:166-171.
- [6] Lucky AW, Brio FM, Huster GA et al. Arch Dermatol 1994; 130: 308-314.
- [7] Watson S, Cunliffe W, Keezkesh et al. Br J Dermatol 1995; 133: 249-253.
- [8] Thiboutot D. J Am Acad Dermatol 2002; 47:109-117.
- [9] Guy R, Green M, Kealey T. J Invest Dermatol 1996; 106:176-182.
- [10] Kligman AM. J Invest Dermatol 1974; 62:268-287.
- [11] Tolman EL. Acne and Acneiform Dermatoses. In Dermatology. 3rd Ed., Vol II, Editors- Moschella & Hurley, 1477-1492.
- [12] Strauss JS, Pochi PE, Downing DT. J Am Acad Dermatol 1985; 12:481.
- [13] Kellu RL, Strangfeld KE. J Invest Dermatol 1972; 58:315-318.
- [14] Downing DT, Stewart ME, Wertz PW et al. J Am Acad Dermatol 1986; 14:221-225.
- [15] Burkhart CG, Burkhart CN Lehman PF. Post Grad Med J 1999; 75: 328-331.
- [16] Vowels BR, Yang S, Leyden JJ. Infec Imm 1995; 63(8): 3158-3165.
- [17] Puhvel SM, Sakamoto M. J Invest Dermatol 1977; 69: 410-406.
- [18] Habif TP. Acne, Rosacea and Related disorders. In Skin Disease-Diagnosis and Treatment 2001; 72-103.
- [19] Lasek RJ, Chren MM. Arch Dermatol 1998; 134:454-458.
- [20] Leyden JJ. New Eng J Med 1997; 336(16): 1156-1162.
- [21] Gollnick H. JEADV 2001; 15(3): 1-4.
- [22] Weiss JS, Shavin JS. J Am Acad Dermatol 1998; 39:S50-S54.
- [23] Shalita AR, Chalker DK, Griffith RF et al. Cutis 1999; 63: 349-354.
- [24] Bladon PT, Burke BM, Cunliffe WJ et al. Br J Dermatol 1986; 114: 499-50.