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PATHOPHYSIOLOGY AND MANAGEMENT OF ACNE VULGARIS

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ABSTRACT

Acne vulgaris is a common chronic inflammatory disease of the pilosebaceous units, which affects the majority of individuals at some time in their lives, usually during adolescence. Acne is a disorder of the sebaceous follicles, which are special pilosebaceous units located on the face, neck, chest, upper back, and upper arms. These units consist of relatively large sebaceous glands associated with small hair follicles. Inflammation is a direct or indirect result of P acnes proliferation. Follicular rupture and extension of inflammation into the dermis result in formation of the inflammatory lesions of acne vulgaris papules, pustules, and nodules. Retinoids (isotretinoine) is the only drug which acts on the four main factors in acne and is considered a revolution in treatment of acne. While is used commonly especially in problematic types like classical acnes, it may also be currently used in persistent moderate classical acnes which lead to psychological problems. They decrease production of sebum, inactivate sebaceous glands with active inflammation and reduce them. They change the structure of lipids. They indirectly reduce the number of bacteriae by decreasing the amount of sebum.

Keywords: Acne vulgaris, Definition, Pathogenesis, Management

INTRODUCTION

Acne vulgaris is a chronic inflammatory disease caused by the complex influences of abnormal lipid metabolism (endocrine factors), abnormal keratinization and bacterial proliferation. It is characterized by different areas of scaly red skin (seborrhea), pinheads (papules), blackheads and whiteheads (comedones), large papules (nodules), and sometimes scarring (piples) [1, 2]. The term acne is derived from Greek word “acme” which means “prime of life”. Although generally considered to be a benign, self-limiting condition, acne may cause severe psychological problems or disfiguring scars that can persist for a

lifetime. Acne is considered a chronic disease owing to its prolonged course, pattern of recurrence and relapse, and manifestations such as acute outbreaks or slow onset. Moreover, acne causes profound negative psychological and social effects on the quality of life of patients [3, 4]. In acne, the skin changes, due to changes in pilosebaceous unit skin structures including hair follicles and their associated sebaceous glands. These changes usually require androgen stimulation. Acne vulgaris is usually due to an increase in body androgens, and occurs more often in adolescence during puberty, regardless of sex. Acne is usually seen on the face, upper part of the chest, and the back of subjects who possess greater numbers of oil glands [5-8]. Acne vulgaris can occur in a few forms: acne comedonica, which is dominated by open and closed comedones, acne papulopustulosa, which is dominated by the inflammatory process and acne conglobata, which is the most severe form of acne and except the changes mentioned above, it is characterized with abscesses, fistulas and scars [9, 10]. Eighty-five percent of those between the ages of 12 and 24 years have acne. Although it is primarily a disease of adolescence, 12% of women and 3% of men battle it into their fifth decade of life [11]. Most people experience acne during adolescence, with >95% of teenage boys and 85% of teenage girls affected. Almost 20% of these young people have moderate-to severe acne, and as many as 50% continue to suffer from acne in adulthood [12-14].

Pathophysiology

The pathogenesis of acne is currently attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, androgen activity, interaction with neuropeptides, exhibition of pro- and anti-inflammatory properties, follicular hyperkeratinization and proliferation of Propionibacterium acnes. The cause of acne is multifactorial, including genetics, hormones, and bacteria. It is known that the number of sebaceous glands that one has is an inherited trait, and that it is unlikely for 1 twin to develop acne of different severity than the other twin. In the pathogenesis of acne, four main components have always been mentioned: a) Increased sebum b) Keratinization of the middle part of the infindibulum (Infrainfundibulum) c) Bacterial colonization of the follicle d) Inflammation of the follicle and its surroundings [15-17].

Increased sebum production: Role of sebaceous glands in the pathogenesis of acne has long been recognized, so much so that the disease is standardly classified as a sebaceous gland disorder. However, such a designation is oversimplification. Sebum production is regulated by many factors that activate pathways involved in cell proliferation and differentiation, lipogenesis, hormone metabolism, and cytokine and chemokine release. Excessive sebum is thought to be a key contributor to acne development. However, not all patients with acne experience hyperseborrhoea. In fact, the correlation between sebum production and acne severity depends on age and sex; in men, acne is more dependent on sebum production. Acne begins to develop at the time of adrenarche when the adrenal gland starts to produce large quantities of dehydroepiandrosterone sulfate, a precursor for testosterone. Conditions of hyperandrogenism are associated with increased sebum production and the development of severe acne. The relevance of hyperandrogenism in male patients is often not considered, whereas in women or prepubertal children suffering from acne, disorders of androgen metabolism are readily suspected. Increased sebum production and alteration of the quality of sebum lipids play a major role in acne

pathogenesis. Increases in free fatty acids, squalene, and squalene oxide and a decrease in sebaceous linoleic acid could all trigger abnormal cohesion of cells in sebaceous follicles. Androgenic hormones control sebaceous gland secretions. Testosterone is the main circulating androgen. In women, however, the adrenal gland and its main androgens dehydroepiandrosterone (DHEA) and sulfate salt of DHEA (DHEAS) have important roles in androgen control of sebaceous glands. Testosterone is assumed to convert to dihydrotestosterone, which then binds to a high affinity specific cytoplasmic receptor protein that is transported to the cell nucleus where the DNA driven events occur [18, 19].

Hypercornification of the pilosebaceous duct: Obstruction of the pilosebaceous canal precedes the development of acne lesions. The obstruction is produced by the accumulation of adherent keratinized cells within the canal that form an impaction obstructing the flow of sebum. Cause is unknown but the process may be under the influence of androgens. It may also be due to an abnormality in the sebaceous lipids resulting in a relative hyperproliferation of corneocytes. Comedone formation may be due to a localized deficiency of linoleic acid in pilosebaceous duct. Linoleic acid is incorporated via plasma into sebaceous gland cells, where it is diluted due to large volume of sebum and the ductal corneocytes are effectively bathed in an inadequately low level of linoleic acid [20-22].

Abnormal bacterial function: Skin surface in acne prone areas is colonized with Staphylococcus epidermidis and Propionibacterium acnes. Selective inhibitory studies suggest that the main organism is P. acnes. The main microorganism which is localized in the follicle and involved in the pathogenesis of acne is Propionibacterium Acnes. It grows well at anearobic conditions and uses sebum as food. Staphylococcus Aureus, P. Orbiculare and rarely Demodex Follicularum are present, but they do not affect the process of inflammation. Inflammation which occurs against growing P. Acnes constitutes the inflammatory elements of acne including papule and pustule; anaerobic diphtheroid that populates sebaceous follicles and is a normal constituent of cutaneous flora. P acnes produce chemotactic factors and proinflammatory mediators that may lead to inflammation. P acnes are the predominant organism in sebaceous follicles, where it grows in a relatively anaerobic lipid-rich environment of microcomedones. P acnes counts on the skin of teenage subjects with acne and P acnes counts on the skin of age-matched control subjects differ significantly. P acnes, however, is not essential for comedogenesis, as was confirmed by research involving children with early acne. P acnes produces an extracellular lipase that hydrolyzes sebum triglycerides to glycerol, used by the bacteria as a growth substrate, and to free fatty acids, which may possess comedogenic and/or proinflammatory qualities [23-25].

Production of inflammation: The association of P. acnes proliferation with inflammatory lesions of acne is best borne out with the significant suppression of P. acnes with antibiotic therapy. Inflammation is a direct or indirect result of P acnes proliferation. Follicular rupture and extension of inflammation into the dermis result in formation of the inflammatory lesions of acne vulgaris—papules, pustules, and nodules. Whether hyperkeratinization of the follicular duct precedes the onset of inflammation or vice versa is debated. The finding that IL-1 activity was found to be increased around uninvolved follicles before the observation of keratinocyte hyperproliferation and activation suggests an inflammatory trigger. Indeed,

once inflammation is established, inflammatory acne lesions up regulate numerous genes, including those that encode matrix metalloproteinases, β-defensin 4, IL-8 and granulysin [26].

Genetics: Genetics have a role in the development of acne, as evidenced by family and twin studies22–24,122. Several genetic polymorphisms affecting the expression and/or function of genes have been investigated. Genes associated with acne included the IGF1 (CA) 19 repeat polymorphism123, the Pro12Ala polymorphism of PPARG124, the IL6-572G/C polymorphism and the IL1A-889C/T polymorphism125; however, further studies in this field are needed. In addition, two genome-wide studies in Han Chinese populations have found acne susceptibility loci (1q24.2 and 11p11.2) [27].

Treatment

Goals of treatment include decreasing inflammation and bacterial load (P. acnes), and reducing retention hyperkeratosis and sebum production [28].

Topical retinoids

Topical retinoids are vitamin A derivatives. The binding of retinoids to their receptors the retinoic acid receptors and the retinoid X receptors in keratinocytes reduce follicular hyperkeratinization and decreases adhesion1. This effect not only results in inhibition of comedogenesis but also might enhance the penetration of other topical acne medications. Topical retinoids for the treatment of acne include tretinoin, adapalene, tazarotene (which is not available in Europe), retinaldehyde and topical isotretinoin (the latter two are not available in the United States), which are all available in various formulations and concentrations. In addition, use of topical retinoids is not recommended during pregnancy; tazarotene is classified as a pregnancy category X drug (that is, fetal risk has been proven in investigational or marketing studies in humans) and is contraindicated, whereas adapalene and topical tretinoin are classified as pregnancy category C drugs (that is, adverse effects have been shown in animal studies, but controlled studies in humans are still lacking) [29-31].

Acids

Alpha hydroxy acids (5-10%) may also be used as supportive products in treatment. Among classical keratolytics, salicylic acid (2-5%) and resorcin are used with a low rate at the present time (3%). In pregnant women, all topical products including mainly retionids should be discontinued. Only azelaic acid is allowed. Two other topical agents frequently used in the treatment of acne are salicylic acid and azelaic acid. Salicylic acid is a keratolytic, bactericidal, and comedolytic agent supplied in concentrations of 3%-6% for use on the face, chest, and back. It acts to decrease cell-to-cell cohesion, allowing for epidermal shedding. It also opens obstructed pores, neutralizes bacteria, and decreases diameter of open pores. It has been used in acne, psoriasis, warts, and other conditions for many years and is the oldest keratolytic agent. Use caution in darker skin types because of increased risk of hyperpigmentation. Azelaic acid is a dicarboxylic acid found in cereals and animal products. It is thought to normalize keratinization leading to decreased thickness of the stratum corneum. There is some evidence of in vitro activity against P. acnes and Staphylococcus epidermidis. Azelaic acid is quite useful in patients with very sensitive skin types, who cannot tolerate other topicals. During pregnancy, this is a great substitute to a topical retinoid; though

it may not be quite as effective [32-35].

Benzoyl peroxide

Benzoyl peroxide (BP) has been used extensively for the treatment of AV for more than six decades, offering the ability to markedly reduce counts and suppress the proliferation of P. acnes, including inhibition of the emergence of antibiotic-resistant strains of the organism. Preparation of benzoyl peroxide has several mechanisms of action, and should be applied to all the affected area. Single-agent benzoyl peroxide works as well as oral antibiotics or a topical antibiotic combination that included benzoyl peroxide for people with mild-to-moderate facial acne. It has greater activity than topical (iso) tretinoin against inflammatory lesions; the results of two further underpowered trials were equivocal. Further studies are needed, especially as combination therapy might be better. Benzoyl peroxide causes initial local irritation. Patients need to be counselled to expect irritation but discontinue treatment if it becomes severe. Irritation will decrease in most cases, especially if patients start applying it every other day and then increase the frequency. Low strength (2·5% or 5%) benzoyl peroxide is recommended, since it is less irritating and there is no clear evidence that stronger preparations are more effective [36-38].

Topical and oral antibiotics

Alteration of the cutaneous flora by antibiotics, either topical or oral, changes the microbiome. This can result in physiological changes within the epidermis as the spectrum of organisms comprising the skin flora is altered. The prevalence of resistant organisms, such as P. acnes and Staphylococcus epidermidis also increases, as doe's colonization of the nasopharyngeal region with bacteria that may potentially be pathogenic to the patient or others (i.e., Streptococcus pyogenes) [39]. Topical antibiotics prevent development of inflammation by inhibiting growth of P. acnes. They are used alternately with other antibiotics or antiseptics, since resistance to antibiotics may occur. In addition, they also have direct anti-inflammatory effects. They have weak effects on old lesions. The most commonly used ones among these include erythromycine, clindamycine, nadifloxacin and tetracycline [40]. The actual action of systemic antibiotics is inhibition of growth of P. acnes. They also indirectly prevent inflammation caused by P. acnes. However, they also have direct anti-inflammatory action. 20% improvement may be expected in 2 months, 60% improvement may be expected in 4 months and 80% improvement may be expected in 6 months. Among systemic antibiotics, tetracyclines are the most commonly preferred ones because of their efficiency and few side effects [41].

Topical antiseptics also act in the same way. Resistance to these against does not develop and it has been reported that they have similar effects as antibiotics (they generally have slower and weaker action). The most commonly used antiseptics include benzoyl peroxide (the most widely used one), azelaic acid and sodium sulfacetamide. They also have mild comedolytic action. Their use in combination with antibiotics increases both the action and decreases the risk of resistance.

Hormonal therapies decrease androgen levels in the circulation and tissues. The cells of the pilosebaceous unit which metabolize androgen including follicular keratinocytes and sebocytes and the androgenic

effects on them are inhibited and a decrease of 12.5-65% occurs in sebum secretion. Antiandrogens are an option only for female patients and their use is limited. They may be preferred when hyperandrogenism (polycystic ovary) is present or when there is no response to classical treatment [42-44].

Conclusion

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit (comprising the hair follicle, hair shaft and sebaceous gland ;) and is among the most common dermatological conditions worldwide, with an estimated 650 million people affected. The pathogenesis of acne is currently attributed to multiple factors such as increased sebum production, alteration of the quality of sebum lipids, androgen activity, interaction with neuropeptides, and exhibition of pro- and anti-inflammatory properties, follicular hyperkeratinization and proliferation of Propionibacterium acnes. Benzoyl peroxide (BP) has been used extensively for the treatment of AV for more than six decades, offering the ability to markedly reduce counts and suppress the proliferation of P. acnes, including inhibition of the emergence of antibiotic-resistant strains of the organism.

Abbreviations

BP: Benzoyl peroxide; DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate salt; IL-8: Interleukin;

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Competing interests

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