Understanding Acne Vulgaris: Multifactorial Pathogenesis and Its Clinical Spectrum

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Abstract

Acne vulgaris is one of the most common dermatological conditions, affecting millions of individuals globally, particularly during adolescence. Its multifactorial pathogenesis involves a complex interplay of genetic, hormonal, microbial, and environmental factors, making it a challenging condition to fully understand and manage. This review provides a comprehensive overview of the current understanding of acne vulgaris pathogenesis and its clinical presentation, highlighting the latest insights from recent research. The pathogenesis of acne vulgaris begins with the overproduction of sebum by hyperactive sebaceous glands, often stimulated by androgens. This is followed by abnormal keratinization within the pilosebaceous unit, leading to the formation of microcomedones. The anaerobic bacterium Cutibacterium acnes plays a pivotal role by colonizing the follicle, inducing an inflammatory cascade through the activation of innate immune pathways. Recent studies have also emphasized the role of the skin microbiome and its imbalance in exacerbating acne. Moreover, systemic factors such as diet, stress, and certain medications have been implicated in worsening the condition. Genetic predisposition further influences individual susceptibility to acne, although specific genetic markers remain under investigation. Clinically, acne vulgaris presents with a wide spectrum of lesions that can be categorized as non-inflammatory or inflammatory. Non-inflammatory lesions include open comedones (blackheads) and closed comedones (whiteheads), while inflammatory lesions encompass papules, pustules, nodules, and cysts. These lesions predominantly occur on sebaceous gland-rich areas such as the face, chest, and back. The severity of acne can vary significantly, ranging from mild cases with a few comedones to severe, nodulocystic acne that may result in significant scarring and psychological distress. Beyond its physical manifestations, acne can profoundly impact an individual's quality of life, contributing to issues such as low self-esteem and social anxiety. This review underscores the importance of understanding the multifaceted nature of acne vulgaris to guide effective therapeutic strategies. Advances in molecular research, particularly regarding the microbiome and immune pathways, hold promise for developing targeted treatments. Addressing both the clinical and psychosocial dimensions of acne is crucial for comprehensive patient care. Future studies are needed to explore emerging therapeutic options and refine existing management approaches

Keywords: *Acne vulgaris, pathogenesis.*

Introduction

Acne vulgaris is one of the most common dermatological conditions, primarily affecting adolescents but persisting into adulthood for some individuals. It is a chronic inflammatory condition of the pilosebaceous unit that manifests as comedones, papules, pustules, nodules, and, in severe cases, scarring. Acne is more than a cosmetic concern; it can significantly impact quality of life, causing psychological distress and lowering self-esteem [1]. Understanding its multifactorial nature is crucial for effective management.

Epidemiology

Globally, acne affects approximately 9.4% of the population, making it the eighth most prevalent disease worldwide. It predominantly affects individuals between the ages of 12 and 24 years, with a peak incidence during mid-adolescence. However, studies reveal that about 12% of adult women and 3% of adult men continue to experience acne beyond the age of 25 years. Geographic and ethnic variations in acne prevalence and severity have been noted, likely influenced by genetic, environmental, and dietary factors [2].

Etiopathogenesis

The development of acne is multifactorial, involving four primary mechanisms: increased sebum production, follicular hyperkeratinization, colonization by *Cutibacterium acnes* (formerly *Propionibacterium acnes*), and inflammation. Androgen hormones play a pivotal role in stimulating sebaceous gland activity, which contributes to increased sebum production. Hyperkeratinization leads to the formation of microcomedones, which can evolve into clinically visible lesions. The proliferation of *C. acnes* within the follicle triggers an immune response, leading to inflammation and the characteristic lesions of acne [3].

Increased sebum production

Several receptors are involved in the regulation of sebum production, including receptors for androgens, corticotrophin-releasing hormone (CRH), insulin-like growth factor (IGF)-1, and leptin, as well as peroxisome proliferator-activated receptors (PPAR) [1].

There is a clear correlation between increased sebum production and acne severity [2]. Sebaceous glands are predominantly stimulated by androgens that stimulate cell division and lipid production. Increasing levels of androgens during puberty are often associated with acne development [3]. Additionally, leptin may alter the sebum composition and enhance the pro-inflammatory cytokines interleukin (IL)-6 and IL-8 in acne patients [4].

Hyperkeratinization of the pilosebaceous duct

Acne lesions are characterized by abnormal hyperkeratinization of the pilosebaceous duct. This may result from androgenic stimulation and irritation by sebum and bacteria, leading to the accumulation of corneocytes and the formation of microcomedones, which represent the primary lesions of AV. Moreover, the pro-inflammatory cytokines, mainly IL-1, may be involved in this aberrant keratinization process [5].

Colonization and proliferation of *P. acnes*

There are different microbiota on the skin surface, with the anaerobic gram-positive *P. acnes* being the most common bacteria in the pilosebaceous unit in both acne patients and healthy individuals. Because of their genetic modifications, *P. acnes* has been reclassified as *Cutibacterium acnes* (*C. acnes*) [6].

C. acnes secretes lipase enzyme that converts triglyceride into free fatty acids, which have chemotactic and inflammatory effects. Additionally, they secrete metalloproteases and porphyrins [7]. Upon exposure to visible light, bacterial porphyrins in the sebaceous glands cause

the generation of reactive oxygen species (ROS) that oxidize squalene, leading to impairment of its protective function against harmful effects of light exposure on skin lipids, proteins, and DNA with subsequent exacerbation of AV [8].

Inflammatory response

The pathogenesis of AV involves the development of an inflammatory response, mainly due to the stimulatory effect of *C. acnes* on both innate and adaptive immune systems [7].

Innate immune system

I. Toll-like receptors

A Toll-like receptors (TLRs) are transmembrane receptors expressed on keratinocytes, Langerhans cells, macrophages, dendritic cells, and lymphocytes. Moreover, TLR-2 is expressed on both basal and infundibular keratinocytes as well as sebaceous glands [9]. Increased expression of TLR-2 and TLR-4 on keratinocytes and TLR-2 on macrophages was detected in patients with inflammatory acne [10]. This may be attributed to *C. acnes* that interacts with these receptors, leading to the production of pro-inflammatory cytokines including IL-1α, IL-8, IL-12, and tumor necrosis factor (TNF)-α [11].

II. Antimicrobial peptides

Antimicrobial peptides (AMPs) are an important part of innate immunity with a significant role in chronic inflammatory diseases. They include human α- and β-defensins, S100 protein, ribonuclease, and cathelicidin (LL-37). They are often expressed at a low level in healthy skin but are overexpressed in cases of cutaneous inflammation and infection [12].

III. Monocytes

Monocytes are pivotal cellular constituents of the innate immune system that may have a role in acne pathogenesis. It has been demonstrated that *C. acnes* may stimulate monocyte differentiation into distinct cell subsets: CD1b+ dendritic cells, which stimulate T cells to release pro-inflammatory cytokines, and CD209+ macrophages, which efficiently phagocytose and kill *C. acnes* [11].

IV. Inflammasomes

Inflammasomes are intracellular proteins that transform inactive pro-caspase-1 into active caspase-1, which activates pro-IL-1β to its active form. This pathway also involves the nucleotide-binding oligomerization domain (NOD)-like receptor domains-containing protein 3 (NLRP3) [13].

b. **Adaptive immunity**

Adaptive immunity plays an important role in acne pathogenesis. The immunogenic proteins of *C. acnes* may be processed by Langerhans cells, which present antigens to CD4+ T cells in local lymph nodes [14].

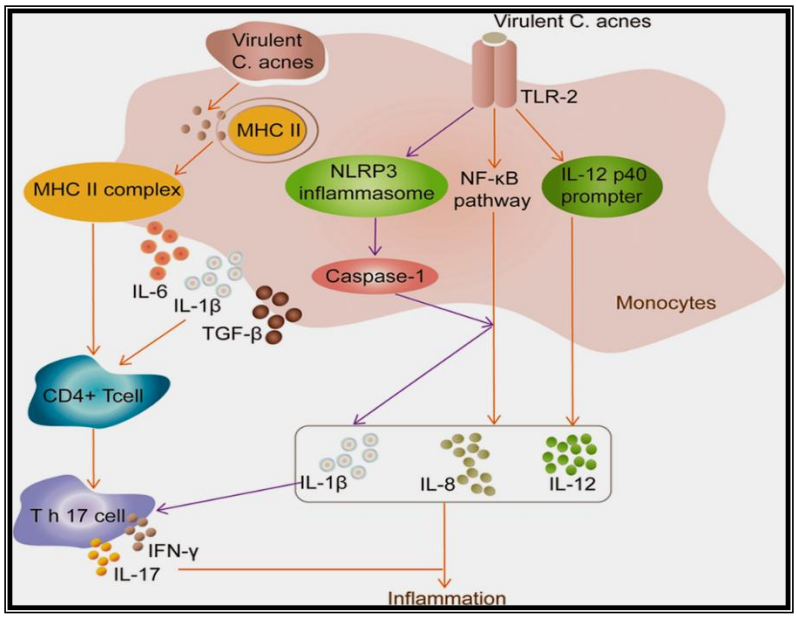

Figure (1): Inflammatory events in acne vulgaris [14].

Genetic Predisposition

Polymorphisms of several genes have been found to affect acne severity and prognosis. The TNF gene is the most frequently studied gene in AV [16]. Also, polymorphisms of genes encoding several interleukins (e.g., IL1A, IL1B, IL6, IL8, IL10, IL17A, IL17F) and related receptors have been detected in acne patients [17]. Furthermore, acne severity has been found to be correlated with serum IGF-1 levels. This may be attributed to IGF-1 gene polymorphisms [18]. Androgen receptor gene polymorphism has also been detected in healthy men and men with AV, while it wasn't detected in women [19]. Moreover, polymorphisms of genes encoding the cytochrome P450 and the 3-beta hydroxysteroid dehydrogenase enzymes, controlling sebogenesis, have been detected in acne patients [20, 21].

Hormonal Factors

a.**Androgens**

The importance of androgens in acne development has long been recognized. Increasing prevalence of AV has been observed during puberty and in females with hyperandrogenism [22]. However, it is crucial to recognize that the majority of AV patients do not have abnormal androgen levels in their blood [23]. The pilosebaceous unit cells are targets for circulating androgens, but they can also synthesize testosterone and dihydrotestosterone (DHT) from androgenic precursors via local enzymatic activity, such as the 5 α-reductase enzyme, or de novo from cholesterol [24]. Androgens regulate sebaceous gland activity via binding to androgen receptors and stimulating the expression of genes promoting sebogenesis [25]. This action is mediated in part by PPAR activation. The activation of PPAR-γ is critical for the effects of DHT on sebocyte differentiation, sebogenesis, and androgen-induced inflammation [26]. Moreover, the pro-inflammatory action of androgens may be due to their stimulatory effect on the expression of proinflammatory cytokines, such as IL-6 and TNF-α [27].

b.Insulin and Insulin-like Growth Factor-1

High-glycemic diet and dairy products have been linked to a higher incidence and severity of acne. This may be attributed to their ability to increase insulin and IGF-1 levels [25]. Moreover, a significant association was detected between insulin resistance and AV [28]. Also, higher serum

IGF-1 levels have been detected in acne patients compared to healthy controls [29]. The IGF-1 decreases the secretion of sex hormone-binding globulin (SHBG), causing an increase of free androgens in the circulation. Also, it increases the production of gonadal and adrenal androgens [30]. Moreover, IGF-1 activates the phosphoinositol-3-kinase (PI3K)-Akt pathway that inhibits the nuclear forkhead box-O1 (FoxO1) transcriptional activity, causing stimulation of androgen receptor signaling [31]. Furthermore, IGF-1 stimulates the release of inflammatory cytokines such as IL-1β, IL-6, IL-8, and TNF-α through upregulation of TLR-2 and TLR-4 expression [32]. It may also mediate the comedogenic effects of growth factors and corticosteroids. Meanwhile, insulin can stimulate IGF-1 production by the liver [33]. Furthermore, the activity of the mechanistic target of rapamycin complex-1 (mTORC-1) has been found to be increased in the skin and sebaceous glands of acne patients. This may be attributed to the effects of insulin and IGF-1. This will increase lipogenesis by upregulating sterol regulatory element-binding proteins (SREBPs), causing hyperseborrhoea in acne patients. Interestingly, metformin has been shown to counteract this effect by suppressing the mTORC-1 activity [34].

c.Estrogen

Oral contraceptive pills containing estradiol can be used for treating AV. They act by reducing sebum production due to the anti-androgenic and anti-sebogenic effects of estrogen [35].

d.Progesterone

Progesterone is known to have androgenic and sebogenic properties, which explains the acne flares before menstruation and during pregnancy [36]. On the other hand, third-generation progestins such as norgestimate and norgestril and other progesterones with reduced androgenic potential have been developed and added to oral contraceptives. They have been used as antiandrogenic agents for the treatment of various conditions, including AV [37].

e.Corticosteroids

Corticosteroids are thought to increase acne eruptions through increased expression of the TLR2 gene and further release of proinflammatory mediators [38]. Clinically, this manifests as an acneiform eruption, known as steroid acne, that results from topical and systemic corticosteroids [39].

f.Corticotrophin-releasing hormone

High levels of CRH stimulate the adrenal production of androgens and corticosteroids, and both will cause acne. Moreover, sebaceous glands have CRH receptors that, on stimulation, will enhance sebum production [40]. This may explain why stress aggravates acne. Activation of the hypothalamic–pituitary–adrenal (HPA) axis is the main adaptive response to stress with CRH acting as a central coordinator for neuroendocrine responses to stress [41].

Oxidative Stress

The ROS generation causes oxidative stress, which is a major factor in AV etiology. Various cutaneous cells, including keratinocytes, release ROS in response to various stimuli, including UV light, diet, pollution, and cosmetics. ROS stimulate signaling pathways linked to nuclear factor-κB (NF-κB) and mitogen-activated protein kinase (MAPK), causing tissue damage in AV lesions [42]. On the other hand, antioxidants present in skin inhibit this oxidative stress. Endogenous antioxidants include superoxide dismutase (SOD), glutathione peroxidase (GPX), glutathione S-transferase (GST), catalase, and others. While exogenous antioxidants include vitamins C, A, and E, carotenoids, flavonoids, and selenium [43]. Interestingly, the activity of SOD and GPX were found to be significantly reduced in acne patients compared with healthy controls [44]. Also, the level of linoleic acid, which suppresses the generation of ROS, was found to be lower in acne patients [45]. Moreover, serum vitamin A and E levels were significantly

reduced in acne patients [46].

Gut Microbiome

Acne patients have been found to have a gut microbiota distinctive from that of healthy controls. Lower abundance of Actinobacteria and higher abundance of Proteobacteria have been detected in the gut microbiota of acne patients compared with healthy controls [47]. Also, decreased diversity and increased ratio of Bacteroidetes to Firmicutes have been observed in acne patients [48]. The connection between gut microbiota and acne development could be attributed to increased intestinal permeability due to bacterial dysbiosis in the gut, leading to the release of inflammatory mediators, such as lipopolysaccharide endotoxins, into the circulation [49].

Clinical Presentation of Acne Vulgaris

Acne vulgaris is a multifactorial skin condition characterized by a variety of lesions, including comedones, papules, pustules, nodules, and cysts. These lesions typically appear in areas with a high density of sebaceous glands, such as the face, chest, back, and shoulders [50]. The clinical presentation of acne can vary significantly depending on the severity, age of onset, and underlying hormonal or genetic factors [51].

The earliest manifestations of acne are non-inflammatory lesions, which include open comedones (blackheads) and closed comedones (whiteheads). Open comedones result from the accumulation of sebum and keratinous material within dilated pilosebaceous follicles, with a visible dark plug due to oxidation of melanin [52]. Closed comedones, on the other hand, are characterized by a small, flesh-colored papule with no visible opening, caused by complete obstruction of the follicle [53].

Inflammatory lesions arise from the colonization of *Cutibacterium acnes* (formerly *Propionibacterium acnes*) within the pilosebaceous unit, leading to the release of pro-inflammatory cytokines and chemokines [54]. These lesions include papules, pustules, nodules, and cysts. Papules are small, red, tender bumps without pus, while pustules are similar in appearance but contain visible pus [55].

Nodular acne presents as large, painful, solid lesions that extend deeper into the dermis. Cystic acne, the most severe form, is characterized by pus-filled, fluctuant nodules that can lead to significant scarring [56]. Both nodular and cystic acne are more common in individuals with a genetic predisposition and are often associated with hormonal imbalances [57].

Post-inflammatory hyperpigmentation (PIH) is a common sequela of acne, particularly in individuals with darker skin tones. It occurs due to the overproduction of melanin in response to inflammation [58]. Acne scars, on the other hand, result from abnormal wound healing and can be classified as atrophic, hypertrophic, or keloidal. Atrophic scars are the most common and include icepick, boxcar, and rolling scars [59].

Acne vulgaris most commonly presents during adolescence, with a peak incidence between the ages of 14 and 19 years. This is attributed to the surge in androgen levels during puberty, which stimulates sebum production and follicular hyperkeratinization [60]. However, acne can persist into adulthood, particularly in women, due to hormonal fluctuations associated with menstruation, pregnancy, or polycystic ovary syndrome (PCOS) [61].

Adult-onset acne, defined as acne that first appears after the age of 25, is increasingly common and often presents with a distinct clinical pattern. Lesions are typically localized to the lower face, jawline, and neck, and are more likely to be inflammatory in nature [62]. Adult acne is often resistant to conventional treatments and may require a more tailored approach, including hormonal therapy [63].

While acne is prevalent in both sexes, there are notable gender differences in its clinical presentation. Males tend to experience more severe forms of acne, including nodular and cystic lesions, due to higher baseline androgen levels [64]. Females, on the other hand, are more likely to experience hormonal acne, which is often exacerbated by menstrual cycles and conditions such as PCOS [65].

The severity of acne can fluctuate with seasonal changes. Many patients report worsening of symptoms during the summer months, likely due to increased sebum production and sweating in response to heat and humidity [66]. Conversely, some individuals experience improvement in acne during the winter, possibly due to reduced UV exposure and decreased sebum secretion [67].

The clinical presentation of acne is not limited to physical symptoms; it also has a profound psychological impact. Acne is associated with increased rates of anxiety, depression, and social withdrawal, particularly in adolescents and young adults [68]. The visibility of facial lesions can lead to low self-esteem, body image concerns, and impaired quality of life [69].

Acne fulminans is a rare but severe variant of acne characterized by the sudden onset of ulcerative, necrotic lesions accompanied by systemic symptoms such as fever, arthralgia, and leukocytosis. This condition is more common in males and often requires aggressive treatment with systemic corticosteroids and isotretinoin [70].

Acne conglobata is another severe form of acne, characterized by interconnected nodules, abscesses, and sinus tracts. It is often associated with scarring and can lead to significant disfigurement if not treated promptly [71]. This condition is more common in males and may be triggered by anabolic steroid use or underlying endocrine disorders [72].

Acne mechanica is a subtype of acne triggered by friction, pressure, or occlusion of the skin. It is commonly seen in athletes who wear tight-fitting equipment, such as helmets or shoulder pads, and presents as papules and pustules in areas of mechanical stress [73].

Acne excoriee, also known as "picker's acne," is a psychodermatological condition in which patients compulsively pick or scratch at their acne lesions, leading to excoriations and secondary infections. This behavior is often driven by underlying anxiety or obsessive-compulsive tendencies [74].

Neonatal acne, which occurs in the first few weeks of life, is thought to result from maternal androgen stimulation of the infant's sebaceous glands. It typically presents as small papules and pustules on the face and resolves spontaneously within a few months [75]. Infantile acne, which appears between 3 and 6 months of age, is less common and may be associated with more severe lesions and a higher risk of scarring [76].

Certain medications, including corticosteroids, lithium, and anticonvulsants, can induce or exacerbate acne. Drug-induced acne typically presents as monomorphic papules and pustules and may resolve upon discontinuation of the offending agent [77].

Occupational acne is caused by exposure to industrial chemicals, such as chlorinated hydrocarbons, oils, and tars. It is commonly seen in workers in the manufacturing and automotive industries and presents as comedones and inflammatory lesions on exposed areas of the skin [78].

Acne in individuals with darker skin tones often presents with more pronounced post-inflammatory hyperpigmentation and a higher risk of keloidal scarring. The inflammatory response in these patients may be more intense, leading to prolonged erythema and pigmentation [79].

Emerging evidence suggests that diet may influence the clinical presentation of acne. High-glycemic-index foods and dairy products have been linked to increased acne severity, possibly

due to their effects on insulin and IGF-1 levels [80].
Stress is a well-known exacerbating factor for acne, likely due to its effects on the hypothalamic-pituitary-adrenal (HPA) axis and subsequent increases in sebum production and inflammation [81].

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