Pathogenesis of acne vulgaris

Amany A. Nassar¹, Afnan Samy Ali¹, Ayman E. Yousef¹

¹Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Zagazig University, Egypt.

ABSTRACT

Acne is a chronic inflammatory disease of the pilosebaceous unit. Its pathophysiology includes hyperseborrhoea, abnormal follicular keratinization and Propionibacterium acnes proliferation in the pilosebaceous unit. Recent research reported the pro-inflammatory activity of the cutaneous microbiome, dyseborrhoea which is alteration of the sebaceous lipid profile during adolescence. External factors as stress, irritation, cosmetics and potential dietary factors involved in formation of acne lesions. Another important process that triggers acne. Propionibacterium acnes activates the innate immunity via the expression of protease activated receptors (PARs), tumour necrosis factor (TNF) a and toll-like receptors (TLRs), and the production of interferon (INF) c, interleukins (IL-8, IL12, IL-1), TNF, and matrix metalloproteinases (MMPs) by keratinocytes, resulting in the hyperkeratinization of the pilosebaceous unit. The aim of this article to highlight the update on the sebaceous gland involvement, the immunity role and the cutaneous microbiome in acne vulgaris pathogenesis.

Key words: acne vulgaris, sebaceous gland, propionibacterium acnes, inflammation, immunity.

INTRODUCTION:

Acne vulgaris is a stressful inflammatory skin disease and represents the top three most prevalent dermatological disease which nearly affecting 9.4% of people worldwide (1). It is a global condition that has a multifaceted pathophysiology. Its pathology is clearly based on four classic principles based on the pilosebaceous unit; there exists ductal hyperkeratinization, increase of sebum secretion, bacterial involvement and inflammatory response. However, new studies have explained the relationship that occurs inside the acne lesion. The immune system has a chief role since it is stimulated by the other factors involved, such as phylotypes of propionibacterium acnes (P. acnes), antimicrobial peptides (AMPs), sebaceous glands (SGs), matrix metalloproteinases (MMPs), and other immune system pathways (2). The acne primary lesion types are non-inflammatory (comedones, open or closed) and inflammatory lesions (papules, pustules, and nodules). The typical distribution involves the sebaceous gland–rich areas of the face, upper back, chest, and shoulders. Secondary changes of scarring, post-inflammatory hyperpigmentation, or erythema should
be noted and will affect the management of acne (3). The aim of this review is to explain the recent mechanisms involved in acne and role of the immune system in the development of this pathology.

**METHODS:**

Search was done via PubMed and Google Scholar by the use of the following keywords: acne vulgaris, sebaceous gland, propionibacterium acnes, inflammation, immunity. The suitable studies were included. The study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

**Economic Burden of AV**

This disorder is generally considered mild but represents a high economical and psychological burden for the society (4). Patients experience high levels of anxiety, depression and low self-esteem which leads to impaired quality of life. Therefore, treatment should focus on early intervention to decrease the physical and esthetic burden of the disease, and improvement of quality of life (5).

**Clinical Diagnosis**

Acne lesions typically occur on the face, chest, or upper back. The lesions may be noninflammatory closed comedones (i.e., papules formed by the accumulation of sebum/keratin within the hair follicle; also called whiteheads); open comedones (i.e., distension of the hair follicle with keratin leads to opening of the follicle, oxidation of lipids, and deposition of melanin; also called blackheads); or inflammatory papules, nodules, pustules, and cysts. Inflammatory lesions result from follicle rupture triggering an inflammatory response. Based on the extent and types of lesions, acne severity may be classified as mild, moderate, or severe (6).

**Etiopathogenesis:**

Four primary pathogenic factors including increase in sebum production from the enlarged sebaceous gland, abnormal hyperkeratinization of the pilosebaceous duct with comedo formation, colonization and proliferation of the duct with bacteria, most commonly Propionibacterium acnes (P. acnes) and inflammatory response caused by the immunological activity of P. acnes (7).

**Increased sebum production by the sebaceous gland from the enlarged sebaceous gland:**

Diverse types of receptors are involved in sebum production include classic histamine receptor stimulated by histamine, the hormonal dihydrotestosterone (DHT) receptor stimulated by androgens and the corticotrophin-releasing hormone receptor activated by stress. However, there are new findings such as the peroxisome proliferator-activated receptors (PPAR α, β and γ), the insulin-like growth factor (IGF)-1 receptor, and the leptin receptor. Leptin organizes lipid droplets and activates the proinflammatory enzyme, IL-6 and IL-8. The facts support that leptin has a key role in promoting inflammation and modifying the lipid composition in SGs (8).
Sebaceous glands (SGs) are mainly activated by androgens; they stimulate cell division and lipid production. During puberty, the higher levels of androgens are closely associated with the prevalence of acne and sebum production. The SGs related to acne lesions are atrophic, and a “comedone switch hypothesis” has been proposed. It suggests that the comedones occur due to an altered differentiation of progenitor cells that originate in the infundibulum and SG (10). It has been proposed that that there is modification in the ratio of saturated and unsaturated fatty acids of the sebum could activate the follicular inflammation and stimulate the innate immunity system response (11).

**Abnormal hyperkeratinization of the pilosebaceous duct with comedo formation:**

Acne vulgaris starts with microcomedones which are the primary acne lesions without inflammation. These acne lesion are developed due to excessive sebum from follicular wall desquamated epithelial cells; a core feature in acne is that the epithelial cells are not shed in a normal manner and lead to sebaceous gland blockage. These microcomedones become comedones that are closed (whiteheads) or open (blackheads) since they have pigmented epithelial cells because of retained melanin (12). Microcomedo which is the primary eruption in acne gives rise to a cascade of inflammatory lesions. The factor determining evolution of the microcomedo into a comedo is intrafollicular keratinization which is caused probably by irritation of the hair follicle walls by sebum and bacteria which leads to excessive production and accumulation of corneocytes this accompanied by excessive production of tonofilaments, desmosomes and keratin K6 and K16. Cytokines mainly IL-1 with the proinflammatory effect, are involved in the keratinization process. The inflammatory infiltration in acne is considered related to hypersensitivity type 4 which may be a response to propionibacterium acnes or one or more of its major antigenic components (13).

**Colonization and proliferation of the duct with bacteria, most commonly P. acnes :**
According to the pilosebaceous unit, P. acnes, an anaerobic gram-positive bacterium, is the most prevalent in acne patients and individuals without this condition. In recent times, the denomination of P. acnes has been changed to Cutibacterium acnes (C. acnes) due to their adaptive genomic changes(14). These bacteria colonize at the pilosebaceous follicles and induce variable inflammation by converting triglycerides to free fatty acids and producing various mediators as well as chemotactic factors. Other flora that are potentially part of this acne process include coagulase-negative Staphylococcus epidermidis and the yeast Pityrosporum ovale. The microbiome of the preadolescent (i.e., 7–10 years of age) with acne contains Streptococcus bacteria that clinicians managing this age group must consider (15). Jahns et al., (16) demonstrated extensive P. acnes biofilms in the sebaceous follicles of patients with acne. They did not find any qualitative differences between P. acnes biofilms in acne and controls, indicating that phenotypic, rather than genetic, changes associated with biofilm formation may account for the pathogenic role of P. acnes. P. acnes secretes lipases, chemotactic factors, metalloproteases and porphyrins. All interact with molecular oxygen generating toxic, reduced oxygen species and free radicals causing keratinocyte damage (17).

**Inflammatory response caused by the immunological activity of P. acnes:**

The immune response to C. acnes has a key role in explaining the acne pathogenesis rather than the damage caused by the bacteria itself (18). Moreover, Propionibacterium acnes (P. acnes) interacts with markers of the innate immunity, such as toll-like receptors (TLR), antimicrobial peptides (AMP), inflammatory protease-activated receptors (PAR) and the matrix metalloproteinase (MMP) (19). Inflammatory cytokines throughout the activation of TLRs, PARs and antimicrobial peptides, P. acnes upregulates the secretion of different proinflammatory cytokines (IL-1a, IL-1b, IL-6, IL-8, IL-12, TNF-α or granulocyte macrophage colony stimulating factor) by human keratinocytes, sebocytes or macrophages and strongly activates the inflammasome of human peripheral neutrophils (20).

Figure (2): Interactions of the immune system in acne vulgaris (21)
i-Toll-like receptors (TLR):

Toll-like receptors (TLR) are transmembrane receptors of the innate immunity system, detecting the invasion by exogenous pathogens (22). In patients with acne, TLR-2 and TLR-4 are overexpressed in the superficial layers of the epidermis. In vitro, protein extracts of *Propionibacterium acnes* (P. acnes) stimulate the expression of TLR-2 and TLR-4 by keratinocytes as well as of TLR-2 by macrophages (23). Dreno et al. (24) showed that more cells express TLR-2 acne severity increases as this is leads to more production of proinflammatory cytokines, including TNF-α and IL-1, IL-8 and IL-12. This may be one explanation for why agents that target TLR-2, such as topical retinoids, have been shown to have greater efficacy in patients with more severe acne. Antimicrobial peptides like defensins and matrix metalloproteinases (MMP) are also produced in proportion to interaction between P. acnes and TLR-2. The link between TLR2 and C. acnes stimulates the NF-κB signal pathway. After a serine specific complex called IkB kinase (IKK) is phosphorylated, IkB is released in the cytoplasm and NF-κB goes to the nucleus. NF-κB is responsible for the transcription of many inflammatory genes in acne, being the fundamental product IL-1β, via the NLRP3 inflammasome and caspase-1 activation (25). All these factors increase inflammatory mediators leading to the breakdown of comedones, which further raises the inflammatory process (26).

ii-Antimicrobial peptides (AMPs):

Antimicrobial peptides (AMPs), important elements of innate immunity system, are the first involved in the defense against microbes and elicit a quick response by acting as natural antibiotics. However, AMPs also have an immunomodulatory role as chemotactic functions, by stimulating angiogenesis and activating cytokine functions. Acne biopsies show an excessive expression of Human beta-defensin (hBD)-2 in pustules and lower production of hBD-1. Also, in vitro observations suggest that C. acnes stimulates hBD-2 expression in keratinocytes and sebocytes. Therefore, AMPs may act as a beneficial factor against C. acnes but at the same time, the reaction may stimulate more inflammation in acne. Literature clearly illustrates its antibacterial activity; nonetheless, there is not enough evidence to support that AMPs trigger the inflammatory consequences in acne (27).

iii-Matrix metalloproteinases (MMPs):

Matrix metalloproteinases (MMPs) are involved in tissue destruction and scar formation and can participate in the innate immune response. In healthy skin, MMPs have an essential role in regulating the skin matrix. Acnes have been shown to upregulate several MMPs. The process is mediated by transcription factor activator protein-1 (AP-1) in acne lesions. Targeting MMPs has an important role in acne therapy as this may be a potential way to minimize scar development and abnormal skin remodeling. Moreover, the proliferation of P. acnes in acne lesions induces an increase in MMP secretion enhancing the rupture of the follicle and the spread of the inflammation in the dermis (28).

iv-Adaptive immunity:

Agak et al. (29) found that *C. acnes* strains that were associated with healthy skin induced Th17 clones with good microbicidal activity. In contrast, those associated with acne did not induce Th17 clones with a sufficiently effective response.
Substance P also induces, both directly and indirectly, inflammation by modulating the release of proinflammatory cytokines and chemokines. This neuropeptide affects the activity of the pilosebaceous unit by stimulating proliferation and differentiation of sebaceous glands, lipid synthesis and induction of neutral endopeptidase expression in sebaceous cells and of E-selectin in perifollicular vessels. Substance P stimulates mast cell proliferation, degranulation and release of proinflammatory cytokines, among others: IL-1, IL-2 and Tumor necrosis factor-alpha (TNF-α). It has chemotactic effect on monocytes, lymphocytes T and neutrophils (30).

**CONCLUSIONS:**

In conclusion, mechanism of acne involves various factors resulting in inflammation and the formation of acne lesions. These factors include the alteration of the sebum secretion triggered by internal factors such as genetic and hormonal factors, and external factors such as high glycemic diet, drugs and mechanical rubbing. P. acnes strains are other important factor that trigger acne. P. acnes activates the innate immunity via the expression of PARs, TNF-a and TLRs, and the production of INF-γ, IL-8, IL-12, TNF, IL-1 and MMPs by keratinocytes, resulting in the hyperkeratinization of the pilosebaceous unit. Limiting the proliferation of P. acnes on the skin using topical antibacterials and regulating the sebum production are the main acne treatment challenges.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References:**


