A Review on Acne Epidemiology and Regulation from A to Z

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Acne vulgaris

Acne vulgaris is a common chronic multifactorial disease of the pilosebaceous unit, manifesting as comedones, papules, pustules, and less commonly nodules and cysts [1].

The word acne is derived from "acme"; a Greek word meaning any pointed thing that comes out of the surface. The earliest documentation of the disease was in the Roman literature as "Akmas," meaning the prime of life in the roman language, referring to the most commonly affected pubertal age group [2].

Though it has no sequelae affecting the patient's life span, it is considered to have a detrimental effect on the patient's quality of life, similar to diabetes mellitus and coronary artery disease [3]. Adolescents with acne have low self-esteem and a higher incidence of social isolation, unemployment, and depression than those who hadn’t experienced acne [4].

1) Epidemiology:

The global burden of acne is now 9.38 % [5]. Acne ranks the 8th most prevalent disease worldwide, affecting up to 85 % of adolescents. Recent epidemiological data states that the risk is higher in developed countries than in developing countries [6].

Age and Sex:

Acne is mostly a disease of adolescence; however, it can persist into adulthood in 25% of women and 13 % of men. There are two subtypes of adult acne: persistent acne and late-onset acne. When adolescent acne continues until the age of 25, it is known as persistent acne. Late-onset acne is when people experience acne for the first time at an adult age [7].

Younger girls are more likely to be affected at a young age than boys, particularly at 8 to 10 years, at the prepubertal stage, before menstruation. The male prevalence rises as they reach puberty with more incidence for scarring, but the incidence of women affection after teenage years tends to rise again [8].
Race:

It affects people of all ethnic groups [9], but the prevalence varies with different ethnicity, for example, African Americans, Hispanics, Asians, Caucasians, and Continental Indian women, at 37%, 32%, 30%, 24%, and 23% respectively [10].

Course:

Acne is mostly a self-limiting disease that usually resolves after adolescence with or without treatment; however, in some cases, it can take many years and persist till adulthood [11].

II) Risk Factors:

1. Diet:

A. Glycemic diet:

It is now proved that a high glycemic diet is incriminated in increasing the incidence of acne vulgaris, and populations with a lower glycemic index diet have a lower incidence of acne [12].

Studies were made to correlate the body mass index (BMI) with acne, conflicting results were observed. While most studies suggested that increased BMI is associated with increased insulin glycemic factor-1 (IGF-1) and acne severity [13]; other studies suggested that there is no correlation between increased BMI and acne, as much as it is related to high sugary food and soft drinks regardless the BMI [14].

B. Milk:

Milk is associated with the flare of acne whether it is full fat, half fat, or skimmed. This is may be attributed to amino acids in milk as leucine which activates signaling pathways within the sebaceous glands, leading to increased lipogenesis and protein synthesis ending by ductal plugging [15].

C. Whey protein and casein:

Whey protein and casein in supplements predispose to acne and increase its severity [16].

D. Omega-3:

Studies showed that supplementation with omega-3 in the form of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) resulted in improvement of acne [17].
E. Antioxidants:
Polyphenols in green tea have a sebum-reducing effect, thus improving acne severity [18].

2. Genetic predisposition:
By studying the acne pattern in twins, it was found that it is heritable in 81% of cases [19].

With the new advances in genomic studies, two main genetic patterns were in the spotlight to be studied for possible involvement in the pathogenesis of acne, those encoding steroid hormones and those regulating the innate immune function of the keratinocytes [20].

In addition, IGF-1 polymorphism was also found to increase the risk of acne [21]. Also, polymorphism in the gene promoter encoding interleukin-1a and interleukin-6 is linked to the pathogenesis of acne [22].

3. Vitamin D:
Vitamin D level is inversely correlated with the degree of severity of acne, and supplementation in deficient patients showed improvement in 50% of cases [23].

4. Stress:
Acne flares with increased stress. This happens either directly by increasing cortisol associated with increased adrenal androgens or indirectly through neuroactive substances, including substance P, that may stimulate sebaceous gland proliferation, aggravating acne lesions [24].

5. Environmental factors and air pollution:
Repeated exposure to ultraviolet rays without photoprotection increases stratum corneum thickness and sebum production, eventually leading to increased comedogenesis [25]. Moreover, some studies prove that increased air pollutants aggravate existing acne lesions [26].

6. Smoking:
Smoking is thought to aggravate acne. A possible hypothesis is that excess nicotine acts on the nicotinic receptors expressed on keratinocytes, fibroblasts, and blood vessels found in the pilosebaceous unit (PSU). This binding induces vasoconstriction, which delays wound healing by inhibiting the protective immunity necessary to dispose of the rapidly growing bacteria and to fix the ruptured PSU [27].

7. Drugs:

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Several drugs had been suggested to trigger acneiform eruption as halogenated compounds, progestins, corticosteroids, isoniazid, lithium, and epidermal growth factor (EGF) receptor antagonists (gefitinib, erlotinib, cetuximab) [28].

8. Mechanical factors:
Repeated friction by excessive soap usage, friction by veils, hats, etc., induces at the sites of friction "mechanical acne"; a variant from acne similar clinically and histologically [29].

One common type of mechanical acne that emerged after the COVID-19 pandemic is "Maskne". It is acne that erupts, particularly in the chin area, because of the repeated friction of the masks to this area [30].

III) Pathogenesis:
The four main pathogenic events incriminated in the pathogenesis of acne vulgaris are excessive sebum, hyperkeratinization of the follicular epithelium, colonization by Cutibacterium Acnes, and finally, inflammatory changes aggravated by those factors ending by activating innate and adaptive immunity [31].

1. Increased sebum:
Hyperseborrhea is a must in all acne patients. However, increased sebum amount is not the only change observed; abnormal sebum production along with increased monosaturated amino acids are important factors for acne pathogenesis [32].

Also, in people at risk of acne, the amount of lobules per sebaceous gland is more, and the follicle size increases, leading to microcomedones formation; the primary lesion in acne [33].

2. Hypercornification of the ductal epithelium:
Adherent keratinized cells accumulation within the pilosebaceous canal results in impaction of the canal and blocking the flow of sebum within, leading eventually to obstruction. This process is under the influence of sebum. The mechanisms included are hyperproliferation of keratinocytes, abnormal differentiation of the follicular wall keratinocytes, improper desquamation with inadequate separation, and shedding of the corneocytes within the follicle [34].

3. Role of Cutibacterium acnes:
Cutibacterium acnes (C. acnes), formerly known as Propionibacterium acnes, is a commensal bacterium present in the ubiquitous amount on normal skin. Although it is symbiotic under certain conditions, it can become opportunistic. Cutibacterium
Colonization is not an actual infection, and the burden of C. acne doesn’t correlate with the acne severity \[35\].

There are six phenotypes to the C. acnes (IA1, IA2, IB, IC, II, and III). It was found that the main pathogenic event incriminated in the pathogenesis of acne is an increase of the phenotype (IA), which is known for its pro-inflammatory effect over the other phenotypes. At the same time, healthy skin showed the predominance of C. acnes phylotype (II). So, it is not an infection as much as it’s a phenotypic switch to the pro-inflammatory subtype \[36\].

Cutibacterium acnes secretes lipases that act as chemoattractants to pro-inflammatory cytokines and cause hydrolysis of triglycerides into free fatty acids (FFA) such as palmitate and oleate, which in turn promote more growth and adherence to C. acnes \[37\].

Furthermore, C. acnes augments the expression of the degradative pro-matrix metalloproteinases (MMPs) -1 and -9 in human monocytes, which leads to follicular rupture, along with a cluster of differentiation (CD)-4 cells invasion to dermal fibroblasts and sebocytes \[38\].

Another important action of C. acne is the production of biofilm. It acts as a biological glue that traps sebum, obstructing passage to the infundibulum, promoting comedogenesis. Also, it accounts for the observed resistance of C. acnes to the host immune cells and antibacterials \[34\].

In addition, C. acnes leaks antigenic materials that activate important markers of the innate immune system, such as antimicrobial peptides, protease-activated receptors, and toll-like receptors (TLRs)-2; present on the surface of monocytes \[39\].

4. **Inflammatory changes:**

It is now approved that inflammatory changes mediated by host innate and adaptive immunity are the main drive for the clinical lesions of acne and that inflammation is a must for the development of acne lesions, and it is not a secondary event. The early infiltration evidences this by CD-4 and CD-8 cells that precede the formation of microcomedones. CD-4 cells and macrophages are thought to drive inflammation based on their heavy infiltration on the normal surrounding uninvolved skin in acne-prone patients \[40\].

A. **Role of the innate immune system:**

The skin communicates between the exterior and the interior environment through transmembrane receptors called toll-like receptors. Toll-like receptors are pattern recognition receptors that react to pathogen-associated molecular patterns (PAMPs),
expressed by C. acnes. They activate the innate immune system by inducing inflammatory cytokines and metalloproteinases, activating the adaptive immune system [41].

Toll-like receptors are present on keratinocytes, monocytes, macrophages, langerhans cells, T and B lymphocytes, mast cells, and endothelial cells. In the epidermis of acne lesions, the expression of TLRs, specifically TLR-2, and to a lesser extent, TLR-4 is essential for the inflammation. This is proven by the increased TLR-2 expression in sebocytes observed in the lesional area more than in the perilesional area [42].

Cutibacterium acnes are recognized by TLR-2 and TLR-4 and scavenger receptor CD-36 on the surface of keratinocytes. The binding of the bacteria to the receptors activates signaling cascades, including the nuclear factor kappa B (NF-κB) pathway, which in turn upregulates the genes encoding TNF, IL-1β, IL-1α, IL-8, IL-6, MMPs, human β-defensin-2 (hBD-2) [43]. Those cytokines play an important role in developing inflammatory and non-inflammatory acne lesions. TNF stimulates lipogenesis, which starts the process of comedogenesis [44]. Matrix metalloproteinases contribute to dermal matrix destruction and scar formation [39].

**B. The adaptive immune system response:**

The adaptive arm of the immune system plays a role in the immune response to acne. It has been demonstrated that C. acnes promotes a T helper (Th)-1/Th-17 response, and it is proven that acne patients have significantly higher levels of these T cell subsets in both their peripheral blood and in the acne lesions around the pilosebaceous unit very close to sebocytes [45].

Cutibacterium acnes promotes signaling cascades that upregulate inflammatory genes’ expression. The genes involved were IL-23, IL-6, and transforming growth factor-β (TGF-β) genes, which participate in Th-17 cells stimulation [46].

When Th-17 cells are stimulated, the secretion of IL-17A, IL-22, IL-26, and TNF is enhanced. Upon secretion of IL-17 from Th-17 cells and other IL-17 producing cells, it acts on receptors which are located on the keratinocytes, leading to the production of granulocyte colony-stimulating factor (G-CSF) and chemokines such as C-C motif ligand (CCL)-20 & C-X-C motif ligands (CXCLs), which all stimulate neutrophils trafficking. Antimicrobial peptides (AMP), S100 protein, and cathelicidin secretion is upregulated [46].

T cells also exhibit a characteristic Th-1 cytokines pattern demonstrated by the higher interferon-γ (IFN-γ) level than normal, whereas the IL-4 level is in lower quantities [47].
Finally, CD4+ T cells expressing IL-17 together with IFN-γ were also identified, which is characteristic of mixed Th-1/Th-17 differentiation [43].

**C. Role of cytokines in the development of acne lesions:**

Acne nowadays is considered to be a model of chronic immunodeficiency inflammatory dermatoses, with the activation of innate immunity and the subsequent development of the adaptive T-cell immune response. This is concluded from the observed excessive secretion of pro-inflammatory cytokines (IL-1α, IL-2) and vascular endothelial growth factor (VEGF) on the background of decreasing the content of anti-inflammatory cytokines (IL-4, IL-10) [48].

Interleukin-1α causes hypercornification of the infundibulum of pilosebaceous follicles, which is one of the processes involved in comedones formation [49].

Interleukin-1β expression and release are enhanced, which stimulates neutrophil trafficking to produce inflammatory lesions [43].

Interleukin-8 is a strong chemoattractant. Shortly after being released by the binding of C. acnes to the TLR, it triggers neutrophils to undergo shape-changing processes by the bioactivation of integrins and the actin cytoskeleton.

This integrin activation is required for the neutrophils to be capable of adhering to the endothelial cells and migrating to the site of inflammation at PSU. The release of lysosomal enzymes by neutrophils leads to the rupture of follicular epithelium and further inflammation. Once the rupture of the follicular wall, granulomatous lesions with subcutaneous induration, scarring, and keloids are generated. Basophils, T cells, monocytes, and eosinophils also show chemotactic responses to IL-8 [50].

**IV) Regulators:**

1. **Role of androgens:**

Androgens promote lipogenesis by binding to androgen receptors in the nucleus, which enhances phosphorylation of the mechanistic target of rapamycin (mTOR), which forms the catalytic core of the mechanistic target rapamycin complex-1 (mTORC1). mTORC1 enhances the synthesis of lipids by activating sterol regulatory element-binding protein-1 (SREBP-1) [51].

Testosterone normally is converted to dihydrotestosterone (DHT) by the action of 5α-reductase; DHT is ten times more potent than testosterone [52]. In acne patients, the androgen receptors of the sebaceous glands are hypersensitive to androgens, with a higher activity of 1,5 α-reductase [34].

2. **Role of estrogen:**
Estrogen has a protective role probably by its antiandrogenic effect and antiestrogenic effect [53]. Oral contraceptive pills containing estradiol and various types of progestins may be used to manage acne. They work by decreasing the sebum in the face and scalp [54].

3. Role of progesterone:

Progesterone is known to possess sebogenic and androgenic quality and to be the reason behind acne flare before menstruation. Nowadays, new progesterones have emerged that have low androgenic potential as norgestrel, levonorgestrel, and third-generation progestin such as norgestimate. Those new generations are incorporated in oral contraceptives to limit the side effects of estrogen [55].

4. Role of glucocorticoids:

Corticotrophin-releasing hormone (CRH) stimulates the biosynthesis of testosterone and induces the synthesis of the lipid, resulting in a high level of androgen and over-stimulation of sebaceous glands sebum secretion. [7]. This is evidenced clinically by the acnegenic eruption that arises from systemic and topical corticosteroids [56].

5. Role of insulin-like growth factor:

IGF-1 is a small polypeptide hormone that is also known as somatomedin C. It can regulate various signaling pathways that activate lipogenesis and control androgens metabolism [35].

Insulin and IGF-1 can induce various inflammatory and immune responses; this is supported by the increase of NF-κB, IL-1β, IL-6, IL-8, and TNF-α in sebocytes treated with IGF-1 [57].

Also, IGF-1 enhances the androgen biogenic effect by increasing the activity of 5α-reductase in the skin, which converts testosterone to dehydroepiandrosterone (DHEA), and upregulates the synthesis of gonadal and adrenal testosterone [37].

6. Melanocyte Stimulating Hormone (MSH):

The role of melanocyte-stimulating hormone still imposes some sort of controversy. While it is proved in some studies that it increases lipogenesis and sebocyte differentiation, other studies find that it inhibits interleukin-8, which is implicated in the pathogenesis of acne as an inflammatory cytokine [58].

V) Clinical presentation:
Microcomedones are the primary lesion of acne; they compose histopathological changes that are not evident yet clinically. They constitute the follicle impacted with accumulated sebum [59].

Microcomedones then precede to form non-inflammatory lesions that are visible clinically known as comedones which are either closed also known as "whiteheads", or opened as "blackheads". The black color is due to the oxidation of the sebum material [59].

The inflammatory lesions are papules, pustules, nodules, or cysts. Papules are red elevation over the skin, while pustules are the same with an accumulation of small pus material in the middle; nodules are firmly indurated hard lesions more than 5 cm in diameter [60].

Usually, acne lesions are asymptomatic, with no pain or itching, but there may be accompanying erythema or pain[59].

The lesions are mainly found on the areas of the body rich in receptors for DHT as the face, chest, back, proximal[7].

Acne vulgaris either resolves with no sequelae or causes a disfigurement in the form of an erythema, post-inflammatory hypo or hyperpigmentation, or scarring that is either atrophic or hypertrophic but more commonly atrophic [61].

One rare form of acne is acne conglobata. It is a severe form that is more common in men and manifests as grouped comedones and multiple abscesses interconnected by multiple draining sinuses [62].

Another severe form of acne is acne fulminans; it is more common in men and characterized by ulcerative lesions, necrosis, and hemorrhage. It is accompanied by systemic manifestations as fever, prostration, weight loss, and alteration of hepatic and renal function [63].

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