An Overview about ACNE VULGARIS

Amany Abd El Rahman Nassar, Alshimaa Mohamed Ibrahim, Arwa Gamal Youssef

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

Email: drarwajamal@gmail.com

Abstract

Acne vulgaris (AV) is a dermatological disorder, affecting more than 85% of adolescents all over the world. It is the most common skin disease, and although it usually manifests during puberty and worsens throughout adolescence, studies reported that it can occur at any age, Acne is a nonlife threatening disease, however, it has a significant psychological influence and comorbidity which require effective treatment to improve the patient's skin and self-esteem. Acne lesions typically occur on the face, chest, or upper back. The initial acne lesion is the microcomedone. which is an invisible microscopic structure. The lesions can 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. Acne severity may be classified as mild, moderate, or severe based on the extent and types of lesions. The diagnosis of AV is primarily clinical. The common differential diagnosis of acne includes folliculitis, keratosis pilaris, perioral dermatitis. seborrheic dermatitis and rosacea. History and physical examination can help determine if there is an underlying cause of acne, such as an exacerbating medication or endocrinologic abnormality causing hyperandrogenism (e.g., polycystic ovarian syndrome). Acne grading systems have been proposed for use as complementary, easy to use and rapid mode of acne grade assessment and for the selection of eligible patients for therapeutic studies. Overall scales might be less quantitative but more relevant to clinicians and their patients.

Keywords: Acne Vulgaris

1. Introduction

Acne vulgaris (AV) is a dermatological disorder, affecting more than 85% of adolescents all over the world. It is the most common skin disease, and although it usually manifests during puberty and worsens throughout adolescence, studies reported that it can occur at any age**.** Acne is a nonlife threatening disease, however, it has a significant psychological influence and comorbidity which require effective treatment to improve the patient's skin and self-esteem **(1).**

Most patients with active acne delay treatment, which leads to increased acne scarring**.** Acne scarring has been categorized into increased tissue formation (including hypertrophic and keloid scars) and more commonly loss of tissue (including ice pick, rolling, and boxcar type scars) **(2)**.

Etiopathogenesis:

The pathogenesis is multifactorial,

I. Four primary pathogenic factors including:

A. Abnormal hyper keratinization of the pilosebaceous duct with comedon formation caused by increased androgens.

B. An increase in sebum production from the enlarged sebaceous gland caused by increased

androgens.

C. Colonization and proliferation of the duct with bacteria, most commonly P. acnes, although clear evidence of a causal relationship between P. acnes and AV is lacking.

D. An inflammatory response caused by the immunological activity of P. acnes **(3).**.**Abnormal hyper keratinization of the pilosebaceous duct with comedon formation:**

The main acne lesion that accelerates a chain reaction of inflammatory lesions is microcomedon. The process of intrafollicular keratinization, which is mostly due to sebum and bacteria irritating the hair follicle walls, results in an excessive synthesis and accumulation of corneocytes, as well as an excessive production of tonofilaments, desmosomes, and keratin K6 and K16. The keratinization process involves cytokines, most notably IL-1, which has a pro-inflammatory effect. Hypersensitivity type 4 is thought to be connected to the inflammatory infiltration in acne, which may be a reaction to Propionibacterium acnes or one or more of its main antigenic components **(4).**

A. Increased sebum production by the sebaceous gland from the enlarged sebaceous gland:

Sebaceous glands (SGs) have a key role in acne pathophysiology . Different types of receptors are involved in sebum production. The traditional histamine receptor, which is triggered by histamine, the hormonal dihydrotestosterone (DHT) receptor, which is triggered by androgens, and the corticotropin-releasing hormone receptor, which is triggered by stress. The peroxisome proliferator-activated receptors (PPAR), the insulin-like growth factor (IGF)-1 receptor, and the leptin receptor are examples of recent discoveries. The proinflammatory enzymes IL-6 and IL-8 are enhanced and lipid droplets are organized by leptin. Leptin therefore has a role in promoting inflammation and changing the lipid composition in SGs **(5)**.

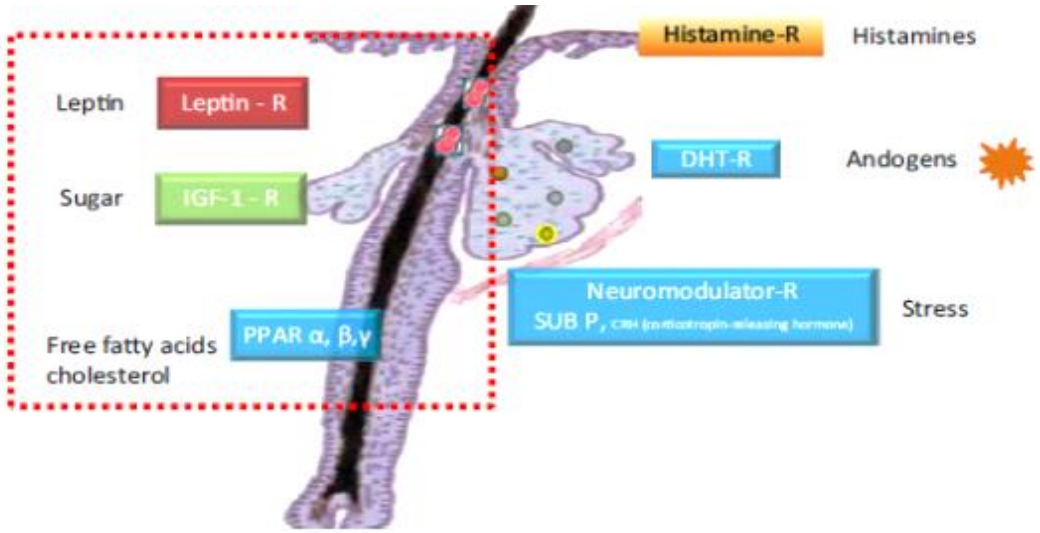

Figure (1): Receptors controlling sebum production **(6)**

Androgens are the primary stimulators of sebaceous glands; they promote cell division and lipid synthesis. The amount of androgens rises during puberty and is directly related to acne occurrence and the production of sebum. According to some theories, altering the sebum's ratio of saturated to unsaturated fatty acids may cause follicular inflammation and trigger the innate immune system**.** In patients with acne, it has been noticed decrease essential fatty acid levels and a lower level of linoleic acid **(7)**.

B. Colonization and proliferation of the duct with bacteria, most commonly P. acnes :

The main cutaneous organisms include Corynebacteria, Propionibacteria, and Staphylococci, which help in maintaining the skin healthy and intact by inhibiting the colonization of other bacteria**.** Numerous factors, such as the local skin anatomy, cutaneous film lipid content, pH, sweat, and sebum excretion, affect the prevalent microbiota**.** The anaerobic gram-positive bacterium P. acnes, which is most common in both people with and without acne, is detected in the pilosebaceous unit. Due to their adaptive genetic modifications, P. acnes has recently been renamed Cutibacterium acnes (C. acnes)**.** By converting triglycerides to free fatty acids, creating several mediators, and chemotactic factors, these bacteria proliferate at the pilosebaceous follicles and cause inflammation. The yeast Pityrosporum ovale and the coagulase-negative Staphylococcus epidermidis are two other flora that may contribute to the acne process**. (8)**

Rather than the harm caused by the bacteria, the immune response to C. acnes plays a major role in explaining acne pathogenesis**.** Propionibacterium acnes interacts with innate immunity indicators like toll-like receptors (TLR), antimicrobial peptides (AMP), inflammatory protease-activated receptors (PAR), and matrix metalloproteinase (MMP) **(8)**

Human keratinocytes, sebocytes, or macrophages secrete a variety of proinflammatory cytokines (IL-1a, IL-1b, IL-6, IL-8, IL-12, TNF-, or granulocyte macrophage colony stimulating factor) when exposed to Probionibacterium acnes. It also strongly activates the peripheral neutrophils. TLRs, PARs, and antimicrobial peptides are also activated **(9).**

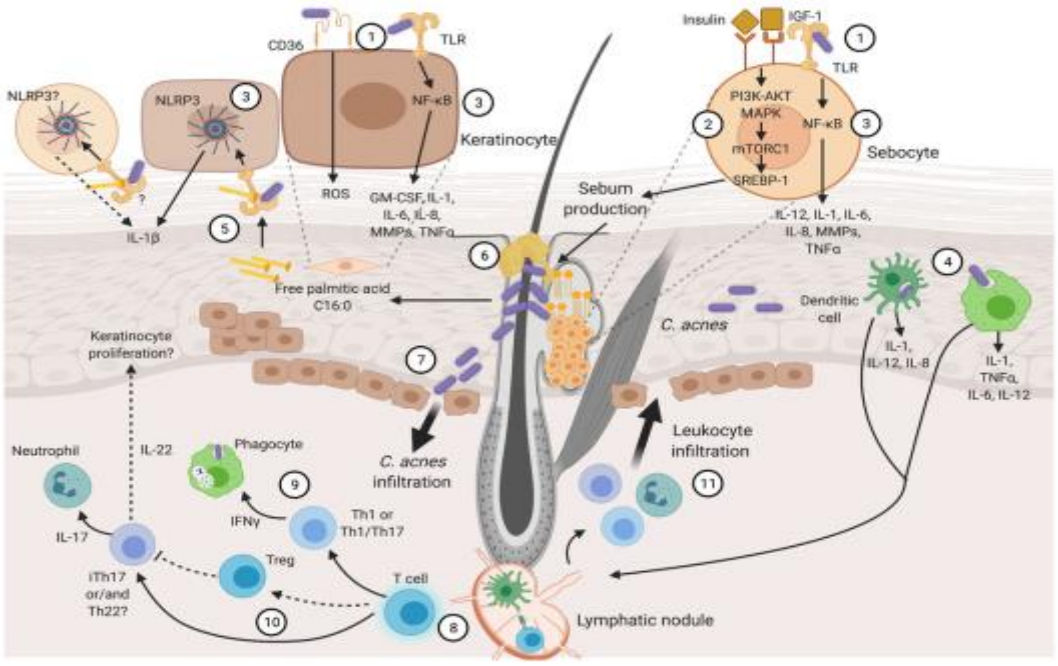

Figure (2): Inflammatory process in acne pathogenesis **(10).**

{NF-κB (Nuclear Factor kappa B), ROS (Reactive Oxygen Species), PI3 (Phosphoinositide 3-Kinase), AKT (Protein Kinase B), (MAPK) Mitogen-Activated Protein Kinase, mTORC1 (Mammalian Target of Rapamycin Complex 1), SREBP-1 (Sterol Regulatory Element-Binding Protein 1), Th (T helper cells), Treg (T Regulatory cells), iTh (Inflammatory T helper cells), TNFa (Tumor Necrosis Factor a), DC (Dendritic Cell). }

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

1. Toll-like receptors (TLR):

The innate immune system's toll-like receptors (TLRs) are transmembrane receptors that detect foreign pathogens**.** TLR-2 and TLR-4 are overexpressed in the outermost layers of the epidermis in acne patients. Keratinocytes and macrophages both express TLR-2 and TLR-4 when P. acnes protein extracts are used in vitro**.** Increased TLR-2 expression causes more proinflammatory cytokines, such as TNF- and IL-1, IL-8, and IL-12, to be secreted, which worsens acne. This could be the reason why drugs that target TLR-2, including topical retinoids, have been proven to be more effective in people with more severe acne. Defensins and matrix metalloproteinases (MMP), which are antimicrobial peptides, are also produced in proportion to interaction between P. acnes and TLR-2 **(11).**

Antimicrobial peptides (AMPs):

Antimicrobial peptides (AMPs), an element of the innate immune system, are the first to get involved in the defense against microorganisms and act as a natural antibiotic by triggering a rabid reaction. However, in addition to their chemotactic effects, AMPs also have an immunomodulatory effect by promoting angiogenesis and triggering cytokine secretion**.** They are composed of beta-defensins and cathelicidins. Human beta-defensin (hBD)-2 is expressed in the pilosebaceous unit, and it is upregulated by C. acnes and increases in acne lesions**.** As a result, AMPs may be effective at preventing C. acne, but the reaction itself may also increase acne inflammation. Multiple studies show its antibacterial effectiveness, however further studies are required to prove that AMPs cause inflammatory effects in acne **(12).**

2. Matrix metalloproteinases (MMPs):

Matrix metalloproteinases (MMPs) have an impact on tissue degeneration, the formation of scars, and the innate immune response. In healthy skin, MMPs have an essential role in regulation of skin matrix. Acnes upregulate several MMPs that mediated by transcription factor activator protein-1 (AP-1) in acne lesions. P. acnes overgrowth in acne lesions causes an increase in MMP secretion, which facilitates follicle rupture and the spread of dermal inflammation**.** this upregulation of genes involved not only in inflammation but also in the remodelling of the matrix **(12)**

Adaptive immunity:

In acne lesions, CD4 and IL-17 cells have been noted in surrounding the pilosebaceous unit near to sebocytes**.** However, C. acnes strains that were associated with healthy skin induced Th17 clones with good microbicidal activity. In contrast, those associated with acne did not elicit Th17 clones with a sufficient effective response. Substance P also induces, both directly and indirectly, inflammation by modifying production 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, IL-1, IL-2, and Tumor necrosis factor-alpha (TNF-α). It has chemotactic effect on monocytes, lymphocytes T and neutrophils **(13).**

Hypoxia caused by increasing pressure from the ductal plug may act as a link between a subclinical lesion and increased inflammatory responses at the pilosebaceous duct. Low oxygen levels permit P. acnes growth in the infra-infundibulum and can stimulate keratinocytes to produce cytokines, which are released as the duct ruptures. Further, P. acnes release into the dermis enhances an intense local reaction of innate immunity. Collections of neutrophils and

lymphocytes in the follicular epithelium also share in breakdown of the follicular wall **(14).**

II. Genetics influence:

Heritability and genetics are thought to play a role in the underlying pathophysiology and clinical variants of acne. the extracellular matrix, which is normally maintained through a balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), may play an important role in the associated abnormal follicular keratinization in acne vulgaris. Some believe that individuals and families with severe acne possess a likely genetic imbalance between MMP and TIMP activity, and respond to isotretinoin therapy because this retinoid decreases levels of MMP-1, MMP-9, and MMP-13**(15).**

III. Hormones implicated in acne pathogenesis:

androgens, estrogens, progesterone, insulin and insulin-like growth factor-1,corticotrophin-releasing hormone, adrenocorticotropic hormone (ACTH), glucocorticoids, and growth hormone (GH), are involved in acne pathogenesis **(16)**

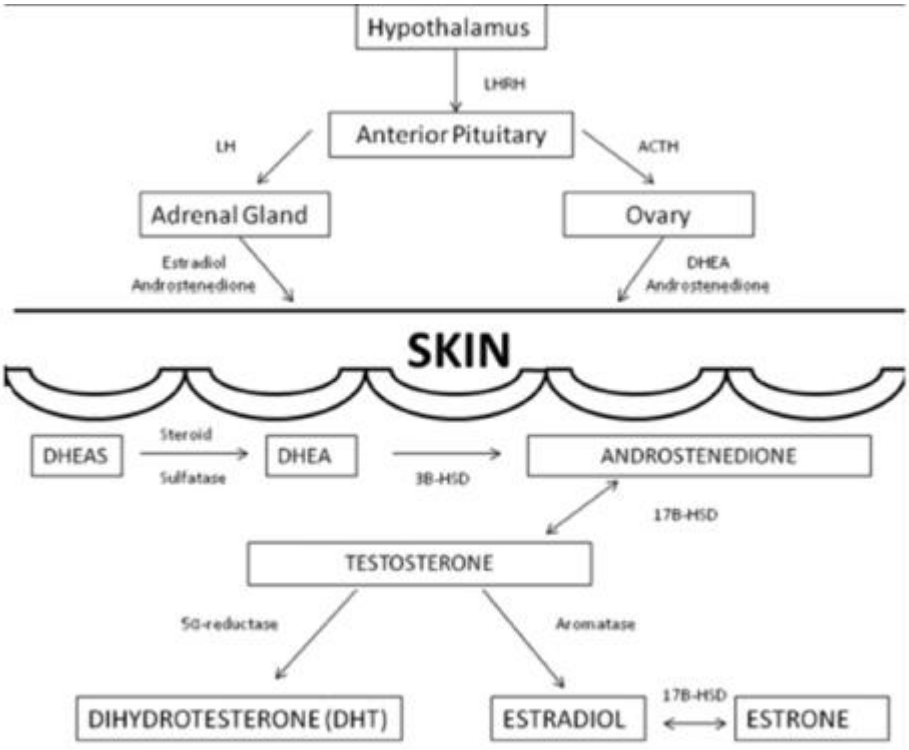

Figure (3): Hormonal regulation of acne pathogenesis **(17)**

A. Androgens:

Androgens is one of the most important hormones that regulate sebum production. During puberty, they stimulate keratinocytes proliferation, increase the size of sebaceous glands and sebum secretion. The source of these hormones differs between men (adrenal cortex and testicles) and women (adrenal cortex and ovaries)**.** Skin structures (sebocyte, hair follicle, dermis, and epidermis) contain enzymes important in converting dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEA-S), and androstendione into the potent androgens as dihydrotestosterone (DHT) and testosterone. DHT and testosterone are the major androgens that interact with the androgen receptors on sebaceous glands**.** 5α-reductase enzyme in the infundibular sebocytes can convert the testosterone to the 5–10 times more active DHT**.** Sebaceous glands in the face and other regions are stimulated to grow because of this chemical reaction due to a cyclic adenosine monophosphate (cAMP) mechanism. Girls with oestrogen

levels that change during the menstrual cycle may experience influences on their acne. Additionally, teenagers with normal hormone levels may experience severe acne due to increased free testosterone levels and DHEAS, which includes decreased levels of sex hormone-binding globulin(SHBG), even though they have normal levels of other hormones **(18)**.

As some acne patients (30-80%) showed various degrees of hyperandrogenemia, dermatologists should examine other clinical signs of hyperandrogenism including hirsutism, androgenic alopecia, menstrual disorders and virilization. Polycystic ovary syndrome is the most common cause of hyperandrogenism in women (70% of cases**) (4).**

B. Estrogen:

High-dose estrogen exerts negative feedback on the gonadal axis. This results in the reduction of sebaceous gland size and sebum formation. Estrogen receptor (Er) α is localized in sebocytes only, while (Er) β is found to be highly expressed in sebocytes, keratinocytes, melanocytes, dermal fibroblasts, endothelial cells, and adipocytes **(19).**

Estrogen may influence sebum formation through:

A. Negative feedback inhibition of gonadal axis.

B. Increased production of sex hormone-binding globulin (SHBG) by the liver, leading to decrease free serum testosterone.

C. Directly counteracting the action of testosterone in the sebocytes.

D. Influencing the genetic regulation of sebaceous gland and sebocyte formation **(19).**

C. Progesterone:

Progesterone is a competitive inhibitor of 5α- reductase but its role to reduce sebaceous gland activity is minimal. Progesterone has a role in fluctuation of sebum production in women during menstrual cycle and premenstrual flare **(20).**

D. Insulin and insulin like growth factor 1:

Growth hormones (GH) upregulated by insulin lead to maturation of sebeaceous gland. Moreover, insulin inhibits SHBG production from the liver and have a positive feedback effect on adrenal and ovarian androgenesis**.** Insulin-like growth factor 1 levels increase during puberty under the influence of the growth hormone, and it positively links with the clinical course of acne**.** The levels of circulating IGF-1 and insulin-growth factor binding protein (IGFBP-3) are affected by hyperinsulinemia, which has a direct impact on keratinocyte proliferation and apoptosis. In hyperinsulinemia, the level of IGF-1 increases whereas the level of IGFBP-3 decreases, this imbalance results in increased keratinocyte proliferation. Comedogenic factors such as androgens, growth hormone and glucocorticoids are also affected by Insulin-like growth factor 1**(21)**.

Corticotrophin-releasing hormone:

Corticotrophin-releasing hormone (CRH) secreted by the hypothalamus is converted to pro-opiomelanocortin in the anterior pituitary. Proopiomelanocortin is converted to Adrenocorticotropic hormone (ACTH) and melanocyte-stimulating hormone, which upregulate the cortisol production cycle. CRH targets the sebaceous glands and induces lipogenesis by enhancing androgen bioavailability and by stimulating the conversion of DHEA to testosterone **(22).**

E. Pituitary hormones:

Different pituitary hormones can influence acne as:

1. **ACTH:** sebum production stimulator.
2. **GH:** activates the differentiation of the sebocytes and stimulates the conversion of testosterone to DHT by 5 alpha-reductase enzymes.
3. **LH:** androgens are secreted by the ovaries under regulation of Luteinizing hormone (LH).
4. **Prolactin:** prolactin receptors are well expressed in the adrenal glands. In cases of hyperprolactinemia, adrenal androgens are secreted in an increased manner and contribute to the rapid formation of acne pimples **(23).**

Glucocorticoids:

Steroids are thought to increase acne eruptions (steroid acne) through their increased Toll-like receptor 2 gene expressions and further release of the proinflammatory mediators **(24).**

F. Exogenous factors may have a role in aggravating acne vulgaris:

There is a positive association between acne, menstruation, heat, humidity, sweating, use of makeup and cosmetic products, oily hair products, use of topical steroids, sleep disorders, excessive skin washing and squeezing pimples. Undesirable stressful life events and psychiatric comorbidity were more in acne patients than in controls**.** Stress stimulates the release of pro-inflammatory cytokines and CRH, leading to increased levels of cortisol. Sleep deprivation associated with modern lifestyle and stress have an important impact on the hypothalamic-pituitary-adrenal axis and in increased secretion of stress-related hormones and may also be an aggravating factor for acne **(25).**

Impact of diet in acne vulgaris:

The association between diet and acne can no longer be dismissed.

High glycemic load diets may exacerbate acne (also, Low glycemic load diet that resulted in the improvement of acne lesions)**.** Food with a high glycemic index is rapidly absorbed, increases serum glucose levels, and stimulates increased glucose-dependent insulin signaling. levels stimulate the secretion of androgens and cause an increased production of sebum, growth of the sebaceous glands and hyperkeratinization, which plays a fundamental role in pathogenesis of AV. However, the ratio of omega-6 to omega-3 fatty acids resulting from diet is one of the factors that modulate the inflammatory mechanism. A high intake of omega-3 fatty acids can inhibit the production of proinflammatory cytokines and have ability to lower IGF-1 levels which suggest that they may have a beneficial effect in treatment of acne. Fish oil, especially Eicosapentaenoic Acid (EPA) can inhibit production of leukotriene B4 (LTB4) and prevent inflammatory cascade, although studies do not clearly report a beneficial role of fish oil on acne vulgaris **(26).**

Clinical diagnosis:

Acne lesions typically occur on the face, chest, or upper back. The initial acne lesion is the microcomedone. which is an invisible microscopic structure. The lesions can 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. Acne severity may be classified as mild, moderate, or severe based on the extent and types of lesions **(26).**

The diagnosis of AV is primarily clinical. The common differential diagnosis of acne includes folliculitis, keratosis pilaris, perioral dermatitis. seborrheic dermatitis and rosacea. History and

physical examination can help determine if there is an underlying cause of acne, such as an exacerbating medication or endocrinologic abnormality causing hyperandrogenism (e.g., polycystic ovarian syndrome). Endocrinologic testing is not ordered routinely for women with regular menstrual cycles. Older women, especially those with new-onset acne and other signs of androgen excess (e.g., hirsutism, androgenic alopecia, menstrual irregularities, infertility), should be tested for androgen excess with measurements of total and free serum testosterone, dihydroepiandrosterone and luteinizing and follicle-stimulating hormone levels. Pelvic ultrasonography may show the presence of polycystic ovaries. In pre-pubertal children with acne, signs of hyperandrogenism include early-onset accelerated growth, pubic or axillary hair, body odor, genital maturation, and advanced bone age **(27).**

Assessment tools for acne severity:

Acne grading systems have been proposed for use as complementary, easy to use and rapid mode of acne grade assessment and for the selection of eligible patients for therapeutic studies. Overall scales might be less quantitative but more relevant to clinicians and their patients. One of these tools is the Investigator Global Assessment of acne (IGA), which is accepted by the American Food and Drug Administration (FDA) in 2018, IGA score graded from 0–4 depending on the descriptive criteria of facial acne only. No account on the chest, back, or shoulders considered here. The other method is the global acne grading system (GAGS) that gives a weight to each region (face and back) with a severity score Briefly; GAGS consider six locations of the face and chest/upper back with a factor for each location based on surface area (forehead = 2, Right cheek = 2, Left Cheek =2, Nose = 1, Chin = 1, Chest and Upper back = 3), distribution and density of pilosebaceous units. Each region would be given a score depending on the type of lesions (No lesion =0, One comedone = 1, Papule=2, One pustule = 3, One nodule = 4) and the sum of scores multiplied by the factors (Local score = Factor × Grade from 0 to 4), the sum of local scores gives the global score (0–52). The severity is graded as mild if the score was 1–18, moderate with scores form 19–30, severe with scores form 31–38, and as very severe if the score is more than 38 **(27).**

Acne subtypes:

A. Pediatric acne:

Pediatric acne categorized by age as shown in table (1)

Table (1): Pediatric Acne categorized by age **(28).**

Acne Type	Age of Onset
Neonatal	Birth to ≤ 6 weeks (wk)
Infantile	6 wk to ≤ 1 year (y)
Mid-childhood	1 y to < 7 y
Preadolescent	≥ 7 y to ≤12 y or menarche in girls
Adolescent	≥12 y to ≤ 19 y or after menarche in girls

a-Neonatal acne:

Neonatal acne (acne neonatorum) can be seen in the first four weeks after birth and can be caused by neonatal as well as maternal androgens with resultant increased sebum secretion from sebaceous glands which are typically sensitive to androgen stimulation **(29).**

b- Infantile acne:

Infantile acne is severe acne can develop with scarring, and there is an increased risk for acne later in the adolescent years as well aspositive family history of acne**.** Most infantile acne is self-limited and not associated with underlying endocrine pathology **(28).**

c- Mid-childhood acne:

Mid-childhood acne presents primarily on the face with a mixture of comedones and inflammatory lesions in children between the ages of 1 and 7 years, as children in this age group do not generally produce significant levels of adrenal or gonadal androgens, true acne in these children is rare and should raise the suspicion for hyperandrogenism. Exogenous sources of androgens have also been known to cause acne in children, although being uncommon **(30).**

d-Preadolescent Acne:

Acne may be the first sign of pubertal maturation. Preadolescent acne is characterized by a predominance of comedones on the forehead and central face (the so-called "T-zone") with relatively few inflammatory lesions. Early presentation may include comedones of the ear **(31).**

B. Premenstrual acne:

Studies of adolescent and adult females reflect worsening of comedonal and/or inflammatory acne in the late luteal phase of the menstrual cycle in various females that leads to the term, premenstrual acne; also, there are links to hormonal level fluctuations, prostaglandin PGE2, adrenal androgens, genetic issues in some as well as other factors. Sebaceous glands are affected by various hormonal/ androgen levels and have surface cell receptors that can be stimulated by androgens and hormonal changes in menstruation **(32).**

C. Adult-onset acne:

Adult-onset acne is defined as chronic inflammatory disease of the pilosebaceous units occurring beyond the age of 25 years. It commonly affects females (14%) between the age of 25 and 50 years. It is described as a predominantly inflammatory, mild-to-moderate form, characterized by papules and pustules, mainly located on the lower third of the face, jaw line, and neck, with rare and non-prominent comedonal lesions. The pathogenesis of post-adolescent acne is still not exactly understood. The role of circulating hormones remains controversial **(32).**

There are two distinct types of adult-onset acne:

1. **Persistent acne:** Continuation of acne from adolescence to adult life or middle age. It is characterized by deep-seated painful inflammatory lesions, mainly papules, and nodules commonly involving jaw line, lower third of face and neck **(33).**
2. **Late-onset acne:** Acne occurring for the first time after the age of 25 years**.** Chin and sporadic acne are recalcitrant in nature. Etiology may embrace systemic illness, or it may be idiopathic **(33).**

D. Acne fulminans:

Acne fulminans (AF), also known as acne maligna, it is a rare and severe form of nodular and ulcerative necrotic acne vulgaris with unknown etiology, acute onset and systemic involvement is always present most commonly in male teenagers. It is characterized by sudden onset of highly inflammatory and ulcerative necrotic lesions on the chest, presternal, shoulders, arms and more rarely on the face. Lesions always occur in patients with mild to moderate acne. The general health status is impaired, with fever, loss of appetite, weight loss, myalgias, arthralgias, and polyarthritis of large joints. Sometimes, erythema nodosum, aseptic osteolysis, hepatosplenomegaly or myositis may also be associated. The SAPHO syndrome refers to a group of diseases involving musculoskeletal and dermatological features: Synovitis, Acne, Pustulosis,

Hyperostosis and Osteitis **(34)**.

E. Acne conglobata:

Acne conglobata (Latin: conglobate: to form into a ball or globe); is a chronic, severe nodulocystic acne with deep, interconecting abscesses and cysts draining purulent contents onto the skin. It can be present at any age from infancy to adulthood, though it is more commonly manifested in adulthood. Acne conglobata has been found on the face, scalp, chest, extremities (upper arms, shoulders, thighs), axillae, buttocks and/or groin**.** The cause of acne conglobata is not clear. It is recorded as part of the follicular occlusion triad that includes acne conglobata, hidradenitis suppurativa and dissecting cellulitis of the scalp; adding pilonidal sinus to this group has called it a tetrad. They have a pathological feature in common identified as being disorders that involve follicular occlusion in body areas with apocrine glands. These conditions are usually found as one disorder (i.e., acne conglobata or hidradenitis suppurativa singly), but can occur in variable combinations with other conditions **(35).**

F. Acne inversa (Hidradenitis suppurativa):

Hidradenitis suppurativa (HS) is a chronic, inflammatory folliculitis typically found in intertriginous regions (i.e., axilla, submammary folds, inguinal area, perianal region). It commonly found in the late adolescent years through the third decade of life with increased prevalence in females and African Americans, but any age group and race can be affected. With disease progression, there can be widespread abscesses, sinus tracts, and skin destruction with scarring; pain, pruritus, malodor, embarrassment, and loss of self-esteem **(36).**

Mechanical Acne:

Acne mechanica can be arised from skin friction or pressure in sports, music, neurology (i.e., tics) and others including over-zealous skin washing, wearing tight leotards or helmets as well as other clothes or devices.The pathophysiologic factors of mechanical acne include alteration of the skin barrier and activation of the innate immunity of the skin following mechanical injury. Maskne is a new term created during the 2020 coronavirus disease (COVID-19) pandemic. It refers to a subset of acne mechanica resulting from common reusable fabric mask-wearing to control the pandemic all over the world. Underlying pathophysiology directly relates to the novel skin microenvironment and textile–skin friction created by mask-wearing **(37).**

G. Acne excoriee:

Acne excoriee is caused by scratching and picking of acne lesions trying to remove them as patient thought that this can fix acne appearance, he also feels relief at the time of picking followed by a strong sense of subsequent regret as picking leads to tenderness or bleeding **(38).**

H. Steroid induced acne:

Steroid acne is an acne-like skin condition that occurs in people with high levels of circulating corticosteroids. Steroid acne most often affects adolescent or adult patients who have been taking moderate or high doses of oral steroids such as prednisone or dexamethasone for several weeks or patients with underlying medical conditions as in Cushing disease. Steroid acne commonly occurs on the chest but may also develop on the face, neck, back and arms. The lesions tend to be more uniform in appearance than is usual with acne **(39).**

I. Chemical acne

Chemical acne refers to the worsening of acne vulgaris due to various chemicals that include cosmetics (acne cosmetica), tars, emollient oils (skin or bath), detergents, hair products (i.e., oils, creams), chlorinated hydrocarbons (chloracne) and others **(40)**.

References

1. **Stamu- O'Brien, C., Jafferany, M., Carniciu, S., et al., (2021).** Psychodermatology of acne: psychological aspects and effects of acne vulgaris. Journal of cosmetic dermatology, 20(4), 1080-1083.
2. **Sánchez Viera M. (2015).** Management of acne scars: fulfilling our duty of care for patients. The British journal of dermatology, 172 Suppl 1, 47–51
3. **Li, Z. J., Choi, H. I., Choi, D. K., et al., (2012).** Autologous platelet- rich plasma: a potential therapeutic tool for promoting hair growth. Dermatologic Surgery, 38(7pt1), 1040-1046.
4. **Bergler- Czop, B. (2014).** The aetiopathogenesis of acne vulgaris–what's new?. International journal of cosmetic science, 36(3), 187-194.
5. **Clayton, R. W., Göbel, K., Niessen, C. M., et al.,. (2019).** Homeostasis of the sebaceous gland and mechanisms of acne pathogenesis. The British journal of dermatology, 181(4), 677–690.
6. **Zhang, L., Li, W. H., Anthonavage, M., & Eisinger, M. (2006).** Melanocortin-5 receptor: a marker of human sebocyte differentiation. Peptides, 27(2), 413–420.
7. **Qidwai, A., Pandey, M., Pathak, S., et al.,. (2017).** The emerging principles for acne biogenesis: a dermatological problem of puberty. Human Microbiome Journal, 4, 7-13.
8. **Kim, J. (2005).** Review of the innate immune response in acne vulgaris: activation of Toll-like receptor 2 in acne triggers inflammatory cytokine responses. Dermatology, 211(3), 193-198.
9. **Sahdo, B., Särndahl, E., Elgh, F., et al.,. (2013).** Propionibacterium acnes activates caspase- 1 in human neutrophils. Apmis, 121(7), 652-663.
10. **Farfán, J., Gonzalez, J. M., & Vives, M. (2022).** The immunomodulatory potential of phage therapy to treat acne: a review on bacterial lysis and immunomodulation. PeerJ, 10, e13553.
11. **Dreno, B., Gollnick, H. P., Kang, S., et al., (2015).** Understanding innate immunity and inflammation in acne: implications for management. Journal of the European Academy of Dermatology and Venereology : JEADV, 29 Suppl 4, 3–11.
12. **Harder, J., Tsuruta, D., Murakami, M., et al., (2013).** What is the role of antimicrobial peptides (AMP) in acne vulgaris?. Experimental Dermatology, 22(6), 386-391.
13. **Rokowska-Waluch, A., Pawlaczyk, M., Cybulski, M., et al., . (2016).** Stressful events and serum concentration of substance P in acne patients. Annals of dermatology, 28(4), 464-469.
14. **Danby F. W. (2014).** Ductal hypoxia in acne: is it the missing link between comedogenesis and inflammation?. Journal of the American Academy of Dermatology, 70(5), 948–949.
15. **Greywal, T., Kusari, A., Han, A. M., et al., (2022).** Severe acne and its variants: Exploring its natural history and heritability. Pediatric Dermatology, 39(4), 535-540.
16. **Balachandrudu, B., Niveditadevi, V., & Rani, T. P. (2015).** Hormonal pathogenesis of acne-simplified. International Journal of Scientific Study, 3(1), 183-185.
17. **Ebede, T. L., Arch, E. L., & Berson, D. (2009).** Hormonal treatment of acne in women. The Journal of clinical and aesthetic dermatology, 2(12), 16–22.
18. **Krowchuk, D. P. (2006):** Disorders of the skin. In: Greydanus DE, Patel DR, Pratt HD, eds. Essential Adolescent Medicine . New York: McGraw-Hill;:411–443.
19. **Zouboulis, C. C., Jourdan, E., & Picardo, M. (2014).** Acne is an inflammatory disease and alterations of sebum composition initiate acne lesions. Journal of the European Academy of Dermatology and Venereology : JEADV, 28(5), 527–532.
20. **Bakry, O. A., El Shazly, R. M., El Farargy, S. M., et al., (2014).** Role of hormones and blood lipids in the pathogenesis of acne vulgaris in non-obese, non-hirsute females. Indian dermatology online journal, 5(Suppl 1), S9–S16.
21. **Kucharska, A., Szmurło, A., & Sińska, B. (2016).** Significance of diet in treated and untreated acne vulgaris. Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii, 33(2), 81-86.
22. **Arlt, W., & Stewart, P. M. (2005).** Adrenal corticosteroid biosynthesis, metabolism, and action. Endocrinology and metabolism clinics of North America, 34(2), 293–viii.

23. **Elsaie M. L. (2016).** Hormonal treatment of acne vulgaris: an update. Clinical, cosmetic and investigational dermatology, 9, 241–248.
24. **Shibata, M., Katsuyama, M., Onodera, T., et al.,. (2009).** Glucocorticoids enhance Toll-like receptor 2 expression in human keratinocytes stimulated with Propionibacterium acnes or proinflammatory cytokines. Journal of Investigative Dermatology, 129(2), 375-382.
25. **Chatzikonstantinou, F., Miskedaki, A., Antoniou, C., et al.,. (2019).** A novel cognitive stress management technique for acne vulgaris: a short report of a pilot experimental study. International journal of dermatology, 58(2), 218–220.
26. **Bowe, W., Joshi, S. and Shalita, A. (2010):** Diet and acne. J Am Acad Dermatol; 63: 124-41.
27. **Kraft, J., & Freiman, A. (2011).** Management of acne. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne, 183(7), E430–E435.
28. **Eichenfield, L. F., Krakowski, A. C., Piggott, C., et al., (2013**). Evidence-based recommendations for the diagnosis and treatment of pediatric acne. Pediatrics, 131 Suppl 3, S163–S186.
29. **Tempark, T., & Shwayder, T. (2014).** Dermatology issues in the newborn period. Pediatric and Adolescent Dermatology, 6.
30. **Admani, S., & Barrio, V. R. (2013).** Evaluation and treatment of acne from infancy to preadolescence. Dermatologic therapy, 26(6), 462-466.
31. **Piggott, C., Eichenfield, L. and Lucky, A. (2011):** Acne in children. In: Shalita AR, Del Rosso JQ,Webster GF, eds. Acne Vulgaris. New York,NY: Informa Healthcare;182–197.
32. **Hermanns-Lê, T., Hermanns, J. F., Lesuisse, M., et al.,. (2013).** Cyclic catamenial dermatoses. BioMed Research International, 2013.
33. **Marks, R. (2004).** Acne and its management beyond the age of 35 years. American journal of clinical dermatology, 5, 459-462.
34. **Zimmermann, P., & Curtis, N. (2019).** The role of Cutibacterium acnes in auto-inflammatory bone disorders. European journal of pediatrics, 178(1), 89–95.
35. **Au, J., Gibson, F. T., & Aronson, I. K. (2020**). Follicular occlusion triad: an isotopic response or adverse effect of rituximab?. Dermatology online journal, 26(2), 13030/qt0wr0k6fx.
36. **Goldburg, S. R., Strober, B. E., & Payette, M. J. (2020).** Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis. Journal of the American Academy of Dermatology, 82(5), 1045–1058.
37. **Teo, W. L. (2021**). The "Maskne" microbiome–pathophysiology and therapeutics. International journal of dermatology, 60(7), 799-809.
38. **Khumalo, N. P., Shaboodien, G., Hemmings, S. M., et al., (2016).** Pathologic grooming (acne excoriee, trichotillomania, and nail biting) in 4 generations of a single family. JAAD Case Reports, 2(1), 51-53.
39. **Munroe, M., & Crutchfield, C. (2003).** Steroid acne. Dermatology nursing, 15(4), 365.
40. **Mazioti, M. (2017).** Chemical environmental factors: Can they affect acne?. Indian Journal of Dermatology, Venereology and Leprology, 83, 522.