# Introduction

Acne vulgaris is a common disease with prevalence up to 80% during adolescence. It is characterized by chronic inflammation of the pilosebaceous units with the formation of comedones, erythematous papules and pustules and sometimes nodules or cysts ***(Garcia-Morales et al., 2010).***

The pathogenesis of acne is often associated with several factors, including androgen-induced increased sebum production, altered keratinisation, inflammation, and bacterial colonization of hair follicles on the face, neck, chest and back by propionibacterium acnes (P. acnes). Although early colonization with P. acne, family history might have important roles in the disease, exactly what triggers acne and how treatment affects the course of the disease remain unclear. Other factors such as diet have been implicated. Facial scarring due to acne affects up to 20% of teenagers. Acne can persist into adult hood, with detrimental effects on self-esteem ***(Williams et al., 2012).***

Large, well controlled, observational studies have demonstrated that diets high in dairy products are associated with an increase in the risk for and severity of acne ***(Keri and Rosenblatt, 2008).*** The relationship between milk and acne severity may be explained by the presence of normal reproductive steroid hormones in milk

or the enhanced production of polypeptide hormones such as Insulin-like growth factor (IGF-1), which can increase androgen exposure, and thus, acne risk. Other findings also describe an association between a high-glycemic-index diet and larger acne duration. In addition, randomized clinical trials have demonstrated that a low-glycemic-load diet can improve acne. No study has established a positive association between acne and chocolate, saturated fat, or salt intake ***(Ferdowsian and Levin, 2010).***

# Aim of the Work

The aim of this work is to evaluate the role of IGF-1 as a pathogenic factor in the pathogenesis of acne vulgaris and its relation with the severity of the disease.

# Chapter (1): Acne Vulgaris

Acne vulgaris remains one of the most common diseases ***(Adityan et al., 2009).*** Acne is a chronic condition of the pilosebaceous units which is characterized by inflammatory lesions (papules, pustules, and nodules) and non inflammatory lesions (open and closed comedones) ***(Bowe et al., 2012),*** and less frequently pseudocysts, and ultimate scarring in few of them ***(Rathi, 2011).***

## 1. Epidemiology:

Acne is a very common disease. Its prevalence is about 58% of women and 40% off men, 95-100% off 16-17-year-old males and 83-85% of 16-17 year old females ***(Goodman, 2001).*** Acne persists into the 20s and 30s in around 64% and 43% of individuals, respectively ***(Bhate and Williams, 2013).*** The prevalence of clinical acne decreased significantly only after age 45 years as the vast majority of cases are below 23-25 years of age but 1% of males and 5% of female's exhibit acne lesions at 40 years of age ***(Goodman, 2001).***

Although often considered a disease of teenagers, in whom the prevalence is reported to be from 70% to 87%, 12 years of age is no longer considered the lower end of the age range for acne onset. Acne occur at different ages, including neonates, infants, and young children, and may be associated with differential diagnosis or systemic pathology that differs from teenagers ***(Eichenfield et al., 2013).***

Post-adolescent acne predominantly affects women, in contrast to adolescent acne which has a male predominance ***(Collier et al., 2008).*** It is unclear if ethnicity is truly associated with acne. Black individuals are more prone to post-inflammatory hyperpigmentation and specific subtypes such as 'pomade acne'. The heritability of acne is almost 80% in first-degree relatives. Acne occurs earlier and is more severe in those with a positive family history ***(Bhate and Williams, 2013).***

# 2. Pathogenesis of acne:

## A. Aetiology

The pathophysiology of acne vulgaris is multifactorial ***(Bhambri et al., 2009)*** and is related to the consequences of abnormal follicular epithelial proliferation and keratinization, excess sebum production. Intra-follicular propionibacterium acnes (P. acnes) colonization, and inflammation (fig. 1) ***(Knutsen-Larson et al., 2012).***

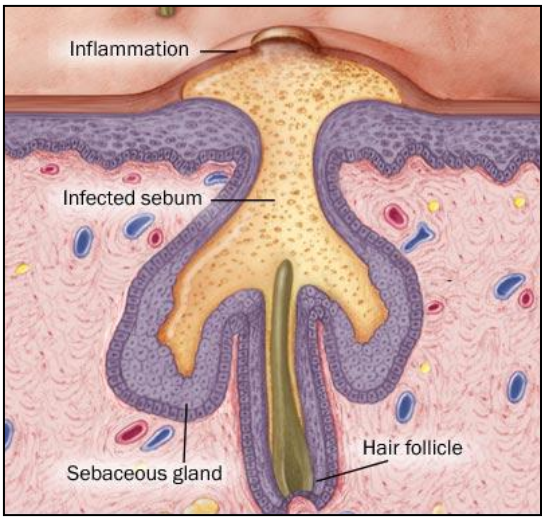


**Fig. (1):** How acne develops ***(Mayo Clinic Staff, 2014)***

Altered follicular growth, differentiation, and sebaceous hyperplasia are the most important factors, because they combine to induce the microcomedo, the primary lesion of acne. The microcomedo can evolve into either a non-inflammatory comedo or become inflamed and present as a papule, pustule, or nodule (Fig. 2) ***(Rademaker et al., 2013).***

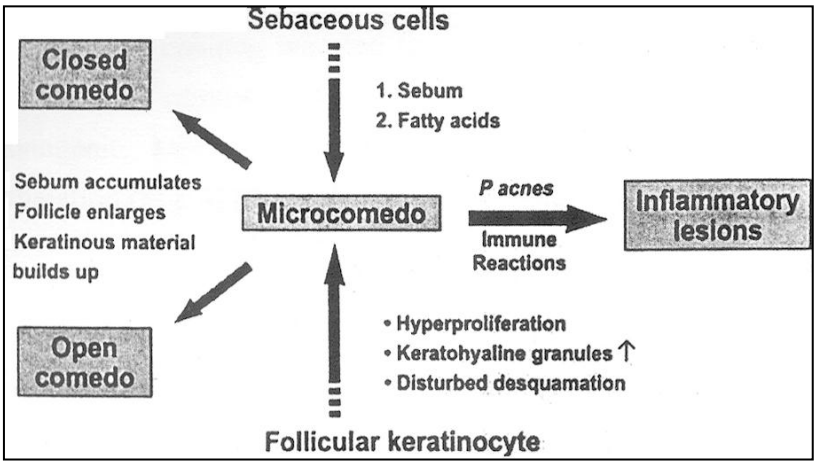


**Fig. (2):** Lesion progression in acne ***(Rademaker et al., 2013)***

## 1) Seborrhea

Role of sebaceous glands in the pathogenesis of acne has so much been recognized so that the disease is standardly classified as a sebaceous gland disorder ***(Kuiri-Hänninen et al., 2013).***

Patients with acne secrete more sebum than normal individuals and severity of acne is related to the degree of seborrhea which is directly dependant on the size and rate of growth of sebaceous glands, which is under the control of androgens ***(Tóth et al., 2011).***

Androgens play an essential role in increasing the size of sebaceous glands and stimulating sebum production as well as in stimulating kerationcyte proliferation in the ductus suboglandularis and the acro infundibulum. Acne-prone skin exhibits a higher androgen receptor density and higher 5 α-reductase activity than the non involved skin (Fig. 3) ***(Kuiri-Hänninen et al., 2013).***

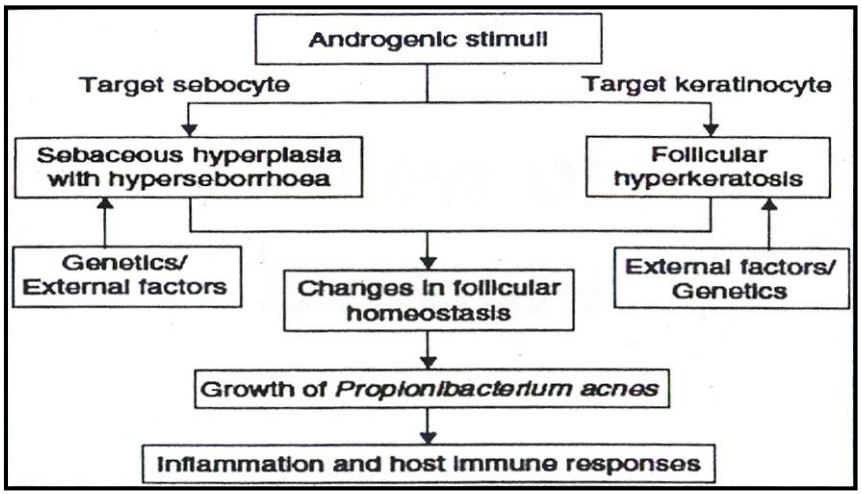


**Fig. (3):** A proposed overall theory for acne pathogenesis
***(Kuiri-Hänninen et al., 2013)***

There are two types of 5 α-reductase, type I and type II ***(Zouboulis, 2004a).*** Type I predominates in the sebaceous glands of the face and scalp and converts free testosterone to dihydrotestosterone, type II is found in the sebaceous glands of areas not affected by acne. These results can explain the predominance of facial acne ***(Sachdeva, 2010).***

**2) <u>Follicular hyperkeratinization and comedone formation</u>**

Increased sebum production and follicular hyperkeratosis result in the development of microcomedones ***(Zaenglein and Thiboutot, 2007).*** This begins in the keratinized lining of the upper portion of the follicle (Fig. 4). Comedone formation occurs when the corneocytes, which are normally shed into the lumen of the follicle and extruded through the follicular ostium, are retained and accumulate, leading to hyperkeratosis ***(Kurokawa et al., 2009).***

As the comedone expands, the sebaceous lobule undergoes regression. Because of the very narrow opening to the skin surface, there is initially an accumulation of loosely packed shed keratinocytes and sebum, with expansion of comedo, the contents become closely packed, creating whorled lamellar concretions. As the forces increase, rupture of the comedo wall with extrusion of immunogenic keratin and sebum occurs, with resultant inflammation (Fig. 4) ***(Zaenglein and Thiboutot, 2007).***

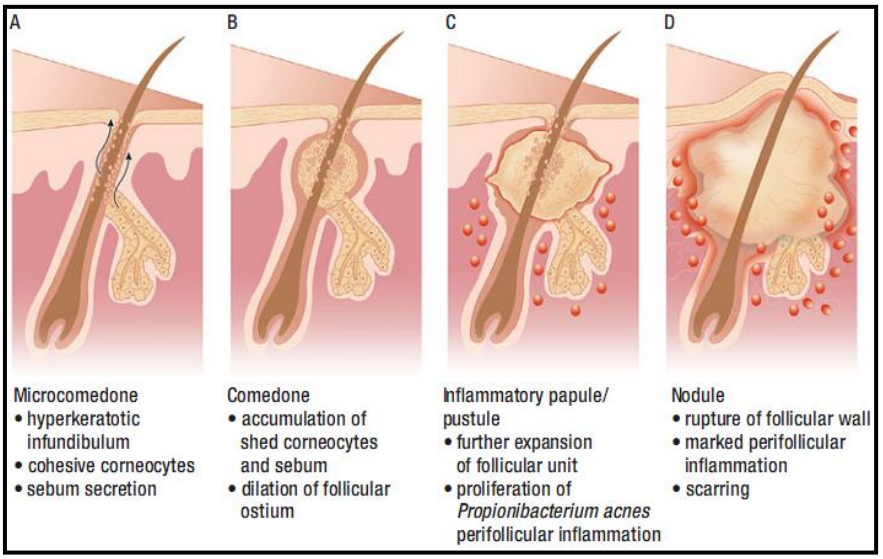


**Fig. (4):** A-D. Acne pathogenesis ***(Bellew et al., 2011).***

### 3) Colonization

Propionibacterium acnes are gram-positive anaerobic bacillus and were first isolated from the skin of acne patients. It is a commensal species in humans, residing the follicle and related apparatus ***(Wainwright et al., 2011).*** It is not pathogenic by normal standards because it is present in nearly 100% of healthy persons ***(Jappe et al., 2002).***

Generally there is no significant difference in the microflora of the skin surface samples from acne and healthy persons ***(Kwon et al., 2013).***

Propionibacterium acnes contribute to the production of acne. P. acnes is primarily responsible for inflammatory acne. It acts through the induction of cytokine secretion and release of substances such as proteases and hyaluronidases ***(Jugeau et al., 2005).***

One mechanism is via humoral and cell-mediated immunity as well as complement activation. Results indicate that keratinocytes and sebocytes, as major components of pilosebaceous unit, may act as immune cells and may be activated by P. acnes via Toll-Like Receptors (TLRs), CD14 and through CD1 molecules. They may recognize altered lipid content in sebum, followed by the production of inflammatory cytokines ***(Kurokawa et al., 2009).***

The Toll-Like Receptor 2 (TLRs-2) has been implicated in the pathogenesis of acne. TLR-2 is a pattern recognition receptor that is activated by P. acnes ***(Kurokawa et al., 2009).*** They are a class of receptors that mediate the recognition of microbial pathogens by immune cells such as monocytes, macrophages and PMNs, Toll-Like Receptor 2 (TLR-2) is found on the surface of monocytes surrounding acne follicles. P. acnes has been shown to release pro-inflammatory mediators (IL-1 α, IL-8 and TNF-α) through this TLR2 pathway ***(Zaenglein and Thiboutot, 2008).***

The increase in IL-8, results in neutrophil recruitment, the release of lysosomal enzymes, and subsequent disruption of the follicular epithelium ***(Zaenglein and Thiboutot, 2008).***

Release of the cytokine interleukin-1α (IL-1α) by keratinocytes of the sebaceous duct was pivotal in the life cycle of the comedone, mediating both its development and its spontaneous resolution ***(Joanne et al., 2013).***

### 4) Inflammation

Inflammation is the key component of acne and the major reason for its morbidity and sequelae (pigmentary disturbances and scarring). Inflammation is dominated by CD4+ T helper cells and a macrophage infiltrate, and that these cells were present in clinically normal skin around uninvolved follicles from acne patients in acne-prone sites. The data therefore showed that subclinical inflammatory events occur before hyper-proliferative events and are the earliest events seen in acne lesion formation ***(Dréno et al., 2013).*** The type of inflammatory response also plays a role in the development of scarring. Early nonspecific inflammation results in less scarring than does a delayed specific inflammatory response ***(Humbert, 2008).***

## B. Factors affecting acne development

### 1) Role of diet:

A potential role for diet in acne is controversial, however, association between acne and intake of milk has been reported. Natural hormonal components of milk or other bioactive molecules in milk could excacerbate acne. Milk and other dairy products contain 5-α reduced steroid hormones and other steroid precursors of dihydrotestosterone (DHT) that drive sebaceous glands (and likely pilar keratinocytes) function. Drinking milk causes a direct rise in insulin-like growth factor-1 (IGF-1) through a disproportionate elevation in blood sugar and serum insulin levels ***(Danby, 2005).***

Studies have shown that the diagnosed acne patients tend to have lower levels of vitamin A circulating in their blood stream than those who are acne free. In addition, people with severe acne also tend to have lower blood levels of vitamin E ***(El-Akawi et al., 2006).***

A difference in the prevalence of acne between non westernized and fully modernized societies has been noted. Diet has been suggested to be a factor, but many other environmental influences are also at play ***(Cordain et al., 2003).***

**2) <u>Role of genetics:</u>**

Genetic influences may determine an individual's susceptibility to comedogenesis, as well as the severity of the disease course ***(Masahiko and Mosaaki, 2001).*** There has previously been some evidence that acne is an inherited disease. A study of sets of twins with acne showed that 98% of identical twin pairs were affected compared with only 46% of dizygotic twin pairs ***(Goulden et al., 1999).***

Interestingly, evidence of direct genetic association of acne with androgen and lipid abnormalities has been observed: neonatal acne was found to be associated with familial hyperandrogenism, and inadequate activity of steroid 21-hydroxylase (CYP21) gene mutations have been reported to be involved in the pathogenesis of acne, and identical sebum excretion rates were described in homozygotic but not in heterozygotic twins. Moreover, the associations with biochemical markers involve lipids: lower

serum levels of apolipoprotein A1 and lower essential fatty acid levels in sebaceous wax esters and in twins acne rather than in non-acne twins ***(Zouboulis, 2010).***

The tendency to develop acne runs in families. For example, school-age boys with acne often have other members in their familywith acne as well. A family history of acne is associated with an earlier occurrence of acne and an increased number of retentional acne lesions ***(Ballanger et al., 2006).***

### 3) Role of stress

Patients frequently complain of acne flares in concomitance with anxiety, stress or frustration. In a series of interviews with consecutive patients with acne, it was revealed that 55% of them noticed a close chronological association between episodes of emotional stress and exacerbation of their skin condition ***(Picardo et al., 2009).***

Cortisol the main glucocorticoid in humans, is considered a stress hormone because its blood level increases under conditions of psychosocial and physical stress ***(Evolahti et al., 2006).*** It can excacerbate inflammatory reactions in acne vulgaris through enhancement of TLR2 gene expression in keratinocytes ***(Shibata et al., 2009).***

Increased corticosteroids and adrenal androgens, both hormones known to worsen acne, are released during periods of emotional stress ***(Ali and Al-Niaimi, 2013).***

In addition receptors for corticotrophin releasing hormones have been identified on human sebocytes, especially acne-involved skin. Corticotrophin-releasing

hormone (CRH) is one of neuroendocrine factors that contributes to the development and exacerbation of acne ***(Ganceviciene et al., 2009).*** It has also been reported that antidepressive medication can improve acne ***(Ali and Al-Niaimi, 2013).***

**4) Role of weight:**

Obesity is frequently accompanied by peripheral hyperandrogenism, which may be associated with increased sebum production and the development of severe acne ***(Min-Chien et al., 2006).***

With hyperinsulinemia, there may be an increase in androgen production, resulting in a stimulation of sebaceous glands. It may be that in a small subset of obese acne patients, hyperinsulinemia may stimulate endogenous androgen production resulting in development or worsening of acne. For this cohort of acne patients, a weight loss diet may be indicated ***(Kidson, 1998).***

**5) Role of sexual activity:**

There are misconceptions regarding variably too little or too much sexual activity and acne. First, that too much sex or masturbation may worsen acne. Second, that somehow when females begin having a regular sex life their acne will be improved. Acne is occurring at a similar stage as sexual adventure and this may be a plausible reason for the uninformed association of the two. One may also possibly look at the beneficial effect of oral contraceptives on acne as a possible explanation for improvement associated with the beginning of sexual activity in females ***(Elsenbrucch et al., 2003).***

### 6) Role of dirt and infection:

There is no evidence that either surface sebum or surface bacteria aggravates acne. Therefore, in order for a soup or topical antibacterial agent to be of aid in the therapy of acne, the topical agent would have to remove the lipids or the bacteria (or both) from within the follicle. Certainly, the action of soap will not remove open or closed comedones. Any dermatologist can readily describe cases of acne that he or she has been in compulsive washers. It would appear that washing as a therapeutic measure is often over-emphasized, but many acne patients do not have a pronounced seborrhea, and washing or cleansing to remove this excessive oil, if not overdone, provides subjective benefit ***(Ramos-e-Silva and Carnneiro, 2009).***

### 7) Role of smoking:

Impaired vaso-reactivity, collagen synthesis and wound healing may be partially responsible for the effect of smoking on the development of acne ***(Freiman et al., 2004).***

Although there is evidence that smokers have a lower incidence of some inflammatory and neuro-degenerative diseases ***(Sopori, 2002).*** A small retrospective study suggested that smoking might have different effects on acne in women and men ***(Chuh et al., 2004).*** Smoking is protective in the development of inflammatory acne at least in girls. The anti-inflammatory effects of smoking may inhibit the development of papulopustular acne ***(Rombouts et al., 2007).***