INTRODUCTION

Acne vulgaris is the most common skin disorder affecting adolescents and young adults. It commonly affects the face, neck and upper trunk**.** Even though it is not life threatening disease, it can produce cutaneous scars and emotional stress **(*Zaenglein et al., 2016).***

The pathogenesis of acne is multifactorial and not completely understood. It involves several key changes in the pilosebaceous unit, follicular hyperkeratinization, increase sebum production, *Propionibacterium acne* colonization and perifollicular inflammation ***(Dawson et al., 2013; Suh et al., 2015).***

Androgen also contributes to this process by stimulating the growth and secretory activity of sebaceous glands. Acne lesions can be subdivided into two main categories: (i) non-inflammatory or comedonal acne, which includes whiteheads and blackheads. (ii) Inflammatory acne lesions, which include papules, pustules, nodules and cysts ***(Dawson et al., 2013; Echenfield et al., 2015).***

Since 1971, isotretinoin (13-cis-retinoic acid, 13-cis-RA) has been available for the treatment of acne ***(Li et al., 2012).*** It is highly effective treatment for patients with nodulocystic acne and moderate to severe acne resistant to conventional therapy ***(Merritt et al., 2009).*** It affects all major etiological factors

involved in the pathogenesis of acne vulgaris ***(Merritt et al., 2009).***

In addition to a variety of clinical side effects, isotretinoin may cause dyslipidemia, increased liver enzymes and reduction of biotinidase activity ***(Rademaker et al., 2010).***

Increased liver enzymes during isotretinoin treatment are a sign of isotretinoin-induced liver dysfunction ***(Vieira et al., 2012).*** This drug may also affect other enzymes, such as cystathionine -β-synthase, which is the responsible enzyme for Homocysteine metabolism ***(Finkelstein et al., 2000)*** and may cause hyperhomocysteinaemia ***(Roodsari et al., 2010).***

Homocysteine (Hcy) is a sulfur-containing amino acid not used in protein synthesis and an intermediate product of the methionine cycle ***(Lynn et al., 2016).***

Hyperhomocysteinaemia is an independent risk factor of coronary artery disease. It increases thrombogenicity, oxidative stress status and endothelial dysfunction ***(Schaffer et al., 2014).***

AIM OF THE WORK

In this work, we aimed to estimate homocysteine level in patients receiving isotretinoin treatment for moderate to severe acne vulgaris.

ACNE VULGARIS

Definition:

The word acne itself is a term derived from a Greek word "ACME" which means prime of life ***(Khan, 2018).***

"ACNE" is defined as a common chronic skin disease involving blockage and/or inflammation of pilosebaceous units (hair follicles and their accompanying sebaceous gland). It can present as non-inflammatory lesions, inflammatory lesions or a mixture of both. It mostly affects the face, but also could have its effects on the back and chest ***(Dawson et al., 2013; Zaenglein et al., 2016).***

Epidemiology:

Acne is considered as one of the most prevalent skin conditions, as it is affect more than 85% of the teenagers around the world. It typically starts with puberty and usually it will resolve slowly as the person reaches 20s; although some people continue to have acne until 40 and 50 years. The Acne develops for both men and women mostly equally. However, some races are may get affected more than others, as cystic acne is prevalent in the Mediterranean region ***(Szepietowski et al., 2018).***

There is often significant physical and psychological morbidity such as permanent scarring, poor self-image, depression and anxiety ***(Zaenglein et al., 2016).***

The direct cost only of the disease is estimated to exceed three billion dollars per year ***(Bhate et al., 2013).***

Pathogenesis:

Generally, the current understanding of pathogenesis is continuously evolving but basically acne is considered as a multifactorial inflammatory disease affecting the pilosebaceous follicles of the skin ***(Dawson et al., 2013, Suh et al., 2015).***

Acne involves the interplay of four main factors:

- Follicular hyperkeratinization.
- Microbial colonization with *Propionibacterium acne*.
- Increase Sebum production.
- Complex inflammatory mechanisms that involve innate and acquired immunity ***(Gollnick et al., 2015).***

Additional studies have suggested that neuro endocrine regulatory mechanisms, diet, genetic and non-genetic factors all may contribute to the multifactorial process of acne pathogenesis ***(Szepietowski et al., 2018).***

- The primary and pathognomonic lesion of acne is the microcomedone, a microscopic lesion invisible to the naked eye, or lesions such as papule, pustule, or nodule ***(Bissonnette, 2011; Knutsen-Larson et al., 2012).***

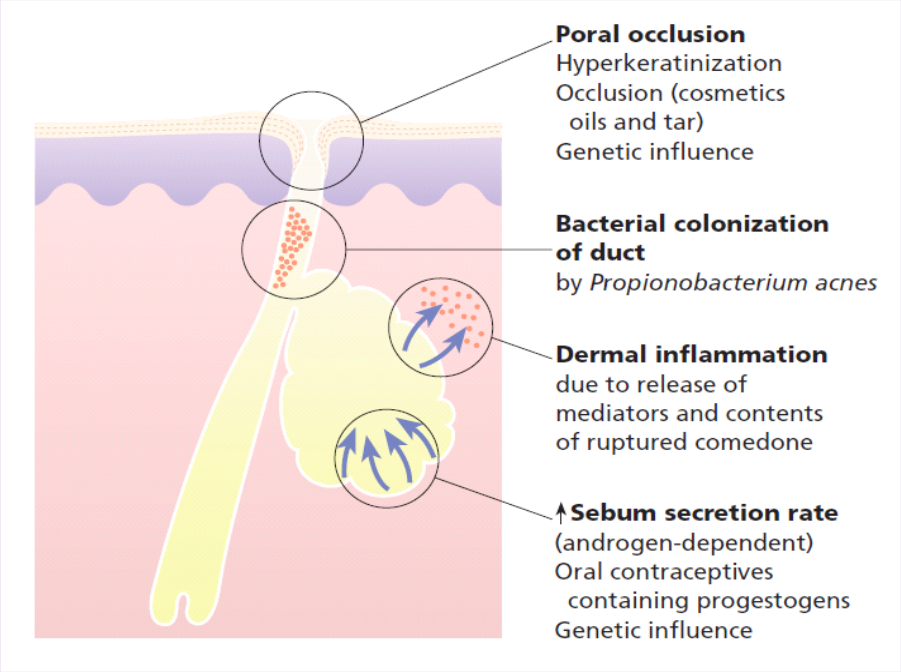

Figure (1): Showing the pathogenesis of acne vulgaris ***(Gollnick et al., 2015).***

The first step is believed to be the formation of the microcomedo, which is the precursor to all other lesions, there is increased proliferation and reduced shedding of intra follicular keratinocytes causing the pilosebaceous unit to become obstructed ***(Cunliffe et al., 2000 and Thiboutot et al., 2009).*** In addition to, it increases production of sebum due to stimulation of the sebaceous glands and follicular corneocytes, in particular by androgens, usually around the puberty ***(Zaenglein et al., 2008).***

Growth of sebaceous glands and increased sebum production are both induced by androgens, particularly dihydrotestosterone (DHT). In men, DHT is mainly derived from testosterone, while in women; androstenedione is the main precursor ***(Knutsen-Larson et al., 2012).***

As sebum and keratinocyte debris accumulate in the microcomedo, larger, clinically visible closed or open comedones develop. Colonization of the infra infundibulum of follicles by *Propionibacterium acne* and the release of inflammatory mediators into the surrounding perifollicular dermis together with attraction of immunocompetent cells leads to the development of inflammatory lesions ***(Beylot et al., 2014).***

Propionibacterium acne stimulates inflammation and an immune response through a variety of mechanisms ***(Beylot et al., 2014)*** as shown in table (1)

Table (1): The role of *Propionibacterium acne* in acne pathogenesis ***(Beylot et al., 2014)***

1	P.acne produces lipases, proteases, hyaluronidases and neutrophil chemotactic factors.
2	P.acne induces the production of TNF-α, IL-1α and IL-8.
3	P.acne induces the expression of pro inflammatory cytokines IL-8, IL-1β and TNF-α by human monocytes in acne patients and in controls.
4	Inflammation triggered through TLR2 is important in the pathogenesis of acne and P.acne was shown to induce monocyte cytokine production (IL-12, IL-8) through a TLR2-dependent pathway.
5	An increase in TLR2, TLR4 and MMP-9 expression by human keratinocytes occurred with incubation with P.acne fractions.
6	P.acne induces IL-8 and β-defensin-2 expression in keratinocytes via TLR2 and TLR4.
7	P.acne induces keratinocytes growth in vitro.
8	P.acne may be involved in the formation of the microcomedones.
9	P.acne biofilm may lead to the increased cohesiveness of corneocytes seen in acne.

IL: interleukin; TNR: tumor necrotic factor; TLR: toll like receptor; MMP: metalloproteinase

Clinical picture:

Acne is typically found in sites with well-developed sebaceous glands, most often the face and upper trunk.

Acne lesions can be subdivided into two main categories:

- Non-inflammatory or comedones, which include whiteheads and blackheads.
- Acne lesions, which include papules, pustules, nodules and cysts ***(Dawson et al., 2013; Echenfield et al., 2015).***

Non-inflammatory lesions

It consists of open and closed comedones, closed comedones (whiteheads) are generally small (~1 mm), skin-colored papules with no apparent follicular opening or associated erythema. In contrast, open comedones (blackheads) are dome-shaped papules with a conspicuous dilated follicular opening that is filled with an inspissated core of shed keratin ***(Dawson et al., 2013).***

Melanin deposition and lipid oxidation within the debris may be responsible for the black coloration. "Ice-pick"-type scarring sometimes results from comedones alone ***(Habif, 2010).***

Inflammatory acne lesions:

It also originates with (micro) comedo-formation, followed by the development of papules, pustules, nodules and cysts of varying severity. Erythematous papules range from 1 to 5 mm in diameter. Pustules tend to be approximately equal in size and are filled with white pus and normal flora. As the severity of lesions progresses, nodules form and become markedly inflamed, indurated and tender. The cysts of acne are deeper and filled with a combination of pus and serosanguineous fluid ***(Dawson et al., 2013).***

In patients with severe nodulocystic acne, these lesions frequently coalesce to form large, complex inflamed plaques that can include sinus tracts ***(Zaenglein et al., 2008).***

Scarring can be a complication of both inflammatory and non-inflammatory acne. There are four general types of acne scars, namely; ice pick, rolling, boxcar and hypertrophic. Ice pick scars are narrow, deep scars that are widest at the surface of the skin and taper to a point in the dermis. Rolling scars are shallow, wide scars that have an undulating appearance. Boxcar scars are wide, sharply demarcated scars. Unlike ice pick scars, the width of boxcar scars is similar at the surface and base. In rare cases, especially on the trunk, the scars may be hypertrophic ***(Friedlander et al., 2010; Mancini et al., 2011).***

Acne Assessment:

Methods of measuring the severity of acne vulgaris include simple grading based on clinical examination, lesion counting and those that require complicated instruments such as photography, fluorescent photography, polarized light photography, video microscopy and measurement of sebum production ***(Adityan et al., 2009).***

The two commonly used measures are grading and lesion counting. Grading is a subjective method, which involves determining the severity of acne based on observing the dominant lesions, evaluating the presence or absence of inflammation and estimating the extent of involvement. Lesion counting involves recording the number of each type of acne lesion and determining the overall severity ***(Adityan et al., 2009; Nast et al., 2012).***

Acne patients were graded according to **the Global Evaluation Acne** (**GEA**) scale proposed in 2011 by the European Academy of Dermatology and Venereology ***(Dréno et al., 2011).***

Table (2): The Global Evaluation Acne (GEA) ***(Dréno et al., 2011)***

0	**Clear**	No lesions Residual pigmentation and erythema may be seen.
1	**Almost clear.**	Almost no lesions A few scattered open or closed comedones and very few papules.
2	**Mild Easily recognizable:**	Less than half of the face is involved. A few open or closed comedones and a few papules and pustules.
3	**Moderate**	More than half of the face is involved. Many papules and pustules, many open or closed comedones. One nodule may be present.
4	**Severe**	Entire face is involved, covered with many papules and pustules, open or closed comedones and rare nodules
5	**Very severe**	Highly inflammatory acne covering the face with presence of nodules.

Treatment of acne:

Treatment must be tailored to the individual patient, the type of acne, its severity, the patient's ability to use the treatment and their psychological state ***(Thiboutot et al., 2009).***

(I) Topical therapy:

The desired vehicle for topical agents depends on the skin type. Usually creams are use in dry or sensitive skin, gels or solutions for those with seborrheic skin. Lotions can be used in most skin types. Commonly used topical acne therapies include BP, salicylic acid, antibiotics, combination antibiotics

with BP, retinoid, retinoid with BP, retinoid with antibiotic, azelaic acid and sulfone agents ***(Araviiskaia and Dréno, 2016).***

1. Topical retinoid:

Topical retinoids are vitamin A derivatives, three active agents are available: tretinoin (0.025-0.1% in cream, gel and microsphere gel vehicles), adapalene (0.1%, 0.3% cream, or 0.1% lotion) ***(Thielitz et al., 2008).***

Retinoids are the core of topical therapy for acne because they are control the formation of micro-comedones, reduce the formation of lesions and existing comedones, decrease sebum production and normalize desquamation of the epithelium. It can repair the scarring and hyperpigmentation of the skin ***(Thielitz et al., 2008).***

These agents enhance any topical acne regimen and allow for maintenance of clearance after discontinuation of oral therapy. When combined with topical antimicrobials, it is more effective in inflammatory acne. A common side effect during the first few weeks of topical retinoid treatment is a flare up of acne. This should be however clear as the patient continuing with the treatment ***(Nast et al., 2012; Zaenglein et al., 2016)***.

2. Benzoyl peroxide (Bp):

Benzoyl peroxide is a potent bactericidal agent that reduces *P. acne* within the follicle by releasing free radical oxygen, which degrades the bacterial protein. It also has mild

comedolytic properties, no effect on sebum production and is particularly effective when used in combination with other therapies. Contrast to topical antibiotics, microbial resistance to benzoyl peroxide has not been reported ***(Stein Gold et al., 2016).***

3. Topical Antibiotic:

Topical antibiotics are widely used for the treatment of acne and are available alone as well as in combination with benzoyl peroxide or retinoids. Clindamycin and erythromycin represent the two most commonly utilized antibiotics and the formulations vary from creams and gels to solutions. Erythromycin are effective in treating inflammatory acne, but have limited efficacy against non-inflammatory lesions ***(Simonart and Dramaix, 2005).***

Monotherapy with topical antibiotics in the management of acne is not recommended because of the development of antibiotic resistance ***(Williams, 2012).***

4. Dapsone:

It has been suggested that dapsone's mechanism of action in the treatment of acne may be due to antimicrobial and anti-inflammatory effects. Dapsone gel (5%) can be used to reduce inflammatory as well as non-inflammatory acne lesions. This agent's lower cost makes, it more favorable for use in

developing countries however, it is not recommended as first-line therapy ***(Couthinho, 2010).***

5. Azelaic acid:

A natural dicarboxylic acid inhibits protein synthesis of the P. acnes species. It is an effective agent because it has bacteriostatic, anti-inflammatory, antioxidant and anti-keratinizing properties. Therefore, no bacterial resistance of P. acnes exists with azelaic acid. It has also been suggested that when azelaic acid is used in conjunction with clindamycin, benzoyl peroxide or α-hydroxy acids, it will be more effective in acne treatment ***(Gollnick et al., 2015).***

(II) Systemic Treatment:

Is required when acne is resistant to topical treatment, or it manifests as nodular lesions and leaves scarring. It is the preferred choice in the treatment of inflammatory lesions. Systemic treatment may also be required to prevent social embarrassment and psychological impairment in people suffering from acne. The most common systemic treatment includes oral antibiotics, hormonal agents and isotretinoin ***(Zaenglein et al., 2016).***

- **Oral antibiotics:**

Oral tetracycline derivatives, especially doxycycline and minocycline and less often macrolides (e.g. erythromycin, azithromycin) are prescribed for moderate to severe inflammatory

acne, which unresponsive to topical combinations. This class also has anti-inflammatory effects, including inhibiting chemotaxis and metalloproteinase activity. Previous guidelines recommended minocycline as superior to doxycycline in reducing P acne ***(Sinclair, 2005; Strauss et al., 2007).***

Azithromycin, erythromycin and clindamycin have anti-inflammatory activity and mainly work by reducing the levels of P. acne. Since these antibiotics are used repetitively at low doses for extended periods during acne treatment, increasing resistance has developed overtime which has resulted in limited use of these agents. To reduce resistance and improve the efficacy, oral antibiotics should be combined with topical benzoyl peroxide or retinoids ***(Katsambas and Dessinioti, 2008).***

- **Hormonal therapy:**

It is an established second-line treatment for female patients with acne and can be very effective; irrespective of whether or not the serum androgen levels are abnormal can be used as an alternative for adolescent and adult females. These hormones are most commonly given in the form of oral contraceptive pills ***(Arowojolu et al., 2012).***

- **Oral contraceptive pills (OCPs):**

A Cochrane review in 2009 demonstrated that the combined oral contraceptive pill compared with placebo significantly reduced inflammatory and non-inflammatory