Assessment of Plasma Malondialdehyde in Acne Patients on Isotretinoin Therapy

Thesis

Submitted for Partial Fulfillment of the Master Degree in Venereology and Andrology

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2018

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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 ***(Yentzer et al., 2010; Barnes et al., 2012; Zaenglein et al., 2016).***

The pathogenesis of acne is multi factorial and not completely understood. It involves several key changes in the pilosebaceous unit follicular hyper keratinization, 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; and (ii) inflammatory acne lesions, which include papules, pustules, nodules, and cysts ***(Dao et al., 2007; 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 ***(Cooper, 2003; Merritt et al., 2009).***

In addition to a variety of clinical side-effects, isotretinoin may cause dyslipidaemia, increased liver enzymes, and reduction of biotinidase activity ***(Schulpis et al., 1999; Zane et al., 2006; Kaymak et al., 2006; Rademaker et al., 2010).***

Increased liver enzymes during isotretinoin treatment are a sign of isotretinoin-induced liver dysfunction ***(Zane et al., 2006; Vieira et al., 2012).***

The most important problem related to the side effects of isotretinoin is that it reduces patients' compliance. Recently, Georgala et al. showed that isotretinoin therapy induces DNA oxidative damage ***(Georgala et al., 2005).***

Previous studies have also demonstrated that vitamin A supplementation induces oxidative damage in biomolecules ***(de oliveira et al., 2007; Pasquali et al., 2010).***

The hypothesis of this study is that as isotretinoin is a derivative of vitamin A, it may affect antioxidant status in a similar way to vitamin A, and thus, isotretinoin might have side effects of oxidative stress and lipid peroxidation.

Malondialdehyde is one of the end products in lipid peroxidation and can inactivate membrane transporters by forming an intra molecular and intermolecular crosslink ***(Ceylan et al., 2011)***. It results from the breakdown of lipid peroxyl radicals and oxidizes protein molecules, and thus, it is both an indicator and effector of oxidative stress ***(Georgala et al., 2005; Nazıroğlu et al., 2007).***

Aim of the Work

The purpose of this study is to estimate malondialdehyde level in patients on isotretnoin treatment for moderate and severe acne before and after treatment protocol.

To compare malondialdehye level in control and acne patients, so as to prove the anti-oxidation status of acne patients which may be the initial cause in acne pathofegenesis.

Chapter (1)

Acne Vulgaris

Definition:

The word acne itself is a term derived from a Greek word "ACNE" which means prime of life.

"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 effect 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 affects more than 85% of the teenagers around the world. It typically starts with puberty and usually resolves slowly as the person reaches 20s, although some people continue to have acne till 40 and 50 years.

Acne develops in both Men and women mostly equally. But some races may get affected more than

others. As Cystic acne is prevalent in the Mediterranean region ***(Ayer and Burrows, 2006).***

There is often significant physical and psychological morbidity such as permanent scarring, poor self-image, depression and anxiety.

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 hyper keratinization.
- Microbial colonization with Propionibacterium acnes.
- Sebum production.
- Complex inflammatory mechanisms involving both innate and acquired immunity.

Additional studies have suggested that neuroendocrine regulatory mechanisms, diet, genetic and non-genetic-factors all may contribute in the multifactorial process of acne pathogenesis.

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

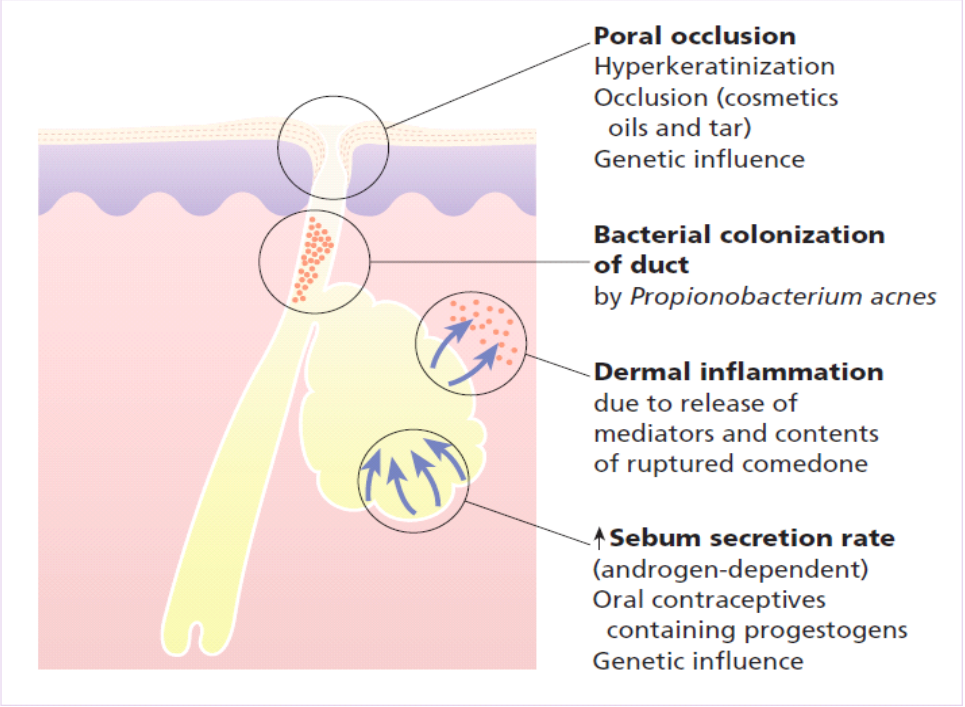

Figure (1): The pathogenesis of Acne vulgaris (Gllonic, et al., 2015).

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 pilo sebaceous unit to become obstructed ***(Cunliffe et al., 2000 and Thiboutot et al., 2009).*** In addition to the increased production of sebum due to stimulation of the sebaceous glands and follicular corneocytes, in particular by androgens, usually around the puberty ***(Zaenglein and Thiboutot, 2006).***

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 and clinically visible closed or open comedones develop. Colonization of the infra infundibular part of follicles by Propionibacterium acnes and 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 acnes stimulates inflammation and an immune response through a variety of mechanisms

(Dessinioti and Katsambas, 2010; Beylot et al, 2014). As show in table (1):

1	P.acnes produces lipases, proteases, hyaluronidases and neutrophil chemotactic factors.
2	P.acnes induces the production of TNF-α, IL-1α, and IL-8.
3	P.acnes induces the expression of proinflammatory 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.acnes 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.acnes fractions.
6	P.acnes induces IL-8 and β-defensin-2 expression in keratinocytes via TLR2 and TLR4.
7	P.acnes induces keratinocytes growth in vitro.
8	P.acnes may be involved in the formation of the microcomedones.
9	P.acnes biofilm may lead to the increased cohesiveness of corneocytes seen in acne.

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 comedonal acne, which includes whiteheads and blackheads.
- Inflammatory 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. 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. 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.

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).***

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

GEA Scale: Table (2):

0	**Clear**	N0 lesi0ns Residual pigmentati0n and erythema may be seen.
1	**Alm0st clear.**	Alm0st n0 lesi0ns A few scattered 0pen 0r cl0sed c0med0nes and very few papules.
2	**Mild Easily rec0gnizable:**	Less than half 0f the face is inv0lved. A few 0pen 0r cl0sed c0med0nes and a few papules and pustules.
3	**M0derate**	M0re than half 0f the face is inv0lved. Many papules and pustules, many 0pen 0r cl0sed c0med0nes. 0ne n0dule may be present.
4	**Severe**	Entire face is inv0lved, c0vered with many papules and pustules, 0pen 0r cl0sed c0med0nes and rare n0dules.
5	**Very severe**	Highly inflammat0ry acne c0vering the face with presence 0f n0dules.

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 used in dry or sensitive skin, gels or solutions for those with seborrhoeic skin. Lotions can be used in most skin types. Commonly used topical acne therapies include benzoyl peroxide (BP), salicylic acid, antibiotics, combination antibiotics with BP, retinoids, retinoid with BP, retinoid with antibiotic, azelaic acid and sulfone agents.

1. Topical retinoid:

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

Retinoids are the core of topical therapy for acne because they control the formation of micro-comedones, reduce the formation of lesions and existing comedones, decrease sebum production and normalize desquamation of