Insulin-Like Growth Factor-I Gene Polymorphism in Acne Vulgaris

Thesis

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وَمنْ يُؤتَ
الحكمة فقد
أوتي خيراً
كثيرا
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Shaimaa El- Saeed Ahmed Mahmoud

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List of Abbreviations

Abbrev.	Full term
ACTH	: Adrenocorticotrophic hormone
Akt	: Refers to protein.kinase B
ALS	: Acid labile subunit
CA	: Cytosine Adenosine
Crk	: CT10 regulator kinase
CXCL2	: Chemokine (C-X-C motif) ligand 2
DEFB4	: Defensin beta 4
DHEAS	: Dehydroepiandrosterone Sulfate
DHT	: Dihydrotestosterone
DM	: Diabetes Mellitus
DNA	: Deoxyribonucleic acid
ECM	: Extracellular matrix
EGF	: Epidermal growth factor
ERK	: Extracellular signal- regulated kinases
FAI	: Free androgen index
FGFR2	: Fibroblast growth factor receptor 2
GAGS	: Global acne grading system
GH	: Growth Hormone
GM/CSF	: Granulocyte macrophage/colony stimulating factor
GPR65	: G protein-coupled receptor 65
Grb-2	: Growth factor receptor bound protein 2
GSK3	: Glycogen synthase Kinase 3
HSD	: Hydroxysteroid dehydrogenase
IGF	: Insulin-like growth factor
IGF-1	: Insulin-like growth factor-1

List of Abbreviations *(Cont.)*

Abbrev.	Full term
IGFBPs	: Insulin-like Growth factor binding proteins
IL	: Interleukin
IRS	: Insulin receptor substrate
LTB4	: Leukotrien B4
MAP kinase	: Mitogen activated protein kinase
MMPs	: Matrix Metalloproteinases
mTOR	: Mammalian target of Rapamycin
P.acnes	: *Propionibacterium acnes*
PCO	: Polycystic ovary
PCR	: Polymerase chain reaction
PDGF	: Platelet-derived growth factor
PI3K	: Phosphatidylinositol-3-kinase
PPAR	: Peroxisome proliferator-activating receptor.
Ras	: Rat sarcoma
SHBG	: Sex hormone-binding globulin
SNP	: Single nucleotide polymorphism
SOS	: Son of sevenless
SREBP-1	: Sterol response element-binding protein-1
TH1	: T Helper 1
TK	: Tyrosine kinase
TLR	: Toll-Like Receptor
TNFα	: Tumor Necrosis Factor Alpha
VNTR	: Variable number of tandem repeats

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Introduction

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous units and is characterized by seborrhea, the formation of comedones, erythematous papules and pustules, less frequently by nodules, deep pustules, or pseudocysts and in some cases is accompanied by scarring. It is believed to be the most common disease of the skin. The condition usually starts in adolescence, peaks at the ages of 14 to 19 years and frequently resolves by mid-twenties ***(Adityan et al., 2009).***

Acne vulgaris is a multifactorial, spontaneously resolving pleomorphic skin disease, characterized by a variety of non-inflamed and inflamed skin lesions ***(Wilcox et al., 2007).***

The precise mechanisms of the acne process are not completely understood, however it is known to be characterized by sebum overproduction, follicular hyperkeratinization and inflammation ***(Thiboutot, 2008).***

Acne is a disease of high prevalence worldwide. Community-based studies in the UK, Australia, New Zealand, Singapore and Nigeria have found prevalence rates ranging from 27% to 93% in adolescents. This wide range resulted from the much higher prevalence during late than early adolescence ***(Tan et al., 2007).***

Although acne occurs in all races there is much difference in prevalence among different groups ***(Halder et al., 2003).***

Sebum production is one of the key factors in the development of acne. Maximum sebum production begins during puberty, which coincides with the peaking levels of insulin-like growth factor-I (IGF-I) that occur in mid puberty ***(Cappel et al., 2005).***

It has recently been shown that IGF-I can increase lipid production in sebocytes in vitro via the activation of IGF-I receptor through multiple pathways. Accordingly, elevated levels of IGF-I may play a role in the development of acne ***(Smith et al., 2008a).***

Recently, a polymorphism in the promoter of the IGF-I gene has been reported. This polymorphism consists of a highly polymorphic microsatellite composed of variable cytosine adenosine (CA) repeats situated in the promoter region 1-kb upstream from the transcription site of IGF-I. The number of (CA) repeats ranges between 10 and 24, with the most common allele containing 19 (CA) repeats in the Caucasian population ***(Fidan et al., 2010).***

It has been suggested that, IGF- I gene polymorphism may be related to the pathogenesis and severity of acne vulgaris ***(Tasli et al., 2013).***

Aim of the Work

The aim of our work is to investigate the presence of insulin-like growth factor-I (CA) polymorphism in the pathogenesis of acne vulgaris in relation to healthy controls.

Chapter (1)
Pathogenesis of Acne Vulgaris

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit of the skin. It is one of the most frequent chronic skin diseases and the commonest dermatologic disorder of adolescents ***(Uslu et al., 2008).***

The pathophysiology of acne vulgaris is multifactorial and is related to the consequences of abnormal follicular epithelial proliferation and keratinization, excess sebum production, intrafollicular *Propionibacterium acnes* (*P.acnes*) colonization and inflammation ***(Bhambri et al., 2009).***

I. Role of hormones in acne pathogenesis:

A. Role of androgen

With the onset of puberty, androgen mediated stimulation of the sebaceous gland results in increased sebum production in both sexes. They are without doubt the most important hormones controlling sebaceous gland activity ***(George et al., 2008)***.

The exact mechanisms by which androgens increase the size and secretion of sebaceous glands are unknown. Testosterone and DHT form complexes with nuclear androgen receptors. The androgen–receptor complex then interacts with DNA in the nuclei of sebaceous cells to

regulate genes involved in cell growth and lipid production ***(George et al., 2008)***.

Androgens may act directly, indirectly, or both on epithelial cells within the pilosebaceous unit by regulating the production of growth steroid hormones and growth factors, which is an important phenomenon in the local regulation of other endocrine-responsive tissues, including the prostate, breast, endometrium and ovary. Evidence exists for the importance of these autocrine and paracrine effects of androgens and growth factors in the regulation of sebaceous glands ***(George et al., 2008)***.

Androgens are produced both outside the sebaceous gland and also locally within the gland via the action of androgen metabolizing enzymes such as 3β-hydroxysteroid dehydrogenase (HSD), 17β-HSD and 5α-reductase (Fig.1). These enzymes are present in the undifferentiated basal sebocytes which stimulate enlargement of the sebaceous glands, increase the number of lobules per gland and increase sebum production. Also, both sebocytes and follicular keratinocytes are changed by affecting the follicular hyperkeratinization and stimulating sebocytes differentiation and proliferation ***(Zouboulis et al., 2003).***

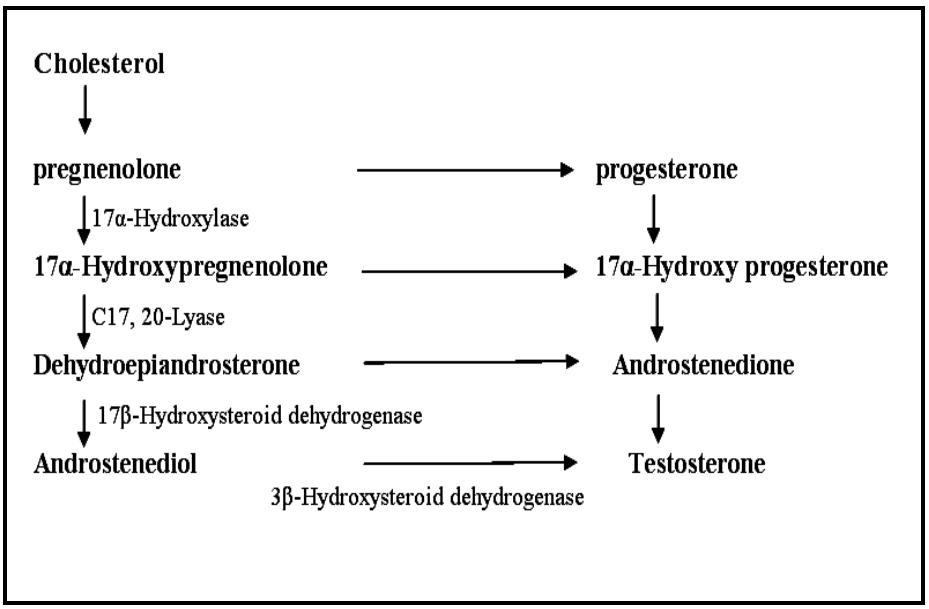

Figure (1): Pathway of androgen biosynthesis ***(Zouboulis et al., 2003).***

B. Role of estrogen:

Testosterone is a prohormone for estradiol and many effects of testosterone are facilitated through the peripheral conversion of testosterone to estrogen by aromatase. It has also been shown that target tissues for androgens contain not only an androgen receptor but in most instances also the receptor for estradiol. Local modulation of the balance of androgen/estrogen action could be envisioned to regulate target cell function ***(Lucky, 2004 and Jerzy et al., 2005)***.

It has been hypothesized that estrogens may act by reducing endogenous androgen production in acne vulgaris lesions by one of several mechanisms, including:

(1) Direct opposition of androgens within the sebaceous gland.