TESTOSTERONE AND ANDROGENETIC ALOPECIA IN MEN : ROLE OF INSULIN – LIKE GROWTH FACTOR I

Thesis

Submitted for partial Fulfillment of
Master Degree in Dermatology, Venereology and Andrology

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(2013)

ACKNOWLEDGMENT

Thanks to ***God*** *first and foremost. I feel always indebted to God, the most kind and most merciful.*

I would like to express my gratefulness and respect to ***Prof. Dr. Ahmed Sadek Mohamed Salem,*** *Professor of Dermatology, , Venereology & Andrology , Faculty of Medicine ,Al Azhar University for his moral and scientific support and for giving me the honor of working under his generous supervision and valuable guidance.*

Special thanks and deepest gratitude to ***Dr. Abd Al Raouf Mohamed Al Mohsen,*** *Assistant Professor of Dermatology, , Venereology & Andrology , Faculty of Medicine ,Al Azhar University, for his constructive and instructive comments and valuable suggestions. He encouraged me all the time for better performance.*

My deep thanks are paid to ***Prof. Dr. Mohamed Saeed Al Shorbagy*** *, Professor of Clinical pathology, Faculty of*

Medicine ,Al Azhar University for his sincere scientific supervision and moral help.

I am very grateful to all ***my stuff members and my colleagues*** *in Dermatology and Venereology, Faculty of Medicine, Al Azhar University, for their help and support throughout the course of the work.*

Words cannot describe my gratefulness and gratitude to ***my Father*** *for his help, patience and great care and my family as they provided me with every mean of support throughout my life.*


بسم الله الرحمن الرحيم

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LIST OF ABBREVIATIONS

ACTH	Adrenocorticotrophic hormone.
AGA	Androgenetic alopecia.
AR	Androgen Receptor.
BMI	Body mass index.
CRH	Corticotrophine Releasing Hormone.
CVD	Cardiovascular disease.
DHEA-S	Dehydroepiandrosterone sulphate.
DHT	Dihydrotestosterone.
ELISA	Enzyme-linked immunosorbent assay.
FDA	Food and drug administration.
FPHL	Female pattern hair loss.
FSH	Follicle-stimulating hormone.
GH	Growth hormone.
IGFBP-3	Insulin like Growth Factor Binding Protein -3.
IGF1R	Insulin like Growth Factor 1 Receptor.
IGF2R	Insulin like Growth Factor 2 Receptor.
IR	Insulin receptor.
LH	Luteinizing Hormone.
MPB	Male pattern baldness.
MPHL	Male pattern hair loss.
PCO	Polycystic ovary.
PG	Prostaglandin.
RFLP	Restriction fragment length polymorphism.
SHBG	Sex -Hormone Binding Globulin.
SREBP-1	Sterol response element binding protein-1.
T	Testosterone.
TGF-β	Transforming growth factor –beta.

Introduction

Androgenetic alopecia (AGA) is a hereditary incomplete thinning or shedding of hair or both induced by androgens in genetically susceptible men and women. Thinning of the hair usually begins between the ages of 12 and 40 years in both sexes, and approximately half the population expresses this trait to some degree before the age of 50 years ***(Sinclair, 2004b)***.

The Hamilton – Norwood classification is a method of categorizing AGA in men. It was initially described by Hamilton ***(Hamilton,1951)*** and then modified by Norwood ***(Norwood,1975).***

The adjective AGA describes the two dominant etiological factors of AGA, namely genetic susceptibility and androgen hormones. Lifestyle also may play a minor role ***(Daly et al., 2005).***AGA is clearly androgen dependent. It was reported that AGA was absent in men casterated before puberty. AGA has not been reported in complete androgen insensitivity syndrome in which there is a failure of androgen receptor expression **(*Olsen et al.,2005*).**

Androgens are thought to be important in the normal regulation of hair growth and patterning, and epidemiological study demonstrated a positive relation between circulating testosterone and baldness ***(Demark-wahnefried et al.,1997).***

Moreover, in a randomized placebo – controlled trial, growth hormone (GH) substitution in adult GH- deficient men has been found to enhance androgen effects on hair growth ***(Blak et al.,1997).***

It was suggested that high level of insulin like growth factor one (IGf-1) may be associated with increased of vertex baldness**.** Few studies have jointly evaluated the function of sex steroids and IGF-I in determining hair patterning in men ***(Signorello et al.,1999).***

Aim of the work

The aim of this study is:

Estimation of the serum level of insulin like growth factor-1, free and total testosterone in male patients with androgenetic alopecia aiming to verify their possible role in the pathogenesis of this type of alopecia.

Chapter I

Androgenetic alopecia

Androgenetic alopecia (AGA) is the most common hair loss disorder, affecting both men and women ***(Blume-Peytavi et al., 2011).***

This condition is also known as male-pattern hair loss (MPHL) or male pattern baldness (MPB) in men and as female-pattern hair loss in women (FPHL) **(*Ellis and Sinclair,2008).***

AGA is a non-scarring progressive miniaturization of the hair follicle with a characteristic distribution pattern in genetically predisposed men and women. In men, AGA typically shows a pattern distribution, most commonly a male pattern, but occasionally a female pattern can be seen ***(Messenger, 2008; Paik et al., 2001).***

Prevalence and frequency

Male AGA occurs in all populations. The prevalence is highest in Caucasians, reaching around 80% in men aged over 70 years .In the Asian population, a prevalence of 46.9–60.0% has been reported in males older than 70 years. There is scant published information on the frequency of balding in African men ***(Blume-Peytavi et al., 2011).***

Etiology

Alopecia means hair loss. The adjective androgenetic describes the two dominant causal factors, namely genetic susceptibility and androgens ***(Sinclair, 2004b).***

Genetics in androgenetic alopecia

Androgenetic alopecia is a familial disease. Twin studies identified heredity as accounting for around 80% of the predisposition to baldness. Polygenic inheritance best accounts for the range of clinical phenotypes and increased risk with increased number of affected family members. It was found that the fathers of 81.5% of affected men have baldness that is higher than that can be explained by autosomal dominant inheritance ***(Rathnayake and Sinclair , 2010).***

Although it is a popular belief that baldness is inherited from the maternal grandfather, the mode of inheritance is usually cited in the scientific literature as autosomal dominant, suggesting that the inheritance of only one autosomal gene conveys full genetic predisposition, it was found that a single autosomal gene, termed 'B', could account for genetic predisposition to baldness, acting in an autosomal dominant manner in men, and in an autosomal recessive manner in women. In other words, men are predisposed to baldness if they inherit either 'BB' or 'Bb'; however women are predisposed only if they inherit, 'BB' ***(Ellis et al.,2002).***

Research indicates that susceptibility to premature male pattern baldness is largely x- linked, that means it is linked to genes on an X chromosome.Other genes that are not sex inked are also involved ***(Hillmer et al.,2005).***

Gene association studies comparing DNA from young bald men with that of old non-bald men have identified an association of male pattern baldness with a polymorphism of the androgen receptor gene on the X chromosome ***(Ellis and Harrap ,2001*)**. Functional confirmation of the importance of the androgen receptor gene in androgenetic alopecia

comes from the recognition that men affected by Kennedy disease, a familial neuromuscular disorder associated with a functional alteration of the androgen receptor, have a reduced risk of developing androgenetic alopecia ***(Sinclair et al., 2007).***

The androgen receptor gene *Stu1* restriction fragment length polymorphism (RFLP) was found in almost all (98.1%) young bald men, and most older bald men (92.3%), but only in 77% of non-bald men **(*Hillmer et al., 2005 ;Hayes et al., 2005).***

Ellis and Harrap (2001) suggested that abnormality of the *AR* gene is necessary but not sufficient to cause the phenotype.

The X chromosomal location of the *AR* gene indicates that the maternal line is the major inheritance of androgenetic alopecia in men. However, family studies have shown resemblance of hair loss between fathers and sons, which cannot be explained by AR gene mutations. This suggests that other autosomal genes might also contribute to the phenotype ***(Hillmer et al., 2008a).***

Some modeling suggests the involvement of at least four genes that combine to modify the age of onset, pattern of loss and rate of progression of MPB**.** Other candidate gene and chromosomal regions have been examined. They include *SRDA1* and *SRDA5*, coding for the two variants of the 5α-reductase enzymes**,** the insulin gene**,** the aromatase gene, the gene for the ER-α estrogen receptor, the non-recombinant area of the Y chromosome and the type II IGF genes**.** Thus far, no association has been found between any of the above-mentioned genetic areas and MPB ***(Ellis et al., 2002*** **).**

Other research suggests another gene on the X chromosome - that lies close to the androgen receptor gene - is an important gene in male

pattern baldness. They found the region Xq11-q12 on the X-chromosome to be strongly associated with AGA in males. They point at the EDA2R gene as the gene that is mostly associated with AGA ***(Petukhova et al., 2008).***

Hillmer et al.,(2008 a) have investigated towards identification of new susceptibility genes in AGA. In a genome-wide scan and fine-mapping linkage study performed on 95 families in which at least two brothers had early-onset AGA and both parents were available. They found strong evidence for an AGA susceptibility locus on chromosome 3q26 .This study could not confirm or rule out the relevance of chromosomes 11q22-q24, 18p11-q22 and 19p13-q13 in causing AGA. Another genome-wide association study done by ***Hillmer et al.,(2008 b)***found that a highly significant association on chromosome 20p11, suggesting that the 20p11 locus has a role in a to be identified androgen independent pathway **.**

Hormonal factors

Androgens in hair growth

The role of androgen in male-pattern hair loss is well established. It has been observed that castrated males did not develop androgenetic alopecia unless they were treated with testosterone. Testosterone is the main circulating androgen and the tissue effects of androgens are mediated by binding through to the intracellular androgen receptor ***(Rathnayake and Sinclair,2010).***

Androgens transform tiny vellus follicles (producing fine, virtually colorless almost invisible hairs in many parts of the body) into larger, deeper follicles forming longer, thicker, more pigmented hairs. Although androgens stimulate hair growth in the axilla and pubis of both sexes and