The Association of Hirsutism with Metabolic Syndrome

Thesis

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✍ *Mayanne Mohamed A.Hamid*

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List of Abbreviations

Abb.	Meaning
3-alpha-diol ..... :	3-alpha-androstanediol
4-AP ..... :	4-aminophenazone
5-alpha- DHT..... :	5-alpha-dihydrotestosterone
17-OHP ..... :	17-hydroxyprogesterone
ACTH ..... :	Adrenocorticotropic stimulating hormone
ADP ..... :	Adenosine-5-diphosphate
Apo B ..... :	Apolipoprotien B
AR..... :	Androgen receptor
ATP III..... :	Adult treatment panel III
BMI..... :	Body mass index
BP ..... :	Blood pressure
CE ..... :	Cholesterol esterase
CHD..... :	Coronary heart disease
Co_x ..... :	cholesterol oxidase
CRP ..... :	C reactive protein
CVD ..... :	Cardio-vascular disease
DAP ..... :	Dihydroxyacetone phosphate
DBP ..... :	Diastolic blood pressure
DHEA..... :	Dehydroepiandrosterone
DHEA-S ..... :	Dehydroepiandrosterone-Sulfate
DHT ..... :	Dihydrotestosterone
DNA ..... :	Deoxyribonucleic acid
E 1..... :	Estrone
E 2 ..... :	Estradiol

List of Abbreviations (Cont...)

Abb.	Meaning
EGIR ..... :	European Group for the study of Insulin Resistance
ELISA..... :	Enzyme-linked immunesorbent assay
FBG. ..... :	Fasting blood glucose
FDA ..... :	Food and drug administration
FFA..... :	Free fatty acid
FSH..... :	Follicular stimulating hormone
G3P..... :	Glycerol-3-phosphate
GnRH ..... :	Gonado-tropin releasing hormone
GPO..... :	Glycerol phosphate dehydrogenase
H_2O_2..... :	Hydrogen peroxide
HAIR-AN syndrome.... :	Hyper Androgenism, Insulin Resistance and Acanthosis Nigricans syndrome
HDL-C ..... :	High density lipoprotein-cholesterol
H-F ----------:	Hirsutism limited to the face
H-FA ----------:	Hirsutism in the face and abdomen
H-FAB ----------:	Hirsutism in the face, abdomen and breast
H-FB ----------:	Hirsutism in the face and breast
HPA-axis ..... :	Hypothalamic pituitary axis
IDF ..... :	International Diabetes Federation
IFG ..... :	Impaired fasting glucose
IGT ..... :	Impaired glucose tolerance
IH..... :	Idiopathic hirsutism
IL-6 ..... :	Interleukin-6
IPL..... :	Intense pulsed light
IR ..... :	Insulin resistance
Laser ..... :	Light amplification by the stimulated emission of radiation
LCL..... :	Lipid clearing factor
LDL-C ..... :	Low density lipoprotein cholesterol

List of Abbreviations (Cont...)

Abb.		Meaning
LH	:	Luteinizing hormone
LPL	:	Lipoproteinlipase
MetS	:	Metabolic syndrome
NC-AGS	:	Non classic adrenogenital syndrome
NCEP	:	The National Cholesterol Education Program
Nd:YAG	:	Neodymium-doped yttrium aluminium garnet
NHLBI	:	National Heart, Lung, and Blood Institute
OCs	:	Oral contraceptives
OGTT	:	Oral glucose tolerance test
PAI-1	:	Plasminogen activator inhibitor-1
PCOS	:	Polycystic ovary syndrome
POD	:	Perioxidase
PVS	:	polyvinyl sulphate
RNA	:	Ribonucleic acid
SBP	:	Systolic blood pressure
SHBG	:	Sex hormone-binding globulin
TC	:	Total cholesterol
TG	:	Triglycerides
TNF- α	:	Tumour necrosis alpha
TVC	:	Trans-vaginal scan
UKPDS	:	UK prospective diabetes study
US	:	United states
WC	:	Waist circumference
WHO	:	World health organization

Introduction

Hirsutism is defined as an increased growth of terminal hair in women in a male pattern. The prevalence of the condition is 5–25% of women in reproductive age. Hirsutism may be a manifestation of Cushing's syndrome, androgen producing tumors, or late onset adrenogenital syndrome (Non classic adrenogenital syndrome). Most hirsute women with rare endocrine diseases can be diagnosed using medical history, clinical examination, and follicular phase blood samples ***(Glintborg et al., 2004).***

Hirsutism is caused by increased androgenicity in the pilosebacceus unit resulting in increased growth of terminal hairs. Hirsute patients have increased dermal activity of the enzyme 5 α–reductase, which is responsible for conversion of testosterone to the more potent androgen; dihydrotestosterone (DHT) ***(Azziz et al., 2000).*** High DHT levels increase terminal hair growth and therefore, 5 α–reductase inhibitors can be used for the treatment of hirsutism ***(Glintborg et al., 2009).*** Individual variations in dermal α–reductase activity may explain the often near normal testosterone levels and the lack of correlation between circulating testosterone levels and clinical hirsute manifestations ***(Azziz, 2000).***

Ninety-five percent of hirsute patients are diagnosed either associated with polycystic ovary syndrome (PCOS) or idiopathic hirsutism (IH). PCOS is clinically defined as oligomenorrhea

associated with hyperandrogenism. IH is defined as hirsutism with regular ovulation, normal testosterone levels, and normal ovaries ***(Azziz, 2000).*** In daily practice, PCOS and IH are difficult to distinguish and the two terms probably represent a continuum. Patients with IH usually are older and leaner and have more modest metabolic and endocrine disturbances than patients with PCOS ***(Azziz et al., 2009).***

Metabolic syndrome (MetS) is a group of abnormalities probably caused by insulin resistance (IR) with systemic hyperinsulinism. It consists of glucose intolerance or type-2 diabetes, arterial hypertension, atherosclerosis, obesity and dyslipidemia ***(Reaven, 1988).***

The most important risk factors for the development of MetS are weight, genetics, endocrine disorders and aging. Most patients are older, obese, and sedentary and have a degree of IR. Stress can also be a contributing factor ***(Poulsen et al., 2001; Pollex and Hegele, 2006).***

Many women with hirsutism associated with PCOS have additional features of MetS, especially IR and obesity. As MetS and PCOS are highly associated with cardiovascular disease (CVD) and type-2 diabetes, studying the association between MetS and hirsutism with PCOS may provide another clue to the clinical signs and symptoms related to both diseases, but unfortunately there is little data on population based studies on this association ***(Grundy, 2006; Cornier et al., 2008).***

Aim of the Work

The aim of this work is to assess the frequency of MetS among women with hirsutism (with and without PCOS) compared to age, sex and socioeconomic status matched control group.

Chapter (1)

HIRSUTISM

Hair anatomy

i. Structure of the hair follicle

Hair follicles consist of several components. The most superficial part of the hair follicle extends from the sebaceous duct to the epidermal surface. This portion includes the hair canal and the distal outer root sheath. The tubular connection between the epidermal surface and the distal part contains the hair shaft. The outer root sheath is contiguous with the basal epithelial layer. The inner root sheath is a multilayered rigid tube that is composed of terminally differentiated hair follicle keratinocytes, surrounded by the outer root sheath. It provides the conduit for the hair to exit at the skin surface, and the hair shaft itself ***(Headington, 1984; Fuchs et al., 2001).***

The hair is composed of keratinized epithelial cells as shown in figure (1), organized in a flexible cylinder that differ in color, thickness and length. Keratin proteins form the hair shaft that grows within the outer hair root sheath in the epidermis.

The sebaceous gland is an acinar gland composed of lipid-filled sebocytes, localized close to the insertion of the arrector pili muscle. The sebaceous gland secretes sebum to the

epidermal surface via a holocrine mechanism. Sebum helps to make hair and skin waterproof. The arrector pili muscle is a tiny smooth muscle that connects the hair follicle with the dermis, and causes, when contracted, the raising of the hair. Together with the hair follicle and the arrector pili muscle, the sebaceous gland forms the pilosebaceous unit.

The bulge is a protrusion of the outer root sheath located below the sebaceous gland at the insertion site of the muscle arrector pili. The bulge contains the hair follicle stem cells. The bulb is a thickening of the proximal end of the hair follicle, which contains undifferentiated matrix, melanocytes and outer root sheath cells. The dermal papilla, consisting of closely packed specialized mesenchymal fibroblasts, is a mesodermal signaling system within the hair follicle. The dermal papilla produces numerous paracrine factors that influence the size and color of the hair produced ***(Schneider et al., 2009).***

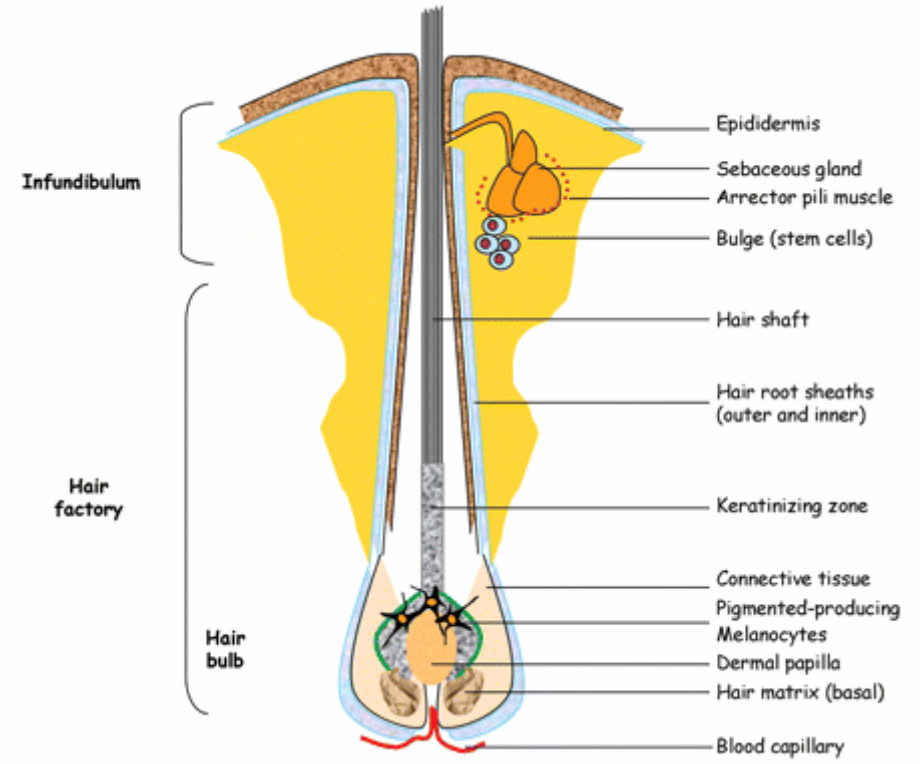

Figure (1): Structure of the hair follicle ***(Fuchs et al., 2001).***

ii. Hair follicle morphogenesis

In humans, organization of the primitive epidermis takes place between 9 and 12 weeks of embryonic life. The master switch for hair follicle development involves canonical Wnt/β-catenin signaling that is essential for hair follicle fate at least in mice. Communication between the developing epidermis and underlying mesenchyme plays a key role in hair differentiation as well as other ectodermal appendages, such as nails, teeth, feathers and scales ***(Andl et al., 2002).***