INTRODUCTION

Androgens affect several functions of the human skin, such as sebaceous gland growth, differentiation, and hair growth. Their effects are mediated by binding to androgen receptors (ARs). The major circulating androgens, dehydroepi-androsterone sulfate and androstenedione, are predominantly produced in the adrenal glands, and testosterone and 5 α-dihydrotestosterone (DHT) in both genders are also synthesized in the skin. Skin cells express all androgen metabolizing enzymes required for cutaneous synthesis of androgens and development of hyperandrogenism–associated conditions and diseases, such as seborrhea, acne, hirsutism, poly cystic ovary syndrome, and androgenetic alopecia ***(Zoubouli and Degitz, 2004).***

Androgens normally stimulate terminal hair production in many sites of the body (e.g the beard and the axillary regions), exert an opposite effect to suppress hair growth on genetically predisposed frontal and vertex scalp ***(Randall, 2008).***

Androgenetic alopecia (AGA) is the most frequent type of hair loss in males. This pathophysiology is resultant from hair follicle miniaturization in predisposed scalp. As in men, hair thinning and loss are commonly found in females which termed female pattern hair loss (FPHL) ***(Otberg et al., 2007).***

Overproduction of androgens or increased sensitivity of hair follicles to androgens is the common cause of hirsutism in females. Minimal unwanted hair growth and mild hirsutism in women can provide important indicators of an underlying androgen excess disorder ***(Di Fede et al., 2010).***

Androgens act through a single nuclear receptor the androgen receptor (AR). Androgen receptor is a ligand–activated, intracellular transcription factor that belongs to the steroid/nuclear receptor superfamily ***(Zouboulis, 2004).***

In human skin, the AR is expressed in epidermal and follicular keratinocytes, sebocytes, sweat gland, dermal papilla cells, dermal fibroblasts and endothelial cells ***(Fritsch et al., 2001).*** Binding of androgens to the AR leads to conformational change of the receptor and translocation of the androgen and androgen receptor complex from the cytosol to the nucleus to elicit transcriptional regulation of target genes, which can be further modulated by various AR corregulators ***(Heemers and Tindall, 2007).***

Aim of the Work

The purpose of this essay is to review role of androgen and androgen receptor in skin related disorders.

ANDROGEN AND ANDROGEN RECEPTORS

The first recognition of the role of androgens in the pathogenesis of cutaneous disorders probably came from Aristotle as early as the 4th century BC, as he noticed the relation between the occurrence of androgenetic alopecia and the gender or sexual maturity ***(Chen et al., 2002).*** In 1942, Hamilton's pioneering work on castrates subjected to testosterone injections provided the scientific evidence for androgen activity on human skin, and hence provoked further investigation of the cutaneous effects of androgens ***(Hamilton, 1942).***

Several functions of the human skin, especially of the appendages, appear to be strongly dependent on biologically active androgens. Their effect is mediated by binding to nuclear receptors. Lack of functional androgen receptors (ARs), e.g. in the total androgen insensitivity syndrome, prevents the action of androgens on skin appendages ***(Imperato-McGinley et al., 1993).***

Androgen activation and deactivation are mainly intracellular events. They can differ from cell type to cell type and between cells in different locations ***(Fritsch et al., 2001).***

The androgens relevant to the skin are the dehydroepiandrosterone sulfate (DHEA-S) and androstenedione

which are predominantly produced in the adrenal glands, and testosterone and 5α-dihydrotestosterone (DHT), they are mainly synthesized in the gonads. These androgens reach the skin via the blood stream, while the testosterone in women and DHT in both genders are also synthesized in peripheral organs, including the skin. Androgens affect several cutaneous structures. Dehydroepiandrosterone sulfate is the androgen which is considered to be the most important regulator of sebum secretion ***(Yamamoto and Ito, 1994)***.

Dehydroepiandrosterone sulfate is only a weak androgen but sebocytes, and probably also dermal papilla cells, have the enzymatic capacity to convert DHEA-S, and also androstenedione, into more potent androgens such as testosterone and DHT ***(Zouboulis, 2000).***

Androstenedione and testosterone have also been shown to stimulate sebum secretion in humans ***(Diamond et al., 1996).*** Dihydrotestosterone seems to be necessary for male beard growth and scalp hair recession, whereas testosterone alone is sufficient for the stimulation of axillary and pubic hair growth ***(Messenger, 1993).*** Thus, the skin is regarded as a peripheral organ that locally synthesizes significant amounts of androgens with intracrine or paracrine actions.

Table (1): Plasma concentrations (nmol/l) and relative androgenic strength of androgens in adults *(Kao et al., 2001).*

	Men	Women	Relative androgenic strength
Dehydroepiandrosterone sulfate	1300–6800	1300–6800	1
Androstenedione	3.0–5.0	3.5–7.0	2
Testosterone	10–35	< 3.5	20
5α-Dihydrotestosterone	0.87–2.6	0.17–1.0	60

Androgen receptor

Androgen receptor is a ligand-activated, intracellular transcription factor that belongs to the steroid/nuclear receptor superfamily**.** Like all nuclear receptors, AR is a soluble molecule with a proclivity for employing transcriptional regulation as a means of promoting its biological effects. In common with other steroid receptors, AR is compartmentalized in the cytoplasm, existing in polymeric complexes that include the heat shock proteins (hsp) hsp 90, hsp 70 and hsp 56 **(Figure 2)**. The association of androgens with AR results in dissociation of the heat shock proteins. This in turn exposes a nuclear translocation signal previously buried in the receptor structure and initiates transport of the ligand– receptor complex to the nucleus. There, AR occupies androgen response elements in the

promoter regions of androgen-regulated genes to initiate the signaling cascade ***(Zouboulis, 2004)***.

Androgen receptor is present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells and genital melanocytes**.** It is stabilized by ligand binding and is up-regulated in fibroblasts and sebocytes ***(Fimmel et al., 2003).***

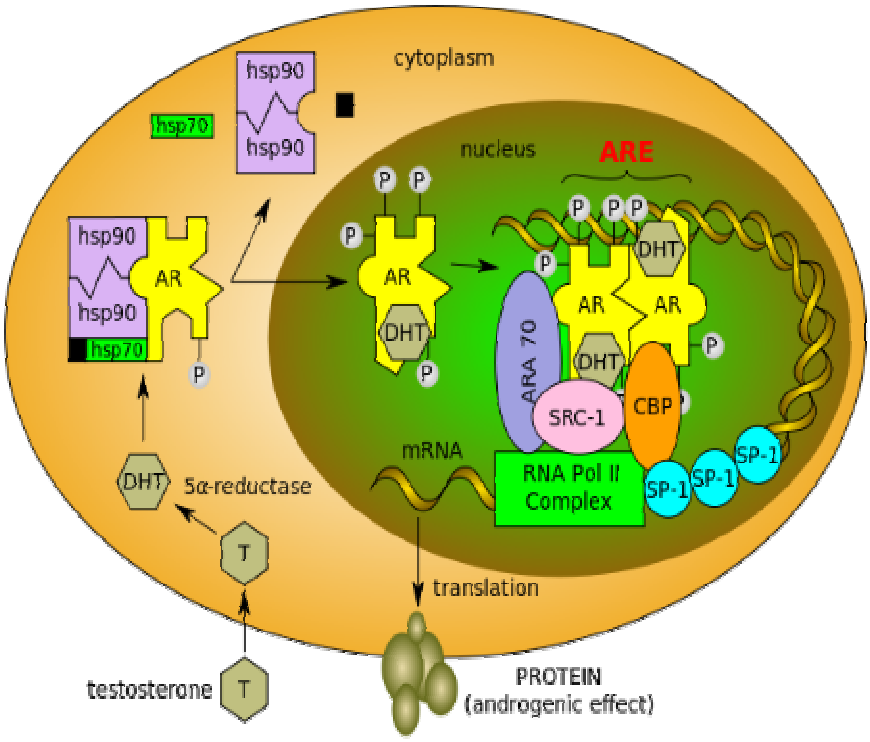

Figure (1): Schematic of the general mechanism of androgens action. Inside the cell, testosterone and DHT bind to the androgen receptor. Once the hormone has bound, the complex will bind to the DNA, altering the expression of specific androgens-dependent genes (***Meehan and Sadar, 2003***).

Androgen metabolism in the skin

The effects of biologically active androgens on the skin, their local synthesis and degradation have received special interest. Five major enzymes are involved in the activation and deactivation of androgens (**Figure 2**). In a first step, steroid sulfatase metabolizes DHEA-S to dehydroepiandrosterone (DHEA). Subsequently, 3b-hydroxysteroid dehydrogenase) 4-isomerase (D5-3b-HSD) converts DHEA to androstenedione. Two isoforms of this enzyme have been described ***(Chen et al., 2002).***

Human skin seems to express exclusively the type 1 isoform. Several studies have led to the conclusion that cutaneous D5-3b-HSD is located in the sebaceous glands ***(Fritsch et al., 2001).*** Enzyme activity has also been detected in the dermal papillae of human terminal hair follicles ***(Hoffmann et al., 2001).***

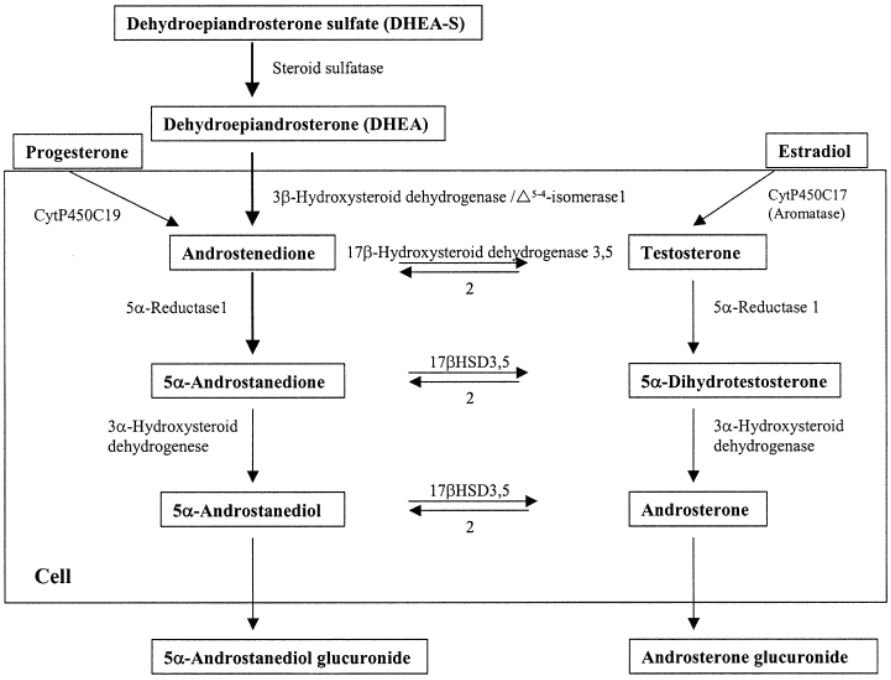

Figure (2): Pathways of cutaneous androgen metabolism and the converting enzymes ***(Chen et al., 2002).***

In a further step, androstenedione is activated by conversion to testosterone through 17b hydroxysteroid dehydrogenase (17b-HSD). The cutaneous expression of 17b-HSD is mainly concentrated in the pilosebaceous unit and epidermal keratinocytes. So far, eight isoforms of this enzyme has been identified ***(Chen et al., 2002).*** 17b-HSD types 1, 3 and 5 support the formation of more active androgens, whereas the oxidative reaction induced by 17b-HSD types 2 and 4 inactivates the potent sex steroids. The human sebaceous gland possesses the cellular machinery needed to transcribe the genes for 17b-HSD types 1–5; of these, strong 17b-HSD type 2

mRNA and protein expression has been detected ***(Fritsch et al., 2001).***

The predominance of the strongly pro-oxidative 17b-HSD type 2 suggests its protective role against the effects of locally excessive amounts of potent androgens ***(Thiboutot et al., 1998).*** A greater reductive activity of 17b-HSD (types 3 and 5) has been noted in sebaceous glands from facial areas compared with acne non-prone areas, suggesting an increased net production of potent androgens in facial areas. In addition, human sebocytes, but not keratinocytes, express 17b-HSD type 3, underlining the major regulatory role of the sebaceous gland in cutaneous androgen activation ***(Fritsch et al., 2001).***

In hair follicles, 17b-HSD is localized in outer root sheath cells. Anagen hair mainly express high levels of type 2 and moderate levels of type 1 17b-HSD. This is compatible with early studies which showed androstenedione to be the major metabolite of cultured human hair follicle keratinocytes incubated with radiolabeled testosterone**.** 17b hydroxysteroid dehydrogenase enzyme activity has also been shown in cultured epidermal keratinocytes and in the microdissected apocrine sweat gland ***(Chen et al., 2002).***

Five α Reductase irreversibly converts testosterone to DHT, the most potent naturally occurring androgen in tissue ***(Grino et al., 1990).*** There are three isoforms of 5α-reductase and their expression pattarns vary across species and tissuses

(Uemura et al., 2008). Type I 5α-reductase mainly express in the sebocytes, keratinocytes, dermal fibroblasts; type II 5 α-reducatse is mainly detected in the seminal vesicles, epididymis, prostate, and fibroblasts from adult genital skin, as well as the inner root sheath of the hair follicle; while the newly found type III 5α-reductase is detected in the prostate cancer and sebocyte cell lines ***(Samson et al., 2010).*** In addition to its steroidogenic activity, type III 5 reductase is critically involved in N-linked glycosylation ***(Cantagrel et al., 2010)***.

In addition to its capacity to activate and inactivate adrenal and gonadal androgens, the skin, especially the sebaceous gland, is capable of synthesizing cholesterol, which is utilized in cell membranes, in the formation of the epidermal barrier, in sebum and, interestingly, also as a substrate for steroid hormone synthesis ***(Thiboutot et al., 2003).***

The autonomous formation of sex steroids provides human skin with the ability to adjust the levels of sex steroids according to local needs. The local level of each sex steroid thus depends on the expression of each of the androgen and estrogen synthesizing enzymes in each cell type, with sebaceous glands and sweat glands being the major contributors ***(Deplewski and Rosenfield, 2000).***

PATHOGENESIS OF ANDROGEN RELATED DISORDERS

The role of androgen and androgen receptors has been implicated in the skin physiology and pathogenesis based on the fact that AR and many androgenic steroidogeneisis enzymes are expressed in the skin ***(Gilliver et al., 2007).***

Androgens and the hair follicle:

Androgens have strong effects on hair growth and act through AR on dermal papilla cells ***(Deplewski and Rosenfield, 2000).*** Dermal papilla cells mediate the growth stimulating signals of androgens by releasing growth factors that act in a paracrine fashion on the other cells of the follicle ***(Paus, 1999).***

Androgens cause enlargement of the hair follicles in androgen dependent areas (beard in male adolescents, axillary and pubic hair) but, paradoxically, in scalp follicles of susceptible men, androgens faster miniaturization and shortage of hair in the anagen stage, leading to common baldness. These controversial effects may be explained by genetically determined differences in the response of papilla cells to androgens in different body areas during a lifetime ***(Deplewski and Rosenfield, 2000).***

As in acne, higher rates of testosterone and DHT are locally produced in androgenetic alopecia ***(Poor et al., 2002).***

In addition, excessive amounts of tissue active androgens have been shown to induce apoptosis of dermal papilla cells ***(Wrobel et al., 2000).***

The conversion of testosterone to the more potent DHT by the enzyme 5α-reductase type II enhances androgenic effects on hair follicles, as deduced from observations in men with a deficiency of the enzyme. These individuals produce little or no beard growth and do not develop androgenetic alopecia ***(Randall et al., 1992).*** Consistently, the inhibition of type II 5α-reductase by finasteride has been proven to slow or even reverse the progression of androgenetic alopecia ***(Kaufman et al., 1998).***

Androgens and the sebaceous gland:

Malfunctions of AR, e.g. induced by polymorphisms, are associated with androgen dependent skin diseases or conditions including acne ***(Sawaya and Shalita, 1998).*** Skin in acne patients produces higher rates of testosterone and DHT than in healthy individuals. In addition, elevated plasma levels of DHT and 3α-androstenediol glucuronide have been found in female patients with acne, whereas DHEA-S, androstenedione and testosterone are normal ***(Lookingbill et al., 1985).***

Androgens stimulate sebocyte proliferation, an effect dependent on the area of skin from which the sebaceous glands are obtained; facial sebocytes are mostly affected ***(Akamatsu et al., 1992)***. In

contrast, androgens as single compounds seem to be unable to modify sebocyte differentiation ***(Chen et al., 2003).***

Hyperandrogenism:

The prolonged, markedly elevated, insulin levels, which are associated with resistance and decreased sensitivity, may stimulate the ovary to generate androgens ***(Dunaif, 1997).*** It is theorized that these high levels of insulin cross-react with insulin-like growth factors, therefore, directly stimulating the overproduction of ovarian androgens ***(Nestler, 1997).*** This gives rise to the hyperandrogenism.

Androgen receptors are actually regulated by both androgens and AR coregulators, and the outcome of AR function is the convergence balace of signals ***(Heemers and Tindall, 2007).*** Androgen receptors activity in case of acne is determined by androgens and insulin/insuline growth factor-1(IGF-1)/FOXO1 signals.

Isuline growth factor-1, the growth hormone of puberty, induces synthesis of androgens and enhances 5α-reductases activity in the skin ***(Melnik and Schmitz, 2009).***

Female Pattern Hair Loss

The Female Pattern Hair Loss (FPHL) is a nonscarring progressive thinning of hair. It results from a progressive decrease in the ratio of terminal hairs to shorter, thinner vellus hairs, a process known as follicular miniaturization ***(Messenger and Sinclair, 2006).*** This miniaturization follows usually a pattern distribution. In women, FPHL typically presents as a diffuse reduction in hair density over the frontal and vertex areas, but parietal and occipital regions may be involved ***(Price, 2003) (*Figure 3).**

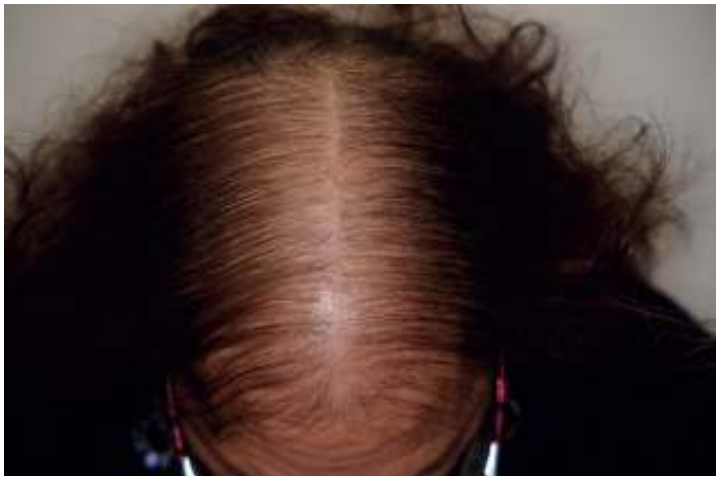

Figure (3): Female pattern hair loss ***(Herskovitz and Tosti, 2013).***

In the past, the term "androgenetic alopecia" (AGA) was the primary term used to refer to this condition in both men and women. The term "andro" from ancient Greek refers to male subjects and "genetic" referred to the contribution of heredity.