Introduction

Androgenetic alopecia (AGA) is the most common pattern of scalp hair loss in both men and women. It results from shortening of the anagen phase of the hair cycle and subsequently, miniaturization of hair follicles ***(Springer et al., 2003)***. In 1942, Hamilton established the significant role of androgens and genetic factors in the etiopathogenesis of AGA ***(Hamilton, 1942).***

Androgens stimulate hair growth in some sites such as the beard, axillary, and pubic areas, whereas suppress the growth of frontal scalp hair in genetically predisposed individuals ***(Randall et al., 2000)***. Although the clinical manifestations are different in men and women, the pathogenic pathways leading to this type of hair loss have long been proposed to be similar in both sexes ***(Hoffman, 2004)***.

In male AGA, vellus hair transformation occurs on the frontal and vertex scalp, while females with AGA showed diffuse hair thinning with preserved frontal hairline. The diagnosis of AGA can usually be established from the clinical appearance. The pattern of hair loss in AGA in men and women is categorized by Hamilton-Norwood and Ludwig classification, respectively ***(Tami and Inui, 2010)***.

Sex hormone-binding globulin (SHBG) regulates the levels of free sex hormones by attaching to circulating sex hormones . Low levels of sex hormone–binding globulin in AGA are a strong risk factor for developing type 2 diabetes in women and men ***(Ding et al., 2009).***

It has been shown that early onset of androgenetic alopecia (age<30 years) is associated with much lower levels of SHBG and hyperglycemia ***(Salvador et al ., 2011).***

Further studies that establish the precise pathogenic relationship between AGA and hyperglycemia in males are warranted in order to permit an earlier diagnosis of previously unidentified hyperglycemia and to initiate appropriate treatment.

Aim of the Work

This thesis is designed to be a case control study to evaluate levels of SHBG & fasting blood sugar as a risk factor for diabetes in male patients with androgenetic alopecia in relation to controls.

Biology of Hair

Hair is a distinct part of the skin, referred to as an appendage. It is composed of the hair follicle and the hair shaft ***(Sperling, 1991)***. The hair follicle is the most prominent miniorgan of the skin ***(Schmidt-Ullrich and Paus, 2005)***. The most obvious function of it is to produce a hair shaft, which is the only part of the hair follicle that exit the epidermis ***(Hashimoto, 1988)***.

I. Functions of Hair

Hair plays a part in controlling the body temperature ***(Bernstein, 2005)***. It is also integral to the body image and can have a profound influence on self-esteem and self-confidence ***(Freedman, 1994)***.

The sebaceous gland, which is a small gland located next to the hair shaft excretes sebum that lubricates the hair, transports fat-soluble antioxidants from and to the skin surface and exhibits a natural photoprotective activity. Sebaceous gland lipids also exhibit anti-inflammatory properties ***(Zouboulis et al., 2008)***.

There are special functions of certain hair, like eyelash hair, which is very important in protecting the eye from dust

and debris and, eyebrows that channel away sweat and other fluids, and help to reduce any excessive glare from sunlight entering the eyes ***(Hess et al., 1990)***.

II. Development and Distribution of Hair

The hair follicle is composed primarily of dermal and epidermal tissues that develop from embryonic mesoderm and ectoderm. It develops from the embryonic epidermis as an epithelial finger ***(Jahoda and Oliver, 1990)***.

In human fetus, the first primordial hair follicles form at approximately 9 weeks of gestation and are distributed mainly in eyebrows, upper lip and chin. The bulk of the remaining follicles begin to develop at approximately 4 to 5 months of gestation in cephalocaudal direction, and by 22 weeks the full complement of follicles is established. Thus, development of hair follicles first begins on the head then expand symmetrically to cover the body saving the palms and soles ***(Lavker et al., 1999)***.

Follicle formation occurs once in the lifetime of an individual, so a mammal is born with a fixed number of follicles, which does not normally increase thereafter. However, postnatal folliculo-neogenesis is probably allowable under certain unique circumstances, like after skin wounding, through stem cells present in the epithelial bulge of the hair

follicle that are responsible for regeneration of the hair follicle ***(Reynolds et al., 1999 and Chuong et al., 2007)***.

The total number of follicles in an adult man has been estimated at about 5 millions, of which about 1 million are on the head and perhaps 80,000 to 150,000 are located on the scalp. There appear to be no significant sexual or racial differences in follicle number ***(Krause and Foitzik, 2006)***.

On the cheek and forehead, the average density of follicles has been recorded as around 800/cm². The greatest density of vellus hairs occurs on the forehead where there are an average 400-450/cm² in young adults of both sexes. However, lower densities of 50-100/cm² are found on the chest and back in both sexes, and only 50/cm² on the thigh and leg. So when the body surface increases, there is a decrease in the actual density of follicles ***(Lee et al., 2002)***.

III. Hair Follicle Morphogenesis

Follicle morphogenesis begins with an inductive event that involves the exchange of signals between epithelial and mesenchymal cells, then proceeds through stages of initiation, elongation and differentiation (Figures 1, 2 and 3) ***(Holbrook et al., 1993)***.

(i) Initiation: Formation of the follicular germ:

Follicle Morphogenesis is initiated by regularly spaced clusters of basal keratinocytes that form an epidermal placode

or follicle germ (Figure 1). The epithelial germs are matched across the basal lamina by mesenchymal cells that are thought to aggregate in response to epidermal signals ***(Hirai et al., 1992)***.

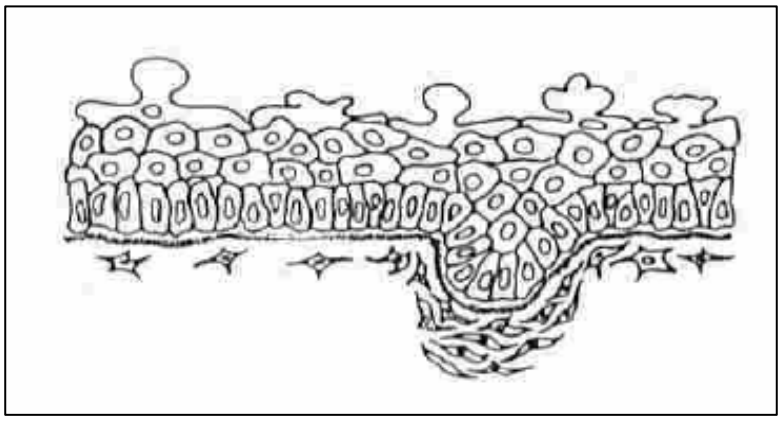

Figure (1): Diagram of the follicular germ illustrating the condensing mesenchyme proximal to the epidermally-derived follicle cells ***(Holbrook et al., 1993)***.

(ii) Elongation: The follicle peg stage:

The next stage is known as the follicle peg in which the follicular germ elongates lengthwise as a cord of cells (Figure 2). It grows into the dermis at an angle relative to the epidermis, still in contact with mesenchymal cells along all surfaces. The outer cells of the hair peg are continuous with the basal epidermal layer ***(Holbrook et al., 1993)***.

At the end of the peg stage the tip of the follicle has flattened, defining (morphologically) the presumptive matrix of

the follicle, while those mesenchymal cells concentrated at the tip eventuate into the follicular papilla and the mesenchymal cells lining the sides of the epidermal cord eventually form the follicular sheath ***(Lavker et al., 1999)***.

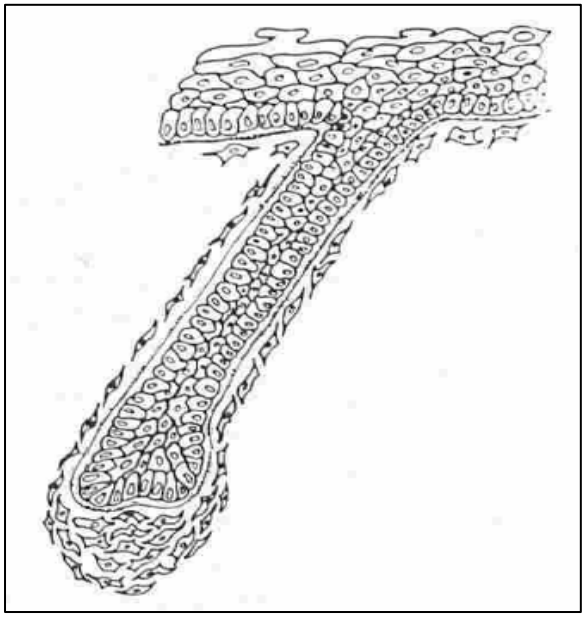

Figure (2): Schematic drawing of the follicle peg stage ***(Holbrook et al., 1993)***.

The mesenchymal cells and the epithelial cells at the flattened tip of the follicle are an epithelial-mesenchymal unit that interacts to promote and sustain follicle differentiation. This interaction has been described as a dermal message in which the mesenchyme tells the follicle epithelium "to make a hair" ***(Hardy, 1992)***.

(iii) Differentiation of the follicle: The bulbous hair peg "Lanugo follicle":

The follicle continues to elongate and begins to differentiate into regions that are defined by the position of three distinct outgrowths "buds" of cells from the outer root sheath (ORS) on the posterior aspect of the follicle (Figure 3). The most superior of the outgrowths is the cell bud closest to the epidermis which may develop into an apocrine (sweat type) gland but regress as the hair follicle matures. The cell bud in the middle is the primordium of the oil producing sebaceous gland. Lastly, the inferior outgrowth is the bulge, the site of attachment of the arrector pili muscle (APM) and the presumptive location and source of stem cells that support regrowth of the follicle at the beginning of anagen of the adult hair cycle ***(Cotsarelis et al., 1990)***. The flattened end of the elongated hair peg molds into a bulb, carrying internally the matrix cells that line the concavity of the bulb and the associated mesenchymal condensation of cells referred to as the follicular, or dermal papilla ***(Holbrook et al., 1993)***.

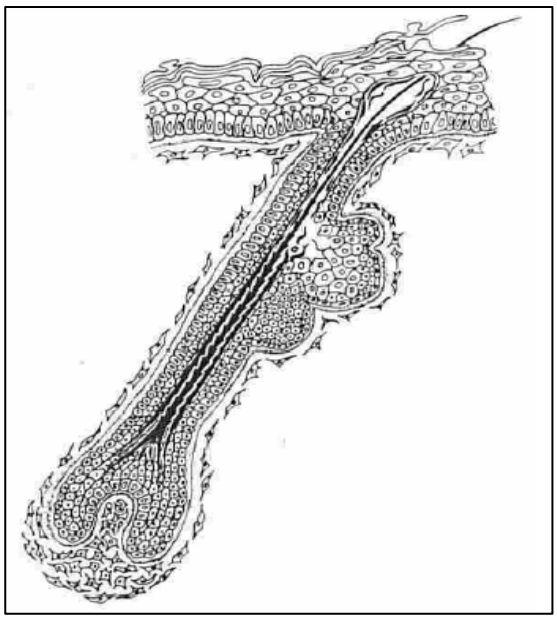

Figure (3): Schematic drawing of the bulbous hair peg stage illustrating the regions of the differentiated follicle including the bulb,matrix, developing hair and layers of the root sheathes. The sebaceous gland and duct, bulge and hair canal are also shown ***(Holbrook et al., 1993).***

(iv) Hair follicle maturation and differentiation:

The bulbous hair peg differentiates into three enclosed epithelial cylinders. The central most cylinder forms the shaft. The outermost cylinder forms the ORS that separates the whole structure from the dermis and maintains contact with the basement membrane. The middle cylinder, the inner root sheath (IRS), guides the shaft in its passage outward serving as the channel for the protruding hair (Figure 4). The shaft and the IRS move outward together ***(Stenn and Paus, 2001)***.

At the end of its morphogenetic phase, the follicle has a cycling inferior (proximal) region and a permanent superficial (distal) region. Once fully formed, the follicle enters its first genuine cycle ***(Ahmed et al., 1996)***.

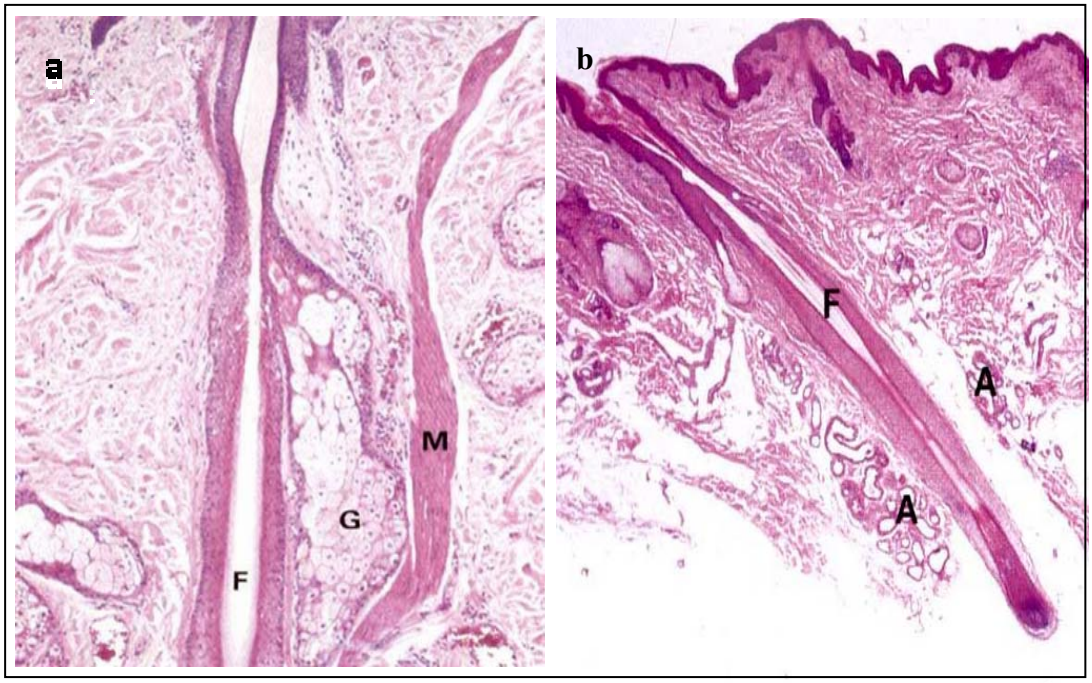

Figure (4): Histomorhological images of human skin illusterating on the left side (a):hair follicle, arrector pili muscle and sebaceous gland, and on the right side (b) hair follicle and apocrine glands. F; hair follicle, G; sebaceous gland, M; arrector pili muscle and A; apocrine gland ***(Weedon, 2002).***

IV. Morphology of the Hair Follicle

The mature anagen hair follicle is composed of a multicylindric stem that contains the hair shaft in its center and

originates as an oval hair bulb proximally. Embraced by the hair bulb, lies an onion-like structure, called the dermal papilla (sometimes referred to as the "follicular papilla" to avoid confusion with the most superficial region of the dermis). The dermal papilla functions as the "command center" of the hair follicle and determines thickness, length, and likely the hair cycle itself ***(Krause and Foitzik, 2006)***.

The portion of hair protruding above the level of the epidermis is called the hair shaft, and the portion within the follicle below the level of the epidermis is the hair root ***(Jankovic and Jankovic, 1998)***.

As regard the hair follicle itself, it can be divided into 3 regions: the lower segment (bulb and suprabulb) extends from the base of the follicle to the insertion of the APM, the middle segment (isthmus) which is a short section that extends from the insertion of the APM to the entrance of the sebaceous gland duct, and the upper segment (infundibulum) extends from the entrance of the sebaceous gland duct to the follicular orifice (Figure 5) ***(Caserio, 1987)***.

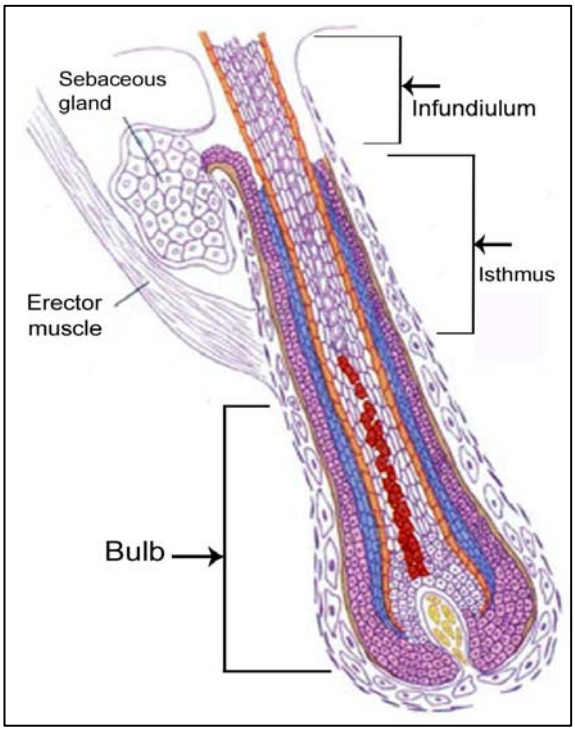

Figure (5): Morphology of the hair follicle ***(Caserio, 1987)***.

V. Structure of the Hair Follicle

The hair shaft is the core part of the hair follicle, and it is surrounded by the IRS. Furthermore IRS is surrounded by another cellular envelope called the ORS ***(Van Steensel et al., 2000)***.

1-Bulb:

The bulb is the base of the hair follicle which includes both specialised keratinocytes, the hair matrix and mesenchymally derived dermal papilla cells (Figure 5) ***(Rochat et al., 1994)***.

The size of the anagen hair bulb, the duration of anagen and the hair shaft diameter are determined by the volume, the number of cells and the secretory activity of the dermal papilla ***(Krause and Foitzik, 2006)***.

a) Hair matrix:

The hair matrix cells are the actively growing portions of the follicle that rapidly divide and move upward (Figure 6) ***(Jahoda and Oliver, 1990)***. Among matrix stem cells, there are melanocytes that produce the pigment of the hair; the melanin ***(Jankovic and Jankovic, 1998)***.

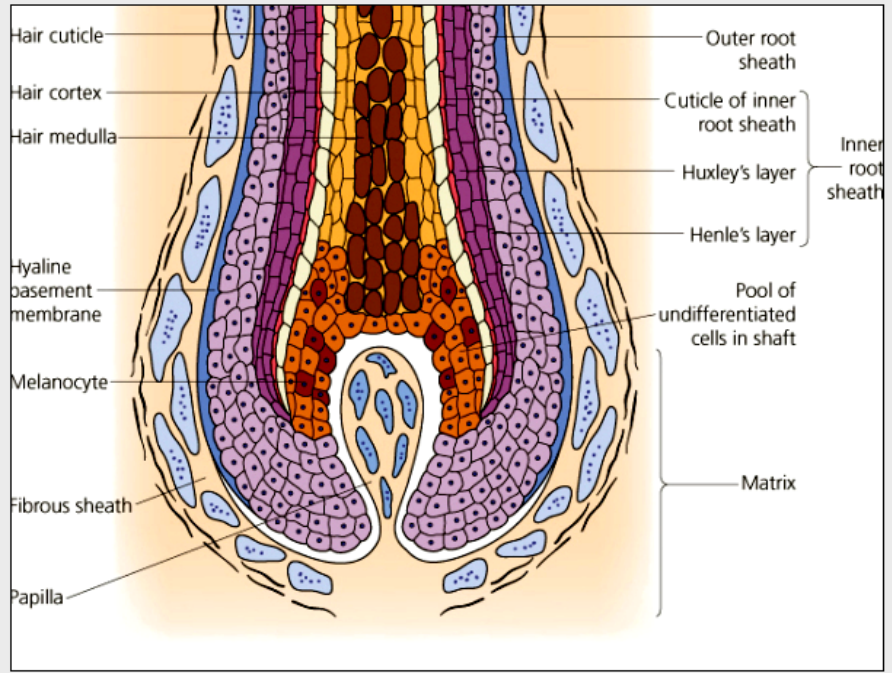

Figure (6): Structure of the hair follicle ***(Murphy, 1997)***.

b) Dermal papilla:

Dermal papilla consists of an egg-shaped accumulation of mesenchymal cells surrounded by ground substance that is rich in acid mucopolysaccharides. The papilla protrudes into the hair bulb and is responsible for directing hair growth ***(Murphy, 1997)***.

2-Suprabulb region:

The suprabulb region extends from the hair bulb to the isthmus and consists of components of the hair shaft, IRS, ORS, vitreous layer, and the connective tissue sheath ***(Sperling, 1991)***.

3-Inner root sheath:

The inner root sheath is adjacent and adherent to the growing hair. It is degraded and sloughed as the hair emerges from the follicle ***(Rogers, 2004)***. It contains no pigment so, it can be easily distinguished from the hair shaft ***(Murphy, 1997)***.

The IRS consists of three concentric cell sublayers as shown in (Figure 6): (a) an inner layer, the cuticle, (b) a middle layer (Huxley's layer), and (c) an outer, Henle's layer cells ***(Schlake, 2007)***. These 3 layers are distinct just above the dermal papilla, but are indistinguishable at higher levels where they function as a single unit covering the hair shaft ***(Allali-Zerah and Mahoudeau, 1994)***.