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).***

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, 2003).***

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 ***(Tami and Inui, 2010). Ludwig*** classified female pattern hair loss (FPHL) into 3 patterns which represent its stages or progressive types ***(Ludwig, 1977).***

This disease is important because of the intense emotional distress it causes by disrupting self image leading to overwhelming effects on the patient's quality of life ***(Hadshiew et al., 2004).***

Current treatments available aim to slow down or stop the progression of hair loss and require continuous use and stimulate only limited hair regrowth ***(Yip et al., 2011).*** Regardless of which medication is utilized, the response is slow, and requires patience and persistence by both the

patient and the clinician ***(Dinh and Sinclair, 2007).*** Finding new therapies for this condition, and improving the effectiveness of the existing ones are therefore of utmost importance ***(Cotsarelis and Millar, 2006).***

Platelet rich plasma (PRP) is an autologous preparation of platelets in concentrated plasma ***(Li, 2012).*** It has been investigated in several disciplines in medicine for its role in wound healing especially orthopedics and dentistry ***(Rogers, 2012).***

Platelet rich plasma was found beneficial in dermatology as in acne scarring, wound healing and fat transplantation. When platelets become activated, the growth factors are released. In turn, they help in tissue mitogenesis, morphogenesis and differentiation ***(Pal et al., 2012).***

Growth factors appear to act in the bulge area of the follicle, where they bind to their respective receptors located on stem cells. They activate the proliferation phase and differentiation of stem cells and hereby produce new follicular units. Therefore, PRP could serve as a potential treatment for androgenetic alopecia ***(Gkini et al., 2014).***

Aim of the Work

To evaluate the efficacy of Platelet Rich Plasma for the treatment of androgenetic alopecia as a new modality of therapy.

Chapter (1): Androgenetic Alopecia

Androgenic alopecia is hair loss that occurs due to an underlying susceptibility of hair follicles to androgenic miniaturization. It is the most common cause of hair loss and affects up to 70% of men and 40% of women at some point in their lifetime ***(McElwee and Shapiro, 2012).*** This condition is also known as male pattern hair loss (MPHL) or common baldness in men and as female pattern hair loss (FPHL) in women ***(Olsen et al., 2007).*** Both male androgenetic alopecia and female pattern hair loss, especially when premature and severe, may have significant psychosocial effects ***(Biondo and Sinclair, 2010)***.

Genetic predisposition and sex steroid hormones are well-established prerequisites for androgenetic alopecia. However, genetic prerequisites and the effect of sex steroid hormones differ between MAGA and FPHL ***(Yip et al., 2011).***

The diagnosis of androgenetic alopecia 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).***

Androgenetic alopecia is manifested as an increase in the absolute number of vellus follicles and a decline in the ratio of terminal: vellus follicles. In normal scalp, the

terminal: vellus ratio is typically in excess of 8:1, whereas in established pattern hair loss, it is no more than 3:1 ***(Whiting, 1996)***. In early pattern hair loss, the total number of follicles is within normal limits, but as hair loss advances, this falls ***(Messenger and Sinclair, 2006).***

Androgenetic alopecia is the most common cause of hair loss that occurs after puberty. Thinning of the hair usually begins between ages of 12 and 40 years in both sexes and approximately half the population express this trait to some degree before the age of 50 ***(Price, 1999)***.

Androgenetic alopecia is important because of the intense emotional distress it causes by disrupting self image ***(Hadshiew et al., 2004).***

Epidemiology

Androgenetic alopecia affects approximately 40% and 50% of men at the ages 40 and 50 years, respectively, whereas approximately 80% and 60% of Caucasian men and women are affected by some degree of hair loss by 70 years of age, respectively ***(Gan and Sinclair, 2005)***.

Two studies in Caucasian women in the United Kingdom and United States reported prevalence rates of 3–6% in women aged under 30, increasing to 29–42% in women aged 70 and over ***(Birch et al., 2011)***. The frequency is lower in oriental women ***(Paik et al., 2001)***.

Etiology and pathogenesis:

The visible thinning of hair of the scalp results from a progressive decrease in the ratio of terminal hairs to shorter vellus hairs, process called follicular miniaturization ***(Yip et al., 2011)***.

The hair follicles are constantly cycling between growth and rest. The growth phase will determine the length of the hair. Hair vary in shaft diameter and length: vellus hairs are depigmented usually non-medulated, thinner and shorter than terminal hairs, which are pigmented and have a medulla. While they both undergo the entire hair cycle, the cycle is shorter for vellus hair ***(Herskovitz and Tosti, 2013).***

The vellus follicles have a shortened hair cycle because their anagen phase is reduced and produce hair shafts that are short and fine. ***(Birch et al., 2011).***

Follicle miniaturization is thought to be caused by a reduction in dermal papilla volume due to reduction in cell number per papilla ***(Tobin et al., 2003)***. Follicular units (grouped individual hairs) from different regions of the scalp and individual hairs within these follicular units vary in their susceptibility to undergo terminal to vellus transformation, leading to macroscopic and microscopic patterns of hair loss, respectively ***(Yazbadi and Sinclair, 2006)***.

The hierarchy of susceptibility between regions of the scalp leads to the ***Hamilton–Norwood*** pattern of

baldness in men, whereas the hierarchy of susceptibility within follicular units leads to generalized thinning and diffuse hair loss in FPHL due to replacement of the usual three- to five-haired follicular units by two- or one-haired units ***(Whiting, 2001).***

The duration of anagen shortens dramatically from 3- 6 years to few weeks or months, whereas the duration of telogen remains the same or lengthens to more than 3 months resulting in an accelerated turnover of anagen hair and significant increase in the proportion of telogen hair from 5-10% to approximately 15-20%. The latter is responsible for the increased hair shedding following combing and washing ***(Singal et al., 2013)***.

Role of Androgens:

The dermal papilla is considered the main site of androgenic action and, in response to androgens, it could alter the production of soluble regulatory factors that influence the growth and activity of other cells, such as hair follicle keratinocytes ***(Yip and Sinclair, 2006).***

Locally and systemically derived testosterone either directly binds to intracellular androgen receptors mainly expressed within the dermal papilla and hair bulb or is metabolized into the more potent dihydrotestosterone (DHT), which, in turn, binds to androgen receptors with an approximate fivefold greater affinity. It is thought that DHT is the key androgen required for the induction of MAGA ***(Shapiro and Kaufman 2003).***

The conversion of testosterone to DHT in hair follicles is predominantly mediated by the 5 α −reductase type II enzyme. Binding of androgens to their androgen receptors (AR) leads to conformational change of the AR-androgen complex which is then transported into the nucleus where it can bind to DNA which has distinctive binding sites: androgen-responsive elements ***(Bienova et al., 2005).***

Changes in a number of factors along the androgen signalling pathway possibly lead to hair follicle miniaturization, including an increase in the expression of androgen receptors, increased androgen sensitivity to bind more steroid ligand and higher levels of 5alpha-reductase Fig. (1) ***(Yip et al., 2011).***

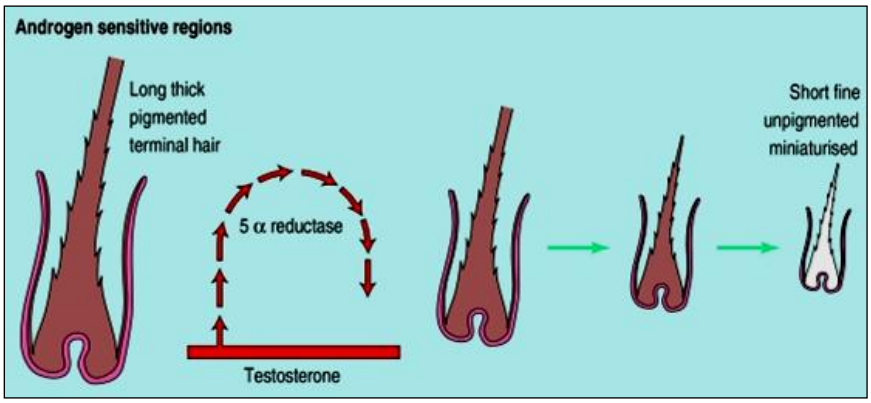

Fig. (1): Miniaturization of the hair follicle ***(Sinclair, 1998)***.

On the scalp, androgen sensitivity and the distribution of androgen receptors are region-specific ***(Sawaya and Price, 1997)***. This may explain why the occipital scalp is resistant to the effects of androgens and is usually spared even in the most severe cases of MAGA ***(Messenger, 2001).***

Cultured dermal papilla cells from a balding scalp grow more slowly than equivalent cells from a non-balding scalp ***(Bahta et al., 2008),*** and are more sensitive to stress-induced cell senescence ***(Winiarska et al., 2006).***

When treated with excess androgens, dermal papilla cells from a balding scalp undergo apoptosis ***(Kwack et al., 2008)*** lose their ability to stimulate the proliferation of keratinocytes ***(Itami and Inui, 2005)*** and increase their secretion of transforming growth factor-ß, which is able to inhibit keratinocyte proliferation ***(Ohnemus et al., 2006).*** These results suggest that, *in vivo*, excess androgen stimulation of susceptible scalp hair follicles compromises the ability of dermal papilla cells to undergo hair follicle cycle remodelling and new hair shaft growth ***(Oslen et al., 2005).***

Role of estrogen:

The ability of the hair follicle to metabolize estrogens has been confirmed by the localization of aromatase and 17 ß-hydroxysteroid dehydrogenase expression within dermal papilla cells and keratinocytes of the outer root sheath ***(Ohnemus et al., 2006).***

Aromatase is the key enzyme required to convert androgens to estrogens in tissue sites (e.g. testosterone into 17 ß-estradiol and androstenedione into estrone) ***(Bulun, 1998).***

There are different clinical and scientific views on whether estrogen is stimulatory or inhibitory to hair growth ***(Sawaya and Price, 1997)***.

From a clinical perspective, the increased prevalence of female pattern hair loss after menopause suggests a stimulatory role for estrogen in hair growth. In addition, high systemic estrogen levels in pregnancy are speculated to partially account for the prolongation of anagen, while decreasing estrogen levels in the post-partum period may partially account for the simultaneous conversion of hair follicles into the telogen phase, resulting in the condition telogen gravidarum ***(Oh and Smart, 1996).***

Lower estrogen levels due to aromatase inhibitor therapy have also been observed to induce hair loss ***(Paus, 2006).***

On the other hand, an evidence for an inhibitory role of estrogen in hair growth is the finding of an aromatase gene variant associated with higher circulating estrogen levels that occurs at higher frequencies in women with female androgenetic alopecia compared with unaffected women ***(Yip et al., 2009).***

Genetic Basis of Androgenetic Alopecia:

Nearly all men afflicted with AGA have normal circulating androgen levels, and the predisposition to AGA is predominately due to genetic factors ***(Chumlea et al., 2004)***.

MAGA and FPHL are complex polygenic traits. The causative genes for baldness could influence predisposition through DNA sequence variation, such as single nucleotide polymorphisms (SNPs), insertion mutations, deletion mutations and copy number variation. The SNPs are the most common form of genetic variation in humans, and one of the most commonly studied DNA sequence variations in human complex diseases, such as baldness. An SNP is defined as a single base change that results in DNA sequence variation ***(Burton et al., 2005*)**.

The mode of inheritance is usually cited in the scientific literature as autosomal dominant, suggesting that inheritance of only one autosomal gene conveys full genetic predisposition ***(Irvine and Christiano, 2001)***.

The first published genetic link with MAGA was the discovery of a marked association with a particular SNP in exon 1of ARs. This SNP is present in almost 100% of young and older balding men ***(Yip et al., 2011)***. Its strong association with MAGA could be explained if it is acting as a marker for the inheritance of another functional SNP (that alter amino acid sequences travelling together with it throughout generations in a concept known as linkage disequilibrium ***(Redler et al., 2011)***. ***Richards et al., (2008)***

examined four distinct European populations and estimated that one in seven men who harboured the MAGA-associated SNPs at both chromosome 20p11 and AR had a sevenfold increased risk of MAGA.

Several genes have been examined but did not show any association with MAGA such as 5a-reductase type I gene (SRD5A1), aromatase gene (CYP19A1), estrogen receptor α gene (ESR1), IGF-2 gene and insulin genes ***(Ellis and Harrap, 2001)***. However, these genes have only been superficially examined using a small selection of SNPs for each gene without coverage of their entire gene regions. These genes cannot yet be completely excluded as causative genes for MAGA until more comprehensive examination is performed to capture any possible association with variants located in the non-examined gene regions ***(Yip et al., 2011)***

There are few studies evaluating the genetic basis and inheritance pattern of FPHL. One of them shows an incidence of 54% pattern hair loss in first-degree male relatives aged > 30 years and 21% in first-degree female relatives > 30 years. Those reports of the occurrence of both FPHL and AGA in individual families suggest that FPHL and AGA share a common genetic background ***(Nyholt et al., 2003).***

Female pattern hair loss is possibly a multigenic disease, but the causative genes are not established. The two major susceptibility loci for the AGA in men are the androgen receptor (AR)/ectodysplasin A2 receptor (EDA2R) locus on the X-chromosome, and a locus on chromosome 20p11, for which no candidate gene has yet

been identified ***(Brockschmidt et al., 2010)***. There are studies that showed no involvement of the well-established locus on chromosome 20p11 in FPHL, but suggested that the X-chromosomal locus containing the androgen receptor (*AR*) and the ectodysplasin A2 receptor (*EDA2R*) genes, may be specifically involved in the pathogenesis of early-onset FPHL ***(Redler et al., 2012).***

The role of aromatase gene CYP19A1 has been reported but not confirmed**.** In other studies there were no associations between steroid 5-alpha-reductase isoform genes or sex steroid hormone receptors and FPHL**.** Neither there was association with melanocortin 4 receptor gene ***(Herskovitz and Tosti, 2013).***

Clinical features:

Hair loss in male AGA begins with bitemporal recession of the frontal hair line, followed by diffuse thinning over the vertex sparing the sides and back in "M" shaped pattern ***(Drake et al., 1996)***. This pattern reflects the distribution of androgen-sensitive follicles in most people ***(Shapiro and Price, 1998)***. Occasionally, a female pattern can be seen in men in the form of diffuse thinning of the crown region with retention of the frontal hairline with a pattern that resembles the Ludwig type ***(Messenger, 2001)***.

As regard classification of MAGA, the most common classification system for this condition has been named ***Hamilton-Norwood*** classification of male pattern alopecia **(*Norwood, 1975*)** (Figure 2) which classify it into:

Class I: No or very minimal hairline recession along the anterior border in the frontotemporal region.

Class II: The anterior border of the hair in the frontotemporal region has symmetric triangular areas of recession which extend no further posteriorly than 2 cm anterior to a line drawn in a coronal plane at the level of the external auditory meatus.

Class IIA: The hairline is anterior to the coronal plane 2 cm anterior to the external auditory meatus.

Class IIIA: The hairline has receded back to a point between the limit of type IIA and the level of the external auditory meatus.

Class III: The triangular areas in type II extend posterior of the coronal plane which is 2 cm anterior to the external auditory meatus. This is the minimal level considered to represent baldness.

Class III Vertex: Most of the hair loss is seen on the vertex. Frontal hair loss may be similar to type I or II but should not exceed type III. This type is most commonly seen with advancing age.

Class IV: Hair loss on the vertex associated with frontal loss more severe than type III, but the frontal and vertex areas are separated by a distinct band of hair.

Class IVA: The hairline has receded beyond the external auditory meatus but has not reached the vertex.

Class V: Greater hair loss than type IV with only a sparse band of hair separating the frontal and vertex areas. The hair left on the occipital and parietal areas begins to form the shape of a horseshoe when viewed from above.

Class VA: The area of denudation includes the vertex. Hair loss more severe than type VA, cannot be distinguished from type VI or VII.

Class VI: The frontal and vertex areas of hair loss are contiguous with greater lateral and posterior areas of denudation.

Class VII: The most severe form of male pattern baldness. Only a narrow sparse horseshoe-shaped band of hair is left extending from the ears posteriorly to the occiput **(*Norwood, 1975*).**

Classes II through V can be designated with a class A variant (Figure 2), which has major and minor features. The major features include that the entire anterior hairline border recedes in unison without leaving the midfrontal peninsula of hair, and that there is no simultaneous balding of the vertex. There are two minor features that include scattered sparse hairs frequently persisting in the entire area of balding, and the horseshoe shaped fringe of hair that remains on the sides and back tends to be wider and reaches higher on the head. These variants exist only in about 3% of the population studies **(*Norwood, 1975*).**