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Copper Deficiency a New Reason of Androgenetic Alopecia?

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1. Introduction

Androgenetic alopecia is the common type of hair loss in men and women since puberty. Typically, AA is the complex result of an androgen-dependent process and this process is located to androgen receptor (AR) areas (frontal and vertex zone). Number of androgen receptors is genetic transmission. The polymorphism involving the CAG triple repeat expansion of the AR protein has been revealed in men with AA. This male pattern hair loss may represents from influence of minimal androgen excess basing on genetically sensitive hair papilla.

Dihydrotestosterone (DHT) is derived from circulating testosterone (T) inhibits cell proliferation in the dermal papilla and local production of vascular endothelial growth factor [1]. As a result, the DHT-dependent process leads to the miniaturization of sensitive hair follicles and progressive thinning the scalp hair. It is known that the follicular dermal papilla controls hair growth. Steroid hormones, including androgens, estrogens and glucocorticoids may influence on timing of hair cycle [2].

More recent studies have focused on androgen-regulated hair growth. But, studies of action of other steroids in the hair follicle have been relatively limited. There are two estrogen receptors (ER α and ER β) which bind to 17 β -estradiol. The effects of estrogens seem complex whereby estrogen prolongs the anagen phase of the hair follicle and stimulates hair shaft elongation [2]. ER β expression was found in outer root shaft and epithelial matrix. In contrast, ER α and AR were expressed in dermal papilla [3]. Therefore, the ratio of ER α to ER β in dermal papilla cells is extremely important. Estrogen also modifies androgen metabolism. The local production of estrogens from androgen precursors has been converted by the aromatase cytochrome P 450 enzyme complex. It is now clear there is aromatase expression in the dermal papilla and the outer root sheath. The activity of aromatase is higher in women in occipital

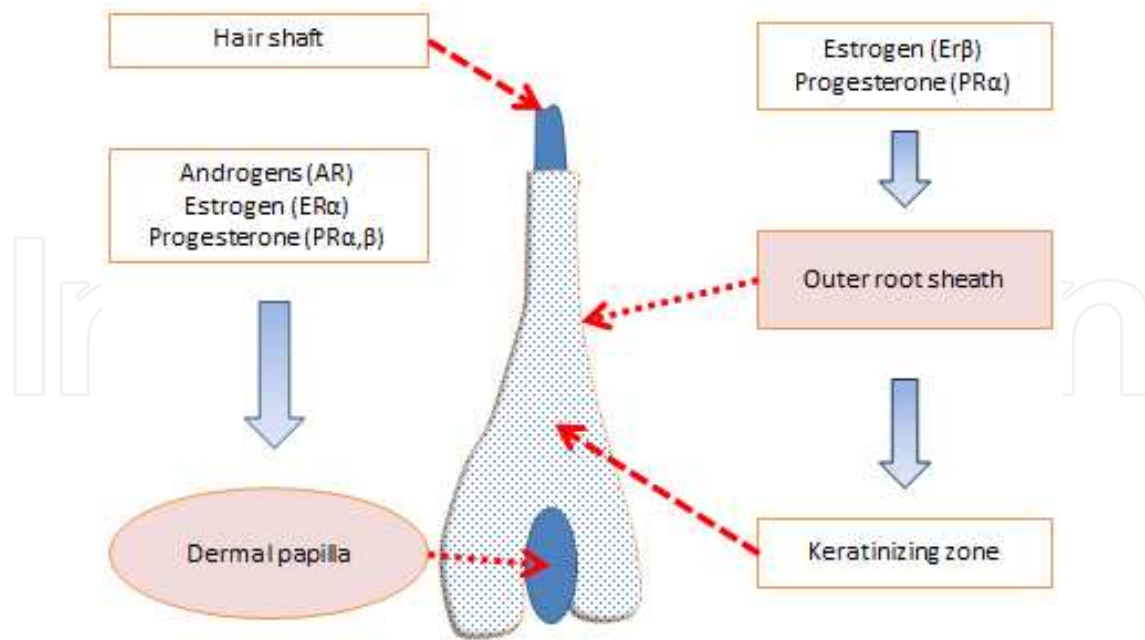


Figure 1. The hair shaft

scalp area compared to the frontal scalp and it has been diminished in AA [4]. Some researchers found that estradiol inhibited 5 alpha-reductase activities [5]. The effects on estrogens might be explained by an increased conversion of T to the weaker androgens such as androstendione and androstendiol. Progesterone is able to modulate activity of DHT in dermal papilla by 75% [4, 6]. Also, progesterone is widely recognized as a marker of estrogen action and has anti-inflammatory properties. Progesterone regulates the expression of matrix metalloproteinases (MMPs) by transforming growth factor- β [7].

However, in women hair loss is not limited to only this location and combined with diffuse alopecia. Except in some cases, treatment of 5 alpha reductase inhibitors is ineffective in women. The origin and mechanisms of AA in women are different and more complicated than in men and remain a challenge.

The aim of the work was to estimate a possible role of trace elements (TE) changes in AA in man and women.

2. Materials and methods

In this study, 97 women and 40 men, ages 20-55 y., with AA were selected for the determination of TE content and CP in serum, hormonal status. Diagnosis of AA was based on clinical findings, pattern of increased hair thinning on frontal/vertex scalp with greater hair density on occipital scalp zone; retention of frontal hairline; and the presence of miniaturized hairs (vellus hair, diameter less 30 μm). Detailed study of the consumption of drugs, iron intake and thyroid metabolism ruled out other types of alopecia. The degree of AA was determined

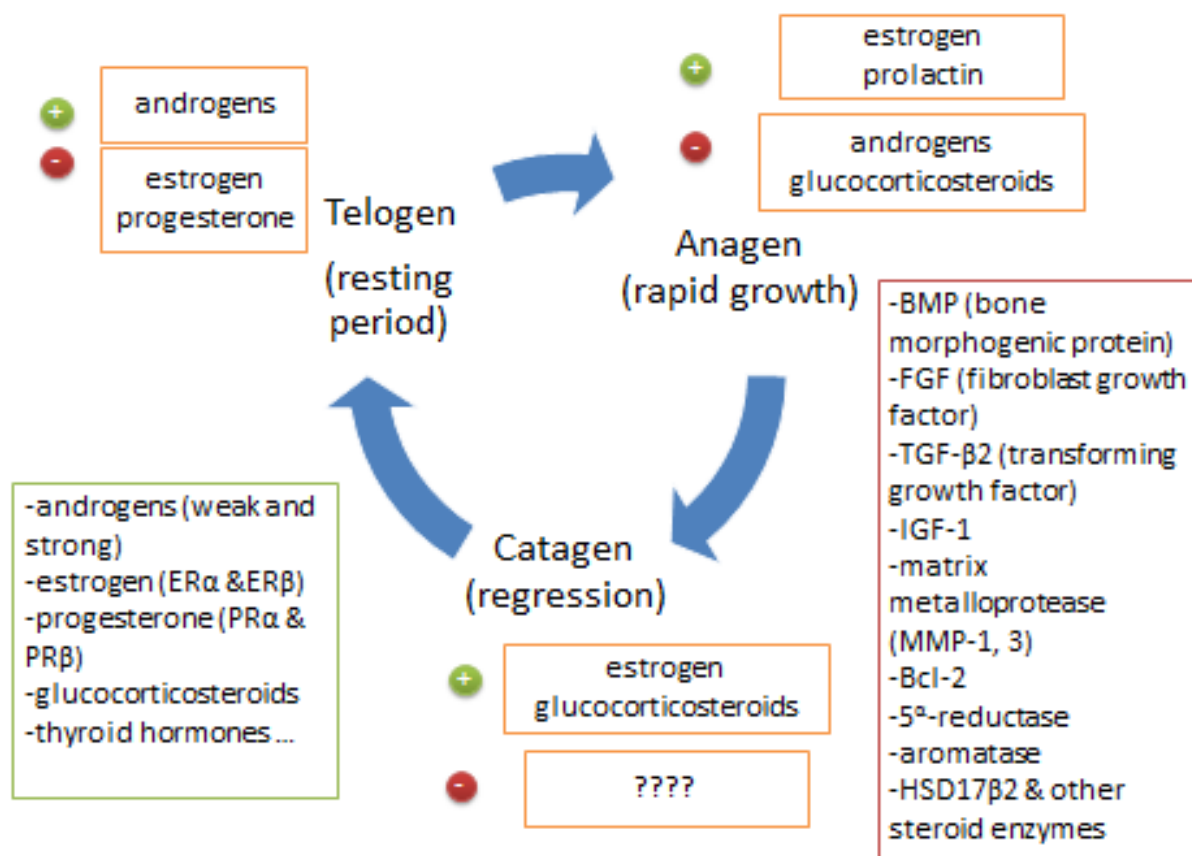


Figure 2. The timing of the hair cycle

by application of Ludwig scales (II–III). Exclusion criteria were: replacement hormone therapy (RHT) with estrogens, progesterone, testosterone, L-thyroxin or corticoids during last 6 months. Women’s group was divided by 5 subgroups: women with excess of androgens, ages before 40 and after 40 y.o. (22 and 19 correspondently), women with excess of estrogens before and after 40 y.o. (24 and 17) and women with obesity at age of 20-40 year (16 patients). Women had both AA and the other sings of elevated androgens level (hirsutism and acne) were included in group with excess of androgens (HA 1 and 2). Women in group with excess of estrogens had endometriosis, uterine leiomyoma or combining both of these (HE 1 and 2). Childbearing aged women with abdominal obesity (waist >88 cm.) and excess of ALT concentration in blood were enrolled in group with obesity (O1). Control group included in age-matched men and women (76 and 32 patients correspondently) who presented no diseases at the time of examine. The concentration of TE has been analyzed by ICP mass-spectrometer Nexion-300D and Elan-9000 (Perkin Elmer Corp., USA). Reference materials of serum and hair samples were used. The level of FSH (follicle-stimulated hormone), LT (leuteotrophic), 17 β -estradiol (E2), progesterone (PR), prolactin, androstendione (A), dihydrotestosterone (DHT) and sex hormone bound globulin (SHPG) was tested by routine laboratory methods.

Statistical analyses were performed with the ANOVA software (Statistics version 7). We applied non parametrical statistics: median, 25 and 75 percentiles. Student’s t-test was used to

compare the values of quantitative variables. Correlations among variables were studied using the Pearson's coefficient. $P \leq 0.05$ was considered significant in all analyses.

3. Results

No significant differences of TE serum content in men and women were found between AA patients and control group. The exception was the concentration of copper (Cu) which was statistically significant differences between men and women suffering from AA and matched control (Table 1). In present work in women with hyperandrogenism there are the some trends in TE content in serum than in men. The key disorder was decreased Cu level in frontal zones of scalp hair and serum.

Element	Men				Women			
	AA group, n=40		Control, n=32		AA group, n=97		Control, n=76	
	Median	Persencile (25-75)	Median	Persencile (25-75)	Median	Persencile (25-75)	Median	Persencile (25-75)
As	0,019	0,015-0,025	0,015	0,008-0,028	0,018	0,007-0,028	0,02	0,01-0,032
Ca	92,3	88,2- 98,5	96,1	91,0-101,0	95,8	90,6-102,4	95,3	89,6-103,3
Co	0,0005	0,0004-0,0006	0,0006	0,0004-0,0007	0,006	0,0005-0,0008	0,0006	0,0005-0,0008
Cu	0,80	0,70-0,85	0,88*	0,75-1,06	0,85	0,77-0,94	0,99*	0,90-1,11
Fe	1,3	1,0-1,5	1,4	1,3-1,5	1,3	1,0-1,6	1,2	0,78-1,46
K	183	169-196	187	178-199	170	158-193	178	157-204
Mg	20,7	19,9-21,2	20,7	19,3-22,4	20,3	19,1-21,5	20,8	19,4-22,4
Mn	0,0034	0,0030-0,0038	0,0037	0,0031-0,0048	0,0032	0,0027-0,0039	0,0032	0,0026-0,0043
Mo	0,0008	0,0007-0,0012	0,0009	0,0007-0,0012	0,0009	0,0007-0,0012	0,001	0,0008-0,0014
Ni	0,006	0,005-0,007	0,006	0,005-0,008	0,006	0,005-0,007	0,006	0,005-0,008
Se	0,14	0,13-0,16	0,16	0,13-0,17	0,14	0,13-0,17	0,14	0,13-0,16
Zn	0,89	0,83-1,04	0,91	0,82-1,10	0,81	0,72-0,95	0,83	0,69-1,06

*- $P < 0,01$ (differences between control group and AA's group)

Table 1. Trace elements content (mkg/ml) in serum in men and women with AA

In spite of sex decreased Cu concentration in serum were obtained in patients with AA. However, Cu level in women was higher in comparison to men.

Median, 25-th and 75-th percentiles values in women with AA and accompanying other diseases are summarized in Table 2.

Element	HA1 n=22	HA2 n=19	O1 n=24	HE1 n=17	HE2 n=16	Control n=76
As	0,017 (0,007-0,031)	0,020 (0,008-0,031)	0,016 (0,006-0,038)	0,014 (0,006-0,023)	0,012 (0,007-0,031)	0,020 (0,010-0,032)
Ca	95,8 (91,5-98,0)	101,1 (89,3-104,0)	91,3 (87,2-97,5)	97,8 (87,1-100,5)	93,5 (91,7-97,1)	95,3 (89,6-103,3)
Co	0,0006 (0,0005-0,0007)	0,0005 (0,0004-0,0007)	0,0006 (0,0004-0,0008)	0,0007 (0,0005-0,0008)	0,0007 (0,0005-0,0010)	0,0006 (0,0005-0,0008)
Cu	0,81* (0,72-0,89)	0,85* (0,80-0,91)	0,94 (0,81-1,08)	0,97** (0,86-1,19)	0,99** (0,89-1,21)	0,99 (0,90-1,11)
Fe	1,3 (1,1-1,7)	1,2 (1,1-1,4)	1,2 (0,8-1,6)	1,3 (0,4-1,5)	1,1 (0,6-1,4)	1,2 (0,8-1,5)
K	183 (164-204)	193 (169-291)	183 (165-194)	195 (175-234)	170 (153-190)	178 (157-204)
Mg	20,4 (19,1-21,8)	20,9 (20,1-22,1)	19,6 (18,4-21,4)	20,5 (18,7-22,3)	19,6 (18,1-20,5)	20,8 (19,4-22,4)
Mn	0,0033 (0,0027-0,0040)	0,0035 (0,0030-0,0039)	0,0031 (0,0026-0,0034)	0,0030 (0,0027-0,0035)	0,0033 (0,0027-0,0036)	0,0032 (0,0026-0,0043)
Mo	0,0009 (0,0007-0,0013)	0,0007 (0,0005-0,0010)	0,0009 (0,0006-0,0011)	0,0008 (0,0006-0,0009)	0,0007 (0,0007-0,0008)	0,0010 (0,0008-0,0014)
Ni	0,006 (0,005-0,007)	0,006 (0,005-0,007)	0,006 (0,004-0,007)	0,005 (0,005-0,006)	0,005 (0,004-0,006)	0,006 (0,005-0,008)
Se	0,15 (0,13-0,16)	0,14 (0,14-0,16)	0,15 (0,13-0,16)	0,14 (0,12-0,16)	0,14 (0,13-0,15)	0,14 (0,13-0,16)
Zn	0,93 (0,82-1,05)	0,85 (0,75-1,07)	0,70* (0,66-0,76)	0,89 (0,80-0,95)	0,79 (0,69-1,19)	0,83 (0,69-1,06)
Cu/Mn	239 (187-306)	245 (213-277)	319 (278-369)	336** (300-438)	349** (282-420)	288 (253-370)
Cu/Zn	0,82* (0,73-1,06)	1,01 (0,76-1,14)	1,31* (1,22-1,40)	1,12 (1,04-1,25)	1,12 (0,82-1,50)	1,22 (0,94-1,42)

*-P<0,005 (differences between control group and others)

**-P<0, 05 (differences between groups with excess of androgens (HA1) and estrogens (HE 1 or 2)).

Table 2. TE content and ratio Cu/Mn and Cu/Zn (Median, 25-75th percentiles) in women with AA and associated with different diseases.

When we separated women with AA into subgroups there have obtained differences between control and investigated groups. No significant differences were found between AA patients and control in the majority of TE content in serum. Although the lowest Cu content was

observed in group combining AA with other sing of excess of androgens such as hirsutism and acne.

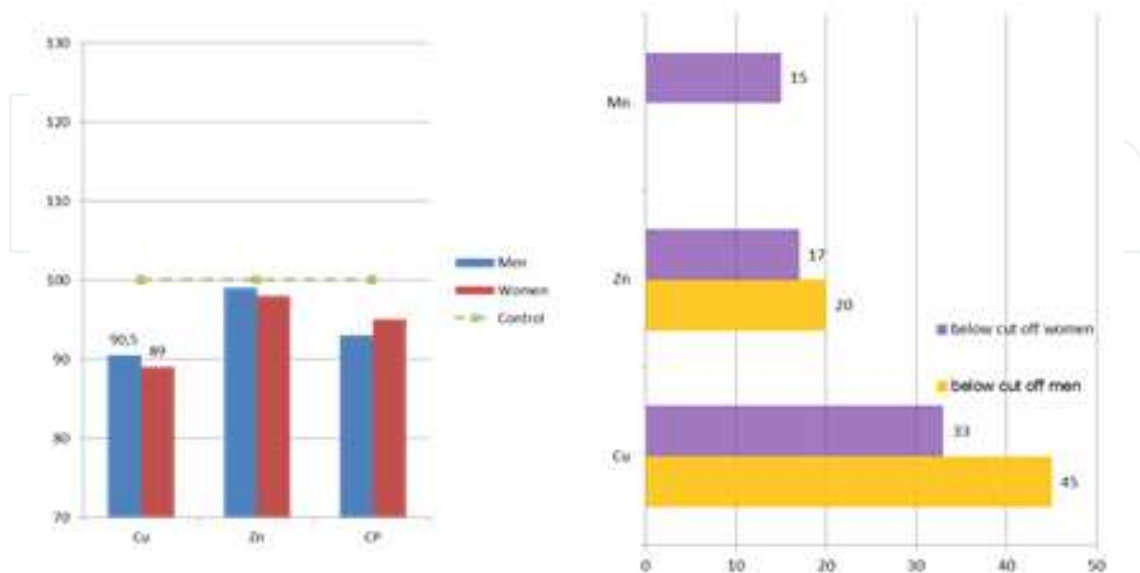


Figure 3. Content of Cu, Zn and ceruloplasmin (CP) in men and women with AA

Cu concentration in groups with elevated androgens level and with appearance of several marks of androgens abundance was lower than in the whole women group with AA. There were statistically significant differences between Cu level in groups with plenty of androgens and estrogen. In case of being endometriosis or uterine leiomyoma (HE1 and 2) in women Cu concentration in serum have maintained the same than in control, although not decreased in patients with AA. The overflowed androgens in women were conducted the reduction Cu content in serum considerably. The zinc (Zn) level was the lowest in women who combined AA and abdominal obesity. There was variety Zn content in serum in women at ages. In women under 40 year of age either elevated androgens or excess of estrogen the Zn level was getting low as compared to women before 40 year. The ratio Cu/Mn in women HE1 and 2 groups has been elevated significantly in comparison with groups with excess of androgens.

There was a tendency to raise the ratio Cu/Mn in women with elevated estrogen level as compared to control. The ratio Cu/Zn was significant lower in women any ages with abundant of androgens than in control. But, in case of abdominal obesity the values of this ratio were higher in comparison with control group.

4. Discussion

The hair follicle represents a unique, highly regenerative neuroectodermal – mesodermal interaction system. These transformations are controlled by changes in the expression/ activity

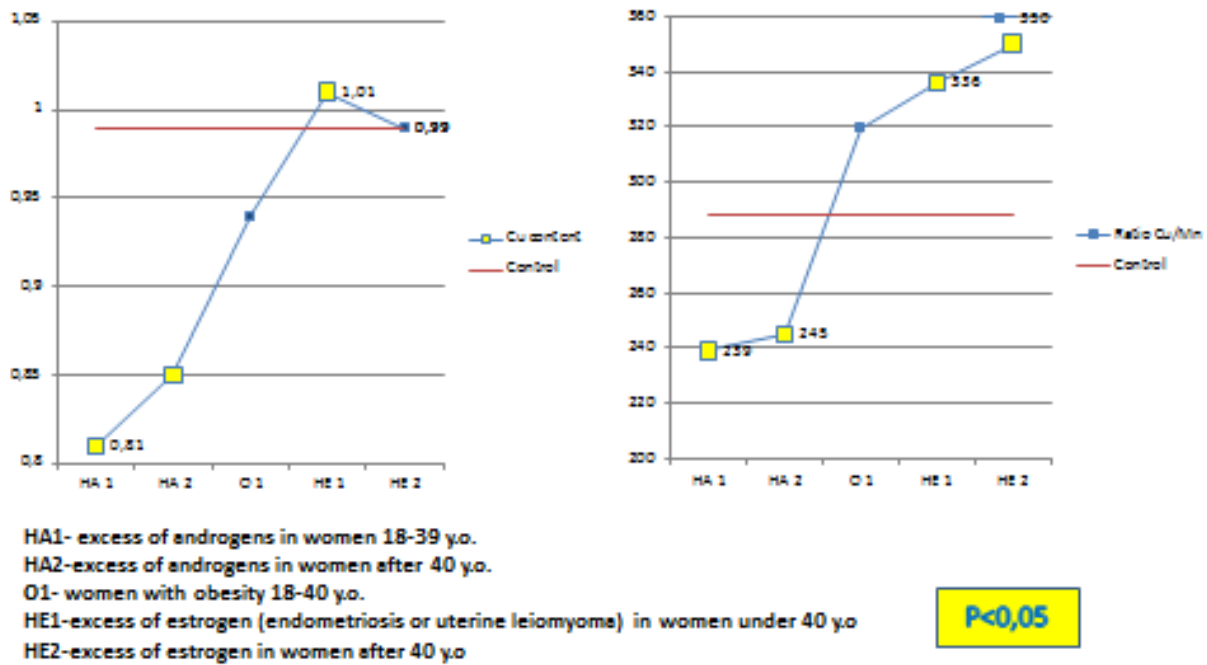


Figure 4. Cu content and ratio Cu/Mn in women with AA

of a numerous growing factors, cytokines, hormones, neurotransmitters, as well as transcription factors and enzymes.

Alopecia areata (AA) is the most common type of alopecia that the onset after puberty in both sexes. AA may affect up to 70 of men and 40% of women [8]. Male and female pattern hair loss are clinically distinct entities but pathogenically indistinguishable. The main role in the onset of AA in men is local disturbances in androgens metabolism which based on genetic predisposes to converse of terminal hair in vellus-like hair. AA is a polygenetic hereditary disease. A low number of CAG repeats in the androgen receptor gene implies increased risk factor for AA; prostate hyperplasia, coronary heart disease. But the role of sex hormones in females is less understood. Some of women suffering from AA are revealed androgens excess with other signs of elevated androgens such as hirsutism, acne, polycystic ovary syndrome. In women there is the appearance of AA combining with diffuse hair loss [9].

AA in men is due to implicate DHT production by 5 alpha-reductase type 2. The primary precursor of DHT in men is testosterone. The androgen receptor (AR) binding leads to increase production of cytokines such as TGFβ-1 and 2, which promote telogen, thinning and shortening hair. There is a low number of AR in occipital hair follicles that hair loss is mostly restricted to the scalp vertex and frontal and temporal areas. The using of a type 2 – selective inhibitor demonstrated the improvements in scalp hair growth in men. On stopping finasteride treatment, the balding process resumed. However, finasteride has been associated with depressive symptoms, persistent sexual side effects (loss of libido and erectile function). In contract to its beneficial effects of finasteride (5 alpha-reductase’s inhibitor) in men; it didn’t

improve hair growth in women with AA. These findings suggested that the molecular mechanisms involved in the different metabolic ways in regulations hair growth in women.

Women with some markers of insulin resistant have increased risk of AA [9]. Several studies have analyzed the relationship between androgenetic alopecia and cardiovascular disease. Women with AGA showed higher significant mean values than non-alopecic women for all the parameters (triglyceridaemia, LDL-C, total cholesterol, total cholesterol/HDL-C and LDL-C/HDL-C) and lower significant HDL-C than controls.

Estrogens are indirect anti-androgens which increase SHMG production by binding to androgens and reducing their bioavailability. The production of estrogens from androgens via aromatase is of the importance in hair follicles. The comparison of scalp biopsies from men and women with AA revealed aromatase levels to be higher in hair follicles from occipital area in comparison to the frontal hair follicles. Furthermore, aromatase levels has found in six times higher in women when compared to men. Recent study has demonstrated that both dermal papilla and outer root sheath expressed aromatase activity. The levels of ER expression and aromatase activity may be modulated by steroid hormones in other tissues it would be important in the hair follicle. Likewise androgens have been reported to alter the ration of ER α to ER β [2]. The alteration in the ratio of ER α to ER β in dermal papilla cells could promote E2 signaling via ER β in preference to ER α .

Since the hair follicles has been shown to express AR, glucocorticoid receptor, ER α , ER β and progesterone receptors (PR α and PR β). Both the dermal papilla cells and surrounding epithelial cells express ER. Additional local productions of E2 via conversion from A by aromatase may act in either an autocrine or paracrine manner to control lair growth and differentiation. In experimental studies PR inhibited the synthesis of DHT in dermal papilla by 75%. E2 was less able inhibit its production [6].

However, no direct effects of prolactin on hair growth have been reported [11]. Progesterone acts via PR receptors on cells to induce secretion of paracrine factor that in turn stimulate the expression 17 β –hydroxysteroid dehydrogenase type 2 (HSD17 β 2). HSD17 β 2 metabolizes E2 to weak estrogenic estrone. The control of hair growth by E2 is much more complex than previously appreciated.

The E2 may modulate hair growth by interfering with androgen metabolism [12]. The estrogenic effects on dermal papilla cells are mediated via ER α .The role of ER β may be to protect tissues from oxidative stress by inducing battery of antioxidative enzymes. Under hyperestrogenic conditions, the ratio PR β to PR α is decreased but ratio ER β to ER α is elevated in endometriosis and uterine leiomyoma. Serum Cu level is known to control by estrogens. Under excess of androgens Cu content in serum was decreased and associated with elevated DHT level which results of 5alpha-reductase type 2 activities. The pathogenic mechanism of AA is case of abundant of androgens doesn't differ in men and women with high androgens level. The development of AA shows up other clinical marks of androgens excess (hirsutism and acne) and reflect the interaction androgens and estrogen metabolism. Both AR and ER α are located into dermal papilla and influenced on hair growth [4]. In some studies have shown there was depressed ratio E2 to androgens [13].

We demonstrated the development of AA in women with endometriosis or /and uterine leiomyoma. These diseases have usually revealed of estrogens excess, high activity of aromatase and decreased level of progesterone. There was a high level of ratio $ER\beta$ to $ER\alpha$ against the background of changed ratio progesterone receptor ($PR\alpha/PR\beta$). The onset and development of AA in this group didn't link to abundant androgens level.

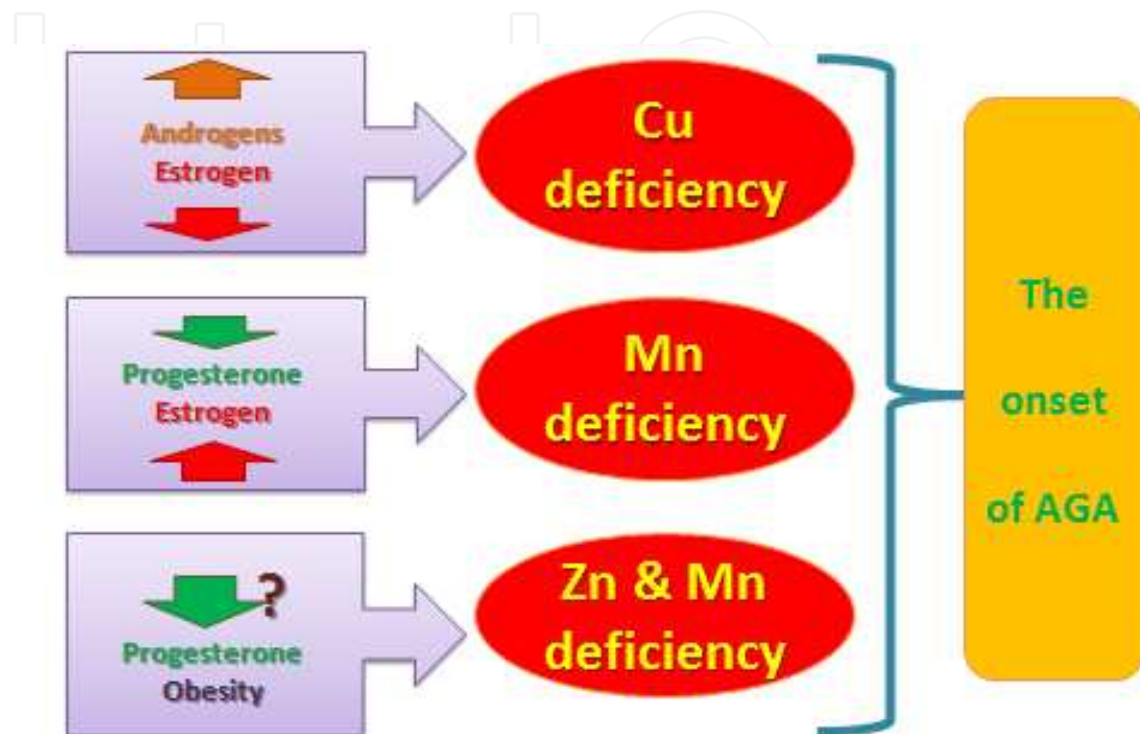


Figure 5. Proposed schema of TE dependent androgenetic alopecia

Normal or excess estrogens concentration and deficiency or resistant to progesterone were typical in these women. Cu content in serum and ratio Cu/Mn determined higher than in control. But, Mn level in these groups remains lower to compare with control. These data suggest that the important value in appearance of AA belongs to the relationship between E2 and PR and ratio of their receptors in peripheral tissues. About 15% from all examined women with AA have been detected the cut-off Mn level. Mn is known to impede the female and male reproductive function. In experimental studies the relationship Mn concentration and progesterone level have been shown. There is the high level of Mn-COD in lutein phase of menstrual cycle [14]. Manganese superoxide dismutase (Mn-COD), an antioxidant enzyme in the mitochondria, protects cells by scavenging superoxide radicals. Mn-COD increases by inducing progesterone. Experimental data suggests that Mn down-regulated steroidogenesis in Leydig cells [15]. Mn influences the receptor signaling pathways and contractile machinery of vascular smooth muscle cells [16]. The expression of Mn-COD was significantly increased by 17β -estrogen and testosterone in neutrophil granulocytes in healthy volunteers [17]. In our work we hypothesize that the assignment of low Mn content may reflect depressed value of PR, changed ratio PR receptors or cell's resistance to PR.

In women serum ferritin levels may also be assessed to determine hair loss. Appreciating the importance of iron as a factor in hair loss may be important in the therapy in a variety of etiologically distinct forms of hair loss. According to obtained findings there was no statistical difference in iron content between control and experimental groups [18].

Condition	excess of A	excess of estrogen
Hormonal status	↑ A→DHT	↑E, ↓Progesterone, ± A
Receptors	AR→ alteration ratio ER α /ER β	alteration ratio ER α /ER β and PR β /PR α
Age	after puberty	middle age and premenopausal
Treatment	decrease level of A and modulation of ratio ER's	increase level of progesterone and modulation of ratio ER's

Table 3. The difference of the onset and development of AA under excess of androgen or estrogen.

In this hypothetical scenario, there were two groups' women with AA. One of them has been registered excess of A in serum (Table 3). The other demonstrated normal level of A but had the alteration of estrogen and progesterone contents in blood. A lot of hormones, growth's factors take part in development of AA. Many diseases have followed by AA. Typically, the excess of A in blood in both men and women with AA have been revealed. Surprisingly, in women with hyperestrogenic condition the onset of AA have shown. The comparable with control level of A has been demonstrated in this group. Therefore, the ratio of ER α to ER β in follicular dermal papilla cells may be important. The alteration of estrogen, progesterone and androgen receptors has the key of metabolic disturbances in dermal papilla cells and outer root sheath. That is why the typical approaches for treatment of AA which include in using hormonal replacement therapy, inhibitors of DHT production and others were not fruitful.

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