Hormonal correlates of acne and hirsutism

Trgovčić, Iva

UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

Iva Trgovčić

Hormonal Correlates of Acne and Hirsutism

GRADUATION PAPER

Zagreb, 2014

This graduation paper has been done at the department of Gynaecology and Obstetrics at the Clinical Hospital Centre Zagreb under the supervision of Prof.dr.sc Dinka Pavičić Baldani and was submitted for evaluation during the academic year 2013/2014.

ABBREVIATIONS

- PCOS – Polycystic Ovary Syndrome
- TT – Total Testosterone
- DHEAS – Dehydroepiandrosterone Sulfate
- A – Androstendione
- T – Testosterone
- FT – Free Testosterone
- DHT – Dihydrotestosterone
- SHBG – Sex Hormone Binding Globulin
- mFG- Modified FerrimanGallwey Score
- 3α-diolG - 3α-Androstenediol Gluconide
- LH- Luteinizing Hormone
- FSH – Follicle Stimulating Hormone
- OC – Oral Contraceptives
- ASI – Acne Scoring Index
- IFT – Index of Free Testosterone
- CPA – Cyproterone acetate
- COC – Combined Oral Contraceptives

TABLE OF CONTENTS

1.1 INTRODUCTION

Clinical traits associated with androgens, acne and hirsutism, are important diagnostic features of polycystic ovary syndrome (PCOS). Current data suggests that the majority of patients with hirsutism, between 75-85%, and between 20-40% of patients with persistent acne only, have PCOS.[1] Androgens are one of the determining elements in the development of acne due to the influence of two major factors in acne pathogenesis: enhanced follicular keratosis and increased sebum production.[2] The growth of sexual hair is also primarily dependent on the presence of androgens. In androgen responsive areas, testosterone initiates growth, increases diameter and pigmentation of the keratin column and, in all probability, increases the rate of matrix cell mitoses in all but scalp hair.[2] As androgens are necessary for the development of cutaneous features found in polycystic ovary syndrome (PCOS), it would be expected that women with severe forms of clinical hyperandrogenism would have more elevated plasma levels of specific androgens.[2] Several studies have reported a correlation between hirsuitism and/or acne and circulating androgen levels with inconsistent results.[6-8] The variances in published results indicate hyperandrogenism not only reflects circulating androgen levels, but is also influenced by the peripheral metabolism of androgens.[9] Although testosterone is the major circulating androgen, and dihydrotestosterone (DHT) is the major nuclear androgen in the pilosebaceous unit and within hair follicles. DHT is formed in target cells from testosterone via 5α-reductase. 3α-androstenediol is the peripheral metabolite of DHT, and its glucoronide, 3α-androstenediol gluconide (3α-diolG) has been described as a marker of local androgen excess due to the increased activity of testosterone metabolism, simultaneously

increasing 5α-reductase activity in the cells of the hair follicle.[10] Although many studies have reported increased serum 3α-diolG in women with cutaneous hyperandrogenism, its role as a marker of peripheral androgen action is still controversial. Furthermore, the manifestation of cutaneous hyperandrogenic stigmata can be influenced by the sensitivity of target tissues to androgens. As previously reported,[12] there is evidence supporting that tissue response to androgen is determined by polymorphisms of the androgen receptor (AR).[11] There also exist other explanations for the differences in the clinical presentation of hyperandrogenism and biochemical values; significant variability among commercial immunoassays used for measuring serum androgen levels, along with a lack of standardization of androgen testing results may give rise to such discordances.[16] It seems that the degree of cutaneous manifestations of hyperandrogenism vary greatly among different ethnic populations. There have been suggestions in some reports, pointing to the notion that distinct ethnic groups may decidedly vary with respect to the concentrations of specific androgens in serum. Therefore, the intent of this review is to analyze the correlation between the severity of the cutaneous manifestations of hyperandrogenism, with focus on acne and hirsutism, with plasma levels of androgens.[1]

1.2 ACNE

Acne vulgaris is a self-limiting disease affecting the sebaceous follicles. It is described in stages and associated with age in patients suffering from the condition. Acne has frequently been recognized as a disorder predominately seen in young adults, however, there has been a noted increase in related referrals of patients over 25 years of age.[1] Post adolescent acne is defined as the presence of acne after the age of 25,

regardless of age at onset. Late onset acne appears for the first time after the age of 25 years. [1] The pathogenic factors involved in this multifactorial disorder include; hyperkeratinization and obstruction of sebaceous follicles, resulting from abnormal keratinization of the infundibular epithelium, androgenic stimulation of sebaceous glands and microbial colonization of the pilosebaceous units with *Propionbacterium acnes,* which subsequently leads to perifollicular inflammation.[1] Acne does not appear without sebum, which serves as the nutrient source of *P acnes,* and androgens are the major sebotropic hormones.[1][6] Increased sebum production in acne patients may be due to two main factors; (1) increased levels of circulating hormones and (2) hyper-responsiveness of the target organ, the pilosebaceous unit, to androgens, or both.[6][1]

Pathogenesis

In the pathogenesis of acne, there are four key factors that have been recognized to contribute to the condition. The most important factor is increased sebum production as the sebaceous glands are tightly controlled by a complex endocrine system; especially influenced by androgens arising from the adrenals. This increased seborrhea may be due to an increase of circulating androgens. Secondly, obstruction of the pilosebaceous ducts, through which sebum passes to the surface of the skin. Bacterial colonization is the third factor giving rise to acne, in particular, colonization by *Propionibacterium acnes*. Lastly, the role played by such bacteria in the obstructive process.[34] It is important to note that androgens enhance the production of sebum and follicular keratosis that in turn, plays the key role in acne etiology[5][12][34] and anti-androgen therapy as a successful option in management of the disease.[5]

It is known that androgen hormones also contribute to the pathogenesis of acne. As such, the enzyme, 5α-reductase is present in the sebaceous glands and converts testosterone to the more potent receptor ligand, DHT. Many investigations have focused their attention on examining disturbed androgen production in the ovaries or adrenal glands, in addition to impaired plasma transport of androgens in women presenting with adult acne or acne associated with hirsutism.[1] In patients with acne, it has been shown that the levels of androgen in serum are increased.[1] Other possible mechanisms involved in the development of acne include increased sensitivity of the sebaceous end organs to androgen and an increased peripheral metabolism.[1] It is notable that in addition to the cosmetic concerns associated with acne, its presence may also imply underlying disorders. Reports have indicated a greater prevalence of PCOS in patients with acne.[1][2][3]

The frequency of acne in PCOS patients should be considered in correlation with hyperandrogenism, in a female acne patient with severe cutaneous manifestations, sudden onset and/or associated with hirsutism or irregular menstrual periods. Acne is recognized as a clinical manifestation of some endocrine diseases.[33] PCOS has the highest prevalence in acne. PCOS, according to the 2003 Rotterdam ESHRE/ASRM-sponsored workshop established that two out of three of the following criteria should be met in order to fit the definition; chronic anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on ultrasound examination.[1]

With regards to the frequency of correlation between PCOS and acne manifestation, varying results have been seen in different studies. According to the study done by Özdemir S, et al., concluded that the prevalence of acne in women with

PCOS was 53% with baseline results indicating that their study population of acneic women had higher median values of DHEAS and FT than women without acne.[17] In comparison, in the results reported by Baldani DP, et al., from their study, three groups were compared according to their acne severity, determined by the acne severity index (ASI). Women placed in Group A had an ASI of 1, indicating minor acne with a grade of <1. Group B consisted of women with an ASI of 2, indicating mild acne with a grade of 1-2.4 and Group C with an ASI of 3, indicating moderate acne with a total grade of 2.5-4. Similarly to the above-mentioned study, mean serum FT levels were highest in Group C, while SHBG levels were lowest in Group C.[1] Notably, in the study done by Cibula D, et al, similarities in the obtained results were seen. Out of ninety women included in the study, a positive ultrasound finding of polycystic ovaries was found in 45 (50%) of patients. LH/FSH ration >1 was found in 34 (38%) of patients and most the most eminent finding was in 73 (81%) of patients had at least one androgen level elevated over the reference values. Furthermore, levels of T, DHEA, DHEAS and androstenedione were elevated in 22 (24%), 17 (19%), 27 (30%) and 71 (79%) patients respectively.[5] Continuing with the results of this study, acne was graded as minor in 43 (48%) cases, mild in 27 (30%) and moderate in 20 (22%). Additionally, 31 (34%) of women had an elevated index of free testosterone (IFT).[5] The results obtained revealed that an increased LH/FSH ratio is a frequent laboratory sign in women with the polycystic ovary syndrome, consequently, the most common cause of hyperandrogenemia.[5] Thus, the important role of androgens in the etiology of acne was supported by the finding of 81% of women within the study were hyperandrogenic.[5] To conclude, although androgens play an important role in the

development of acne, an increased level of androgen production does not have an established effect on the degree of clinical manifestation of the disease.[5] Thus, it is important to note that these results in accordance to acne severity are inconclusive and do not offer a correlation between acne severity and hormone levels.

1.3 HIRSUTISM

Hirsutism is another common cutaneous expression of hyperandrogenism and is also, seen not only in PCOS, but also is one of the diagnosing characteristics. Hirsutism may be defined as "the medical term that refers to the presence of excessive (course) hair in androgen-dependent areas of the female body."[2] Hirsutism is one of the most common clinical conditions referred to endocrinologists, gynecologists and dermatologists by about 5-15% of the entire female population.[4] Structurally, there exist three types of hair. Covering the skin of the fetus is a soft hair known as lanugo hair and this disappears within the first months of postpartum life. Non-pigmented, soft, but larger than lanugo hairs, are vellus hairs and are generally <0.03mm in diameter. The third type of hairs are those known as terminal hairs, which are structurally longer, pigmented with a course texture. In humans they compose the hair of the eyebrows, eyelashes, scalp hair and pubic and axillary hair in both males and females, in addition to the body and facial hair in men.[2]

Pathogenesis

It is known that hair arises from the hair follicle, considered to be a highly productive organ with the ability to regenerate. The hair follicle has the capacity of regeneration, the hair cycle consisting of rhythmic repetitive growth, regression, and tissue remodeling.[2] Hair growth disorders seen in clinical practice represent the

undesirable alterations of this cycle. This includes, prolongation of the hair growth phase, known as anagen, and is noticed when vellus hairs evolve into terminal hairs, which gives notation to the term hirsutism. In contrast, shortening on the anagen phase is what leads to hair loss.[2]

Androgens and hair growth

The development and growth of sexual hair is largely dependent on the presence of androgens. Prior to puberty, vellus hair is small, straight and fair, without developed sebaceous glands. Due to the increased levels of androgens at the time of puberty, the vellus follicles in the pubic and axillary regions of the body of boys and girls develop into terminal hairs, characteristically, larger, curlier and darker. Here, it is important to note that terminal hairs can be differentiated from vellus hairs, primarily by the length of the hair, in this case, longer than 0.5cm, and that terminal hairs are characteristically pigmented.[2] Androgens also increase the size of the sebaceous glands in areas such as the forehead and the cheeks, however the hair in these regions, remains vellus. This owes to the fact that differentiation patterns remain unexplained, androgens have paradoxically different effects on human hair follicles, depending on the area of the body.[2] As has already been mentioned, PCOS is the most common disorder associated with hyperandrogenism. In the analysis done by Escobar-Morreale H.F, et al., 70% of women presenting with the hirsute manifestations, also had PCOS.[2] It is of importance to mention that hirsutism is one of the diagnosing criteria in the guidelines for PCOS, as already reported according to the 2003 Rotterdam Criteria. In addition, hyperandrogenism or androgen excess corresponds with a common endocrinopathy, that affects between 5-10% of women of reproductive age.[13] Most commonly, women are

affected by PCOS as the most frequent hyperandrogenic disorder in 80-85% of women diagnosed with androgen excess.[13] As reported, there exist three currently available definitions of the disorder, and hirsutism is included as a criterion in all of the available definitions.[13]

There exist several methods for the quantification and evaluation of hirsutism in women. Of several systems available for the scoring and/or grading of the degree of hirsutism, the modified Ferriman-Gallwey score (mFG) has now become the gold standard for evaluating and determining hirsutism.[2] The mFG method scores 9 of the 11 body areas which include; the upper lip, chin, chest, upper and lower back, upper and lower abdomen, arm forearm, thigh and lower leg. Areas of the body without hair growth in the examined areas are given a score of 0. A score of 1 is given for minimally visible terminal hair growth, a score of 2 if hair growth is more than minimal but not that of the equivalent to male growth in adults. A score of 3 is given to presentation observed in a not very hairy male, while a score of 4 is given to patient with patterns typical of a well-virilized healthy adult males. Total scores range from 0 to 36. The grading of hirsutism has usually been agreed upon as; mild-having a score up to 15, moderate-from 16-25 and severe above 25.[2] Diagnosing hirsutism requires a cut-off value of the mFG score for establishing the diagnosis. Currently in practice today, clinicians choose a mFG more than or equal to 8, to indicate hirsutism.[2] It is important to note, however, that because terminal body hair can vary substantially from different races and ethnicities, the cut-off value should be adjusted to the population to which it is applied.[2]

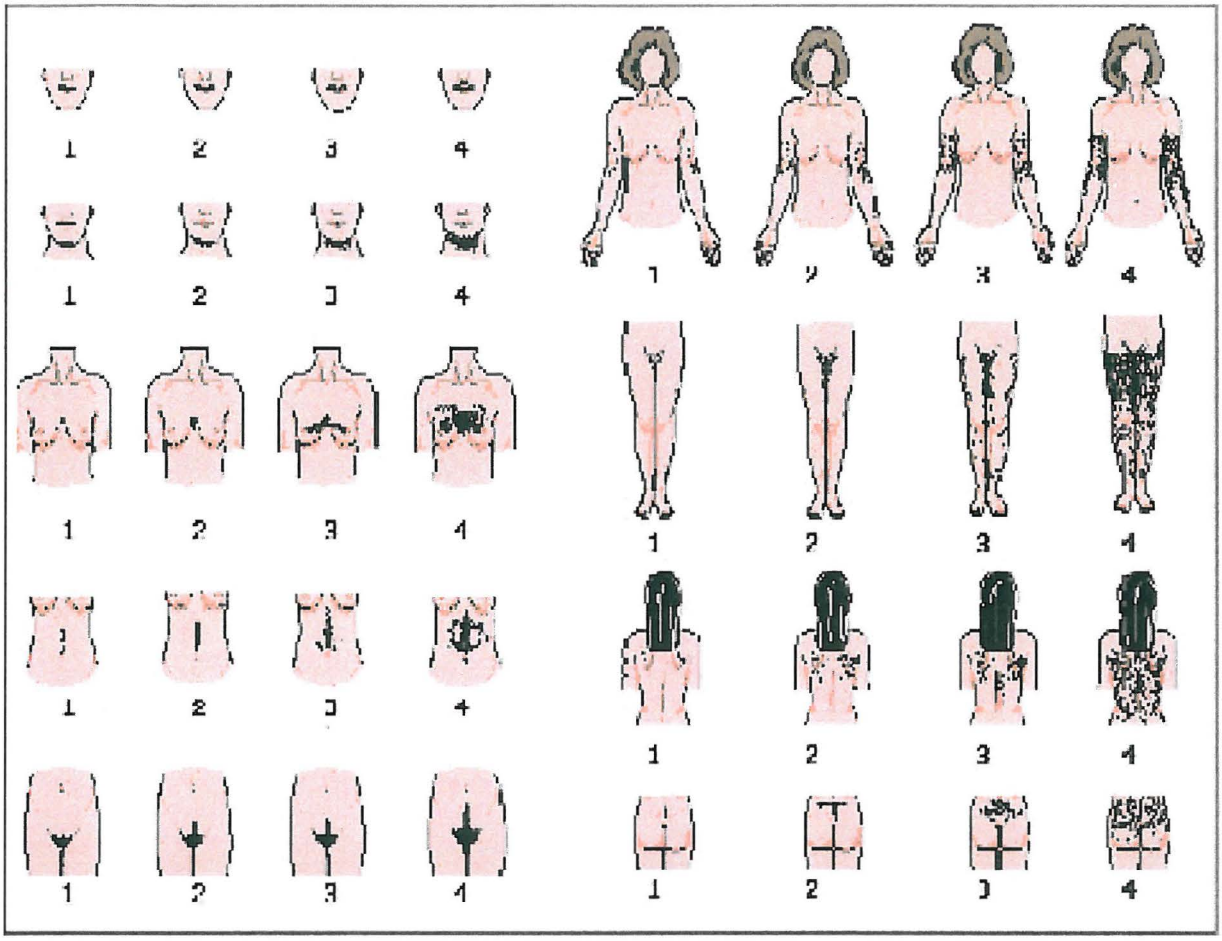

Figure 1 Schematic representation of the mFG score.

Hirsutism is considered to be a direct marker of androgen excess, in particular, as the result of their action at the level of the pilosebecous unit.

As reported in the study by Baldani D, et al., the grouping for hirsute women followed that of acneic women. Mild hirsutism was defined as having a mFG score of 8-9 and these women were placed in Group A. Group B consisted of women with a moderate clinical presentation and an mFG score of 10-14. Group C encompassed women with severe hirsutism and an mFG score >15. It was reported that the severity of hirsutism had a positive correlation with FT levels and negative correlation with SHBG, which

demonstrates that the severity of hirsutism is largely dependent on the bioavailability of unbound testosterone. Circulating androgen levels are not only reflected by the degree of hirsutism, but also by the intra-individual variation of such enzymes as 5α-reductase, which, in turn, affects the intracellular levels of the highly active androgen, DHT, in sebocytes and keratinocytes.[1] In addition, according to Falsetti L, et al., it has been documented from numerous studies that in hirsute women, 5α-reductase activity in the skin is constantly elevated. This enzyme, being responsible for the irreversible conversion of T to DHT, is a key factor in hirsutism. 5α-reductase activity, and thus the formation of DHT and 5α-reductase metabolites, for example, 3α-diolG is stimulated by high levels of circulating androgens.[2] This provides a crucial aspect in terms of determining and providing an adequate treatment. Comparatively, in the report by Meczekalski B, et al., the objective of the study being to assess the role of 3α-diolG as a marker of peripheral androgen action in young women with hirsutism as PCOS and as idiopathic hirsutism (IH) compared to controls, described significantly higher serum levels of 3α-diolG in comparison to the control. Similarly, FT was higher in PCOS women than in the controls. However, there was not a significant difference seen in serum 3α-diolG levels between PCOS and IH patients. In contrast, serum FT levels in PCOS patients were found to much higher than in IH patients.[21] As reported in the last mentioned study, it is of importance to understand the physiologic role of 3α-diolG. In order for T to be active in the skin, it must be converted to DHT by 5α-reductase. 3α-diolG is one of the main metabolites of DHT.[21][35] It has been reported, by Duffy, et al., that the skin is the major site of 3α-diolG and serum levels of 3α-diolG appear to mainly reflect skin DHT metabolism.[21][36] Furthermore, Fassnacht, et al., reported amplified

5α-reductase activity in PCOS, along with Carmina, et al., finding that 3α-diolG showed a positive correlation with total testosterone and FT.[21][37][38]

In order to fully grasp the concept of the conditions of acne and hirsutism as clinical manifestations and the hormonal correlates involved, it is necessary to examine the different treatment options available thus far and the links they provide between the correlates. Hormonal treatments for acne have proved to be popular in treatment of the disease by the process of lowering circulating and local androgen levels. Likewise, hormonal treatments are also able to oppose the effects of hormones on the sebaceous gland, as well, it is believed, on the follicular keratinocytes.[6] There are several options available in terms of providing hormonal therapy for the treatment of acne. Therapies include, anti-androgens, working on the level of blocking androgen receptors, agents which are formulated to decrease the endogenous production of androgens by the ovary or adrenal gland-for example, estrogens, combination oral contraceptives (OC), low-dose glucocorticoids, or gonadotropin-releasing hormone (GnRH) agonists.[6] In particular, the two main categories of drugs, anti-androgens and androgen inhibitors, will be discussed.

Table 1 Hormonal therapy and mechanism of action[6]

Hormonal Therapy	Mechanism of action
Estrogens	• Suppress ovarian production of androgens by suppressing pituitary gonadotropin release via negative feedback • Stimulates the hepatic synthesis of SHBG
Cyproterone acetate (anti-androgen)	• Ovulation inhibition • Androgen receptor blockade
Flutamide (anti-androgen)	• Androgen receptor blockade
Spironolactone (anti-androgen)	• Androgen receptor blockade • 5α-reductase inhibition
Combined oral contraceptives	• Ovarian androgen production inhibition • SHBG hepatic synthesis stimulation
Oral glucocorticoids	• Adrenal androgen production blockade
GnRH agonists	• Ovarian androgen production inhibition

Anti-androgens/androgen receptor blockers work on the level of directly and competitively inhibiting the binding of T and DHT to its receptor. Such agents include cyproterone acetate, spironolactone and flutamide. Oral contraceptives inhibit circulating androgens by acting directly on ovarian function. Agents under the category of gonadotropin-releasing hormone agonists inhibit circulating androgens by acting on pituitary gland function. Oral glucocorticoids inhibit adrenal function, agents such as finasteride and ketoconazole inhibit peripheral androgen metabolism.[6][29]

Cyproterone acetate (CPA) is a progestational anti-androgen working on the blockade of the androgen receptor. It is also the only anti-androgen that by acting on inhibiting ovulation, acts as an anti-gonadotrophin. The mechanism of action of CPA includes: (1) inhibiting the production of FSH and LH, which results in the blockage of ovarian function and thus reduces serum androgen levels, (2) inhibition of DHT at its receptor, and (3) decreases the activity of.[6][29]

Spironolactone functions both as an androgen receptor blocker and inhibitor of 5α-reductase. Its anti-androgen affect is seen at the hair follicle where it competes for androgenic receptors and displaces DHT. It also has an effect on androgen metabolism resulting in the defective steroidogenesis and in turn, a decrease in ovarian testosterone production. It has been reported in some studies that up to 66% of women prescribed spironolactone, described improvement or complete clearing of acne.[29] Spironolactone, when used in combination with OCs, the results improved to up to 85%.[29] It has been reported to be effective in the treatment of mild to moderate hirsutism.[29]

Flutamide is considered to be a purely peripheral androgen antagonist. Some studies have reported significant decreases in T and DHEAS levels. This supports the hypothesis that flutamide may have a central role in reducing androgen synthesis and/or increasing androgen catabolism. Evidence suggests that flutamide changes hormonal levels exclusively in women with PCOS by decreasing T and DHEAS by 20% after 6 months of treatment.[29]

OCPs have long been used in the treatment of women with acne and are a common first line treatment. OCs generally contain an estrogen and progestin and work on the basis of suppressing ovulation, which in turn inhibits the production of androgens by the ovaries. OCs decrease serum androgen levels and therefore reduce sebum production. Increases in SHBG is also achieved by OCs with the consequent reduction of free testosterone.[6] Estrogen given in sufficient amounts will result in a decrease of sebum production, no matter what estrogen is used.[6] The treatment of acne and the results are found to be satisfactory, and hence, several OCs are approved for acne treatment.[29] In addition, it has been reported that within 6-9 months of use, inflammatory lesion counts were seen to be reduced by 30-60%, with improvement rates in 50-90% of patients.[29] In addition to its uses in the treatment of acne, reduction of serum androgens with OCs, also decreases new hair growth and in affect, slows down the growth of terminal hair that is already present.[29] Combination oral contraceptives (COCs) used in long term treatment has been effective in the treatment of acne and mild to moderate hirsutism with a mFG score less than or equal to 14. It has been reported in the literature by Falsetti L, et al., that patients with moderate and severe acne with PCOS treated with COCs for 18 to 24 cycles has shown to be effective.[14] Furthermore, in

women with mild to moderate hirsutism, COCs have shown to reduce the mFG score by 15 to 20% at 6 months, 50 to 60% at 24 months and 100% at 48 months.[14] It is important to note that the efficacy of COCs is increased when combined with anti-androgen treatment.[14]

There are two modes of action of glucocorticoids in terms of acne treatment. For patients with inflammatory disease, shorter courses of a higher dose have been recommended and for those patients with adrenal hyperactivity, low dose corticosteroids have been used to suppress this process.[6] Therefore, oral corticosteroids can are considered to be inhibitors of adrenal function. Lastly, GnRH agonists, such as buserelin, nafarelin or leuproide, are agents that block androgen production by the ovary, hence, they block ovulation by interrupting the cyclic release of FSH and LH from the pituitary.[6] However, due to the expense and side-effects of this treatment, GnRH agonists are reserved for their use in severe forms of androgenization. In addition, GnRH agonists in combination therapy with OCs has also resulted in the increase of SHBG and presents as a prolonged treatment option in hirsutism[29] as it was found to reduce the Ferriman-Gallwey score by 23% to 32.1% and hair diameter by 4.9-63.6%.[14][29]

1.4 DISCUSSION

It is evident that androgens are a crucial factor in the pathogenesis of acne and hirsutism. It has been proven that androgens have the capacity to potentiate increases in sebum production, which in turn results in follicular retention hyperkeratosis. In addition to this, we have seen that anti-androgen therapy is a highly successful treatment

of the disease. In patients with acne vulgaris, studies have shown that there exist elevations in TT, FT, DHEAS and A, which has also been attributed to other signs of hyperandrogenism, such as hirsutism, alopecia and and/or menstrual irregularities. However, it has been argued that although androgens have a key role in the etiology of acne, the role they play in terms of severity has not been well established. In some studies, a positive correlation has been shown between the levels of the adrenal androgen, DHEAs and a negative correlation with the levels of SHBG. In the study by Baldani DP, et al., there was no association drawn between the grade of acne severity in correspondence to laboratory markers of androgen city.[1] According to the results taken from the aforementioned study, the degree of acne, as graded by the ASI score, showed a weak negative correlation with serum SHBG, correlating with the results of other, previous studies. It has also been recommended by other authors that SHBG levels be evaluated in women, in order to predict and select patients who may have a better response to appropriate hormone treatments. Also, all COCs decrease the level of LH while raising the level of SHBG. In addition, only contraceptives with anti-androgenic progestins; cyproterone acetate, chlormadinone acetate, or drosperinone, inhibit androgen receptors and affect 5α-reductase. However, it cannot be concluded that one androgen exclusively is connected with acne severity, at the same time, the correlation seen with SHBG is not considered significant. Furthermore, it can then be assumed that acne severity in patients with PCOS, can mostly be attributed to the peripheral sensitivity to androgens. Therefore, it is believed that patients with PCOS, treatment with anti androgenic contraceptives would be more beneficial. It should be kept in mind that acne pathogenesis is more complex than just the over-production of sebum and

abnormal duct keratinization. Changes in lipid composition, bacterial colonization with *Propionbacterium acnes* and the role of host immune response factors need to be considered.

Hirsutism, defined as the manifestation of terminal hairs with a male pattern distribution seen in women, is reported to affect 5%-8% of women of fertile age.[1][14] Because during puberty, androgens play a specific role in the transformation of vellus into terminal hair, and the growth of terminal hair by prolonging the anagen phase in the androgen-dependent areas of the female body, hirsutism is thus considered a clinical marker of excess androgen levels. Various studies have reported the association between high levels of androgens and hirsutism, in comparison to low levels of SHBG.[1] This correlation also corresponds to those results seen in the study by Baldani D, et al., which showed low levels of SHBG and elevated FT levels, as the most distinct signs of biochemical hyperandrogenism.[1] Similarly, there is also a poor correlation between the severity of hirsutism and the level of androgen excess, as reported by the majority of investigations.[1][26][27] The study by Baldani D, et al., showed that, although there was not a significant relationship between mFG score and LH, FSH, TT, androstenedione and DHEA, the severity of hirsutism showed a possible correlation with FT and a negative correlation with SHBG which gives rise to the notion that hirsutism severity can mainly be attributed to the bioavailability of unbound testosterone.[1] As the degree of hirsutism indicates the level of circulating androgens, it is also seen to be affected by intraindividual variation of 5α-reductase levels, in turn affecting the intracellular levels of DHT in sebocytes and keratinocytes.[1] It was found, in the study of interest, that there was no correlation between the levels of excess 3α-diolG and hirsutism severity.[1]

3α-diolG seems to largely reflect adrenal androgen secretion, however, it is not found to reflect primary peripheral 5α-reductase activity.[1] Thus, 3α-diolG measurements may be useful solely in monitoring therapy using 5α-reductase inhibitors. When choosing treatment options for patients with over-all androgenic symptoms, treatments of choice include those that elevate levels of SHBG.[1]

1.5 CONCLUSION

Even though excess androgen levels play a significant role in the manifestation of acne, in PCOS patients, the degree of severity cannot be linearly associated with serum androgen levels. Their levels, should not, therefore be used in determining the dosage of anti-androgen therapy. In the PCOS patient, the significant negative correlation observed between serum SHBG levels and the degree of hirsutism, gives rise to the fact that hormonal contraception, which increases SHBG levels, should be the therapy of choice in treating the PCOS patient.

1.6 ACKNOWLEDGEMENTS

First and foremost I would like to thank my mentor, Prof. dr.sc. Dinka Pavičić-Baldani for her endless support and her enthusiasm to lead and guide me through the process of writing my thesis. Her knowledge and expertise in the field is truly an inspiration. Thank you to the Department of Gynecology and Obstetrics at KBC Zagreb for the time and effort they dedicate to their students, as well as to the University of Zagreb for giving me the opportunity to study medicine. I am most grateful to my family, to whom I owe so much to, in particular to my mother, without whom any of this would be possible. To A.H and M.L, thank you for always being there, next to me, no matter how far apart.

1.7 REFERENCES

[1]Pavicic-Baldani D, Skrgatic L, Bukvic-Mokos Z, Trgovcic I. Hyperandrogenemia Association with Acne and Hirsutism Severity in Croatian Women with Polycystic Ovary Syndrome. Acta Dermatovenerol Croat. 2013;21(2):105-112. (Clinical Article).

[2]Seirafi H, Farnaghi F, Vasheghani-Farahani A, Alirezaie N-S, Esfahnian F, Firooz A, Zahra Ghodsi S. Assessment of androgens in women with adult-onset acne. International Journal of Dermatology 2007;46, 1188-1191.

[3]Escobar-Morreale HF, Carmina E, Dewailly D, Gambineri A, Kelestimur F, Moghetti P, Pageat M, Qiao J, Wijeyaratne CN, Witchel SF, Norman RJ. Epidemiology, diagnosis and management of hirsuitism: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome Society. Human Reproduction Update. 2011 Nov 6;18(2):146-170.

[4]Swiglo BA, Cosma M, Flynn DN, Kurtz DM, Labella ML, Mullan RJ, Erwin PJ, Montori VM. Antiandrogens for the Treatment of Hirsuitism: A Systematic Review and Metaanalyses of Randomized Controlled Trials. J Clin Endocrinol Metab. 2008 April;93(4):1153-1160.

[5]Cibula D, Hill M, Vohradikova O, Kuzel D, Fanta M, Zivny J. The role of androgens in determining acne severity in adult women. British Journal of Dermatology. 2000;143:399-404.

[6]Katsambas AD, Dessinioti C. Hormonal therapy for acne: why not as first line therapy? Facts and controversies. Clinics in Dermatology. 2010;28:17-23.

[7]Homburg R. Androgen circle of polycystic ovary syndrome. Human Reproduction. 2009 March 11;24(7):1548-1555.

[8]Mancini AJ. Incidence, Prevalence and Pathophysiology of Acne. Johns Hopkins Advanced Studies in Medicine. 2008 March;8(4):100-105.

[9]Timpatanapong P, Rojanasakul A. Hormonal profiles and prevalence of polycystic ovary syndrome in women with acne. J Dermatol. 1997;24:223-229.

[10] Cunliffe WJ, Simpson NB, Disorders of the sebaceous gland. In: Champion RH, Burton JL, Burns DA, et al, editors. Textbook of dermatology. 6th edition. Oxford: Blackwell Science; 1998. p. 1927-84.

[11] Gollnick H, Cunliffe W, Berson D. Management of acne. J Am Acad Dermatol. 2003;49:20-25.

[12] Strauss JS, Krowchuk DP, Leyden JJ. Guidelines of care for acne vulgaris management. J Am Acad Dermatol. 2007;56:651-63.

[13] Yildiz BO, Bolour S, Woods K, Moore A, Azziz R. Visually scoring hirsuitism. Human Reproduction Update. 2009 June 30;16(1):51-64.

[14] Falsetti L, Gambera A, Platto C, Legrenzi L. Management of Hirsuitism. Am J Clin Dermatol. 2000 Mar-Apr;1(2):89-99.

[15] Carmina E, Lobo RA. Evidence for increased androsterone metabolism in some normoandrogenic women with acne. J Clin Endocrinol Metab. 1993;76:1111-1114.

[16] Carmina E, Lobo RA. A comparison of the relative efficacy of antiandrogens for the treatment of acne in hyperandrogenic women. Clin Endocrinol. 2002;57:231-234.

[17] Ozdemir S, Ozdemir M, Gorkemli H, Kiyici A, Bodur S. Specific dermatologic features of the polycystic ovary syndrome and its association with biochemical markers of the metabolic syndrome and hyperandrogenism. Acta Obstetricia et Gynecologica. 2010;89:199-204.

[18] Trapp CM, Oberfield SE. Recommendations for the treatment of nonclassical congenital adrenal hyperplasia (NCCAH): an update. Steroids. 2012 Mar 10;77(4):342-6. www.pubmed.gov

[19] Pugeat M, Raverot G, Plotton I, Brac de la Perriere A, Mirakian P, Dechaud H, Berger N, Peix JL. Androgen-Secreting Adrenal and Ovarian Neoplasms. In: Contemporary Endocrinology: Androgen Excess Disorders in Women: polycystic Ovary Syndrome and Other Disorders, Second Edition. Edited by: R. Assis et al. Human Press Inc., Totowa, NJ. Pp.75-84. 2007.

[20] Lolis MS, Bowe WP, Shalita AR. Acne and Systemic Disease. Medical Clinics of North America. 2009 November;93(6):1161-1181. www.pubmed.gov

[21] Meczekalski B, Slopien R, Warenik-Szymankiewicz A. Serum levels of 3α-androstanediol glucuronide in young women with polycystic ovary syndrome, idiopathic hirsuitism and in normal subjects. European Journal of Obstetrics and Gynecology and Reproductive Biology. 2007;132:88-92.

[22] Baldani DP, Skrgatic L, Goldstajn MS, Zlopasa G, Oguic SK, Canic T, Piljek AN. Clinical and biochemical characteristics of polycystic ovary syndrome in Croatian population. Coll Antropol. 2012;36(4):1413-18.

[23] Borgia F, Cannaro S, Gaumeri SP, Vaccaro M, Gaumeri B. Correlation between endocrinological parameters and acne severity in adult women. Acta Derm Venereol. 2004;84(3):201-4.

[24]Goodarzi MO, Shah NA, Antoine HJ, Pall M, Guo X, Azziz R. Variants in the 5α-reductase type 1 and 2 genes are associated with polycystic ovary syndrome and the severity of hirsutism in affected women. J Clin Endocrinol Metab. 2006;91:4085-91.

[25] Greep N, Hoopes M, Horton R. Androstanediol glucuronide plasma clearance and production rates in normal and hirsute women. J Clin Endocrinol Metab. 1986;62:22-6.

[26] Azziz R, Carmina E, Dewailly D, Diamnati-Kanderakis E, Escobar-Morreale HG, Futterweit W, et al. The Androgen excess and PCOS society criteria for the polycystic ovary syndrome:the complete task force report. Fertil Steril. 2009;91(2):456-88.

[27] Karrer-Voegeli S, Rey F, Reymond MJ, Meuwly JY, Gaillard RC, Gomez F, Androgen dependence of hirsuitism, acne, and alopecia in women:retrospective analysis of 228 patients investigated for hyperandrogenism. Medicine (Baltimore). 2009;88(1):32-45.

[28] Pavicic Baldani D, Skrgatic L, Sprem Goldstajn M. Antiandrogens and androgen inhibitors. In: Update in Dermatologic Drug Therapy, Academy of Medical Sciences of Croatia. Edited by Lipozencic J. 2012:197-210.

[29] Koulouri O, Conway GS. A systemic review of commonly used medical treatments for hirsuitism in women. Clinical Endocrinology. 2008;68:800-805.

[30] Ferriman D, Gallwey JD. Clinical Assessment of body hair growth in women. Journal of Clinical Endocrinology. 1961;21:1440-1447. www.pubmed.gov.

[31]Moghetti P. Use of antiandrogens as therapy for women with polycystic ovary syndrome. Fertility and Sterility. 2006;86(1):30-31.

[32] Paradisi R, Venturoli S. Retrospective observational study on the effects and tolerability of flutamide in a large population of patients with various kinds of hirsuitism over a 15-year period. European Journal of Endocrinology. 2010;163:139-147.

[33] Kalus SI, Chien AJ, Olend JE. Diabetic Mellitus and other endocrine diseases. In: Wolff K, Goldsmith LA, et al., editors. Fitpatrick's Dermatology in General Medicine. 7th Ed. New York:McGraw Hill;2008. P 1462-1482.

[34] Cunliff WJ. Acne Vulgaris: pathogenesis and treatment. Br Med J. 1980;280(6229):1394-1396.

[35] Chen W, Thiboutot D, Zouboulis CC. Cutaneous androgen metabolism:basic research and clinical perspectives. J Invest Dermtol. 2002;119:992-1007.

[36] Duffy DM, Legro RS, Chang L, Stanczyk FZ, Lobo RA. Metabolism of dihydrotestosterone to 5 alpha-androstane-3alpha 17 beta-diol glucuronide is greater in the peripheral compartment than in the splanchnic compartment. Fertil Steril. 1995;64:736-9.

[37] Fassnacht M, Schlenz N, Schneider SB, Wudy SA, Allolio B, Arlt W. Beyond adrenal and ovarian androgen generation: increased peripheral 5 alpha-reductase activity in women with polycystic ovary syndrome. J Clin Endorcinol Metobol. 2003;88:2769-76.

[38] Carmina E, Gentzschien E, Stanczyk FZ, Lobo RA. Substrate dependency of C19 conjugates in hirsute hyperandrogenic women and the influence of adrenal androgen. Hum Reprod. 1995;10:299-303.

1.8 BIOGRAPHY

I was born in Karlovac, Croatia and moved to Toronto, Canada with my parents in 1986 where I completed my primary and high school education. Upon graduating from high school in 2002, I enrolled at the University of Toronto, where in 2006, I graduated with an Honours Bachelor Degree of Arts and Science, with a double major in English and History. Upon graduation, I moved to Zagreb and worked for one year teaching English at a private school in the city. As it had always been a dream of mine, I decided to pursue a career in medicine upon learning about the Medical Studies in English Program at the University of Zagreb. I am currently finishing my time as a student and I am looking forward to graduating in July of this year, 2014.

During my time in Croatia, I have been able to involve myself in various foundations and have volunteered with organizations involved with the rehabilitation of children with mental and physical disabilities using horses as a therapeutic guide. This is one of my passions and I hope to continue helping people in this way. My hobbies include learning French, equestrian sports, running, silks and aerials and the acrobatic arts, all of which I am happy to have been able to continue during my time here.

I intend to stay in Croatia to do my internship training and then for my specialization training, my options remain open for both staying in Croatia or training elsewhere in Europe. I am interested in doing my specialist training in Family Medicine, as I find it most interesting, encompassing a little bit of everything, and I hope to one day excel in my field of practice and build a close relationship with my patients.