THE INTERRELATION BETWEEN HIRSUTISM AND ANDROGEN HORMONE LEVELS AS WELL AS SERUM Tnfα CONCENTRATIONS

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ABSTRACT

Hair growth is subject to numerous factors that influence the development of hair follicles, including conditions such as alopecia areata and hirsutism. Hirsutism, a medical term denoting the excessive growth of terminal (coarse) hair in areas of a woman's body sensitive to androgens, occurs in approximately 7% of reproductive-age women. The majority of hirsutism cases are attributed to androgen excess. Elevated androgen hormone levels can trigger inflammatory responses through an increase in serum TNFα. Data collection involved sourcing articles relevant to the association between hirsutism, androgen hormone levels, and serum TNFα. Inclusion criteria comprised original articles, case-control studies, and review papers focusing on hirsutism, androgen hormones, and serum TNFα. Hirsutism is correlated with both androgen hormone levels and serum TNFα. Hirsutism arises from the interplay between androgen levels and the sensitivity of hair follicles to androgens. Several conditions triggered by high concentrations of androgen hormones can lead to the occurrence of hirsutism. Androgen hormones induce inflammatory effects, as evidenced by the presence of TNFα.

Keywords: Hirsutism, Androgen, TNFα

INTRODUCTION

The majority of the body's skin surface is adorned with hair, except for the lips, palms of the hands, and soles of the feet. Hair constitutes a vital organ in humans, playing a significant role in biological functions such as thermoregulation, sensory information gathering, and protection against environmental factors such as sunlight and cold temperatures (Bienenfeld A, et al. 2019). Hair follicles are small organs formed through the interaction between the epidermis and dermis. Hair undergoes a continuous periodic growth cycle throughout human life, demonstrating a high regenerative capacity primarily due to the presence of numerous stem cell populations within the hair follicles. Hair growth is influenced by various factors that can affect the development of hair follicles, including conditions such as alopecia areata and hirsutism (Barrionuevo P, et al. 2018).

Androgens are steroid hormones, primarily synthesized in the ovaries and adrenal glands. These hormones exert various effects on the skin in different physiological and pathological

processes concerning hair follicles (Bienenfeld A, et al. 2019). Androgens have been shown to increase the size of hair follicles in various parts of the body, hair diameter, and the proportion of time that hair remains in the anagen phase. The conversion of vellus to terminal hair is stimulated by androgens through the prolongation of the anagen phase. Sequential hair cycles and a longer duration of anagen encourage an increase in follicle size. These larger follicles produce longer and thicker hair in areas of the body that are androgen-dependent (Kini S, et al. 2018)

Inflammation is a common occurrence in hyperandrogenic women, often resulting from various metabolic disorders that affect the ovaries (Lizneva D, et al. 2016)*Tumor necrosis factor-alpha (TNF-a) appears to be associated with hyperandrogenism* (Mimoto MS, et al. 2018). TNFα is a protein that plays a crucial role in both the innate and adaptive immune systems, exerting significant influence in tissue degeneration and repair processes (Oner G, Muderris II. 2013). This study aims to obtain information regarding the relationship between hirsutism and levels of androgen hormones and serum TNFα.

Existing Theories

Hirsutism is a medical term that denotes the presence of excessive terminal (coarse) hair in regions of a woman's body that are sensitive to androgens, including the upper lip, chin, chest, back, abdomen, arms, and thighs (Barrault C, et al.(2015). Hirsutism affects 5-10% of women of reproductive age and serves as the most commonly utilized clinical diagnostic criterion for androgen excess or hyperandrogenism (González F, Sia CL, Bearson DM, Blair HE. 2014).

The excessive growth of hair frequently results in significant psychological and emotional stress, adversely affecting the quality of life. Hirsutism can be particularly distressing for patients and has a substantial negative impact on their psychosocial development González F, et al. 2014). The majority of hirsutism patients exhibit abnormalities in adrenal and ovarian steroidogenesis, leading to an excess of androgens and subsequently resulting in hirsutism (Hohl A, Ronsoni MF, Oliveira M de. 2014).

Hirsutism arises from the interaction between androgen levels and the sensitivity of hair follicles to androgens. The majority of women with androgen levels twice the upper limit of the normal range or higher exhibit a certain degree of hirsutism (Kini S. 2018). Approximately 80-90% of women with hirsutism experience hyperandrogenemia (Kalliolias GD, Ivashkiv LB. 2016).

METHODS

The literature review was conducted to thoroughly explore information on the relationship between hirsutism and levels of androgen hormones and serum TNFα. This type of review article aims to gather information on hirsutism based on a specific biomarker. Secondary sources were used as the data foundation. Data collection methods involved extracting relevant information from articles discussing the connection between hirsutism and levels of androgen hormones and serum TNFα. Inclusion criteria comprised original articles, case-control studies (involving human, animal, and cell studies), and review papers on hirsutism, androgen hormones, and serum TNFα within the last 10 years.

LITERATURE REVIEW

Hirsuitism

The term "hirsutism" originates from Latin, signifying excessive growth of coarse hair, particularly in women and children with a distribution pattern resembling that of adult males. Hirsutism is frequently associated with underlying endocrine disorders, most commonly polycystic ovary syndrome, and can lead to psychosocial challenges and a diminished quality of life. The prevalence of hirsutism ranges from 5% to 10% (Pasquali R, Gambineri A. 2014). Approximately 80-90% of women with hirsutism experience hyperandrogenemia. Hirsutism is a primary hyperandrogenic symptom defined as excessive body hair growth in areas of a woman's skin that are sensitive to androgens. This condition is attributed to elevated androgen concentrations and increased sensitivity of the pilosebaceous unit (PSU) to normal androgen levels (Polat S, et al. (2020).

Epidemiology

Hirsutism occurs in approximately 7% of women of reproductive age. The extent of terminal hair varies based on ethnic background and the methodology used for evaluation.[13] Its prevalence in adults ranges from 3 to 15% in both black and white populations but is somewhat lower in Asians (1-3%). Recent epidemiological surveys have contributed limited data on hirsutism in adolescents, suggesting that the condition is estimated to be relatively common in post-pubertal years, with prevalence ranging from 8 to 13%. The most common cause of hirsutism is polycystic ovarian syndrome (PCOS). In women, hirsutism often tends to be more severe in the presence of obesity. While hirsutism does not fully predict ovulatory dysfunction, some studies have found that it may predict residual metabolic symptoms in women with PCOS (Barrault C, Garnier J, et al. 2015).

Etiology

The majority of hirsutism cases are attributed to androgen excess. Polycystic Ovarian Syndrome (PCOS) is associated with abnormally elevated androgen levels, causing 75% to 80% of hirsutism cases. Approximately 10% will experience idiopathic hirsutism, and the remaining cases may be linked to rare disorders, including nonclassical congenital adrenal hyperplasia (NCAH), hyperandrogenism, insulin resistance, and acanthosis nigricans (HAIR-AN), as well as androgen-secreting neoplasms. Hirsutism can also be associated with conditions such as Cushing's syndrome, acromegaly, thyroid dysfunction, and hyperprolactinemia. The use of androgens, anabolic steroids, and valproate can also induce hirsutism (Szczuko M, et al. (2016).

Patiphysiology

Specifically, women have terminal hair only in the eyebrows, eyelashes, scalp, pubic area, and axillae. Hair emerges from a highly dynamic complex structure known as the hair follicle, comprising several components and following a rhythmic growth cycle. The hair follicle growth cycle consists of three main phases: anagen (rapid growth phase), telogen (relatively quiescent phase), and catagen (apoptosis-mediated regression). Hirsutism follows changes in the hair follicle cycle, particularly the elongation of the anagen phase, resulting in the transformation of vellus to terminal hair. These changes are influenced by androgens and play a role in the regulation of sexual hair growth. The androgens

involved in hair follicle regulation are testosterone and dihydrotestosterone (DHT), which are produced through both de novo synthetic pathways from cholesterol and shortcut pathways from circulating dehydroepiandrosterone-sulfate (DHEA-S) (Polat S, et al. 2020).

Diagnostic Procedure

Hirsutism is clinically diagnosed based on the Ferriman-Gallwey (FG) score, which assesses hair growth from 0 to 4 in 9 androgen-dependent areas. Hirsutism should be differentiated from hypertrichosis, characterized by increased hair growth in a non-sexual and non-androgen-dependent general distribution. Typically, hypertrichosis indicates the growth of common or local vellus (non-terminal) hair throughout the body (Spritzer PM, et al. (2022).

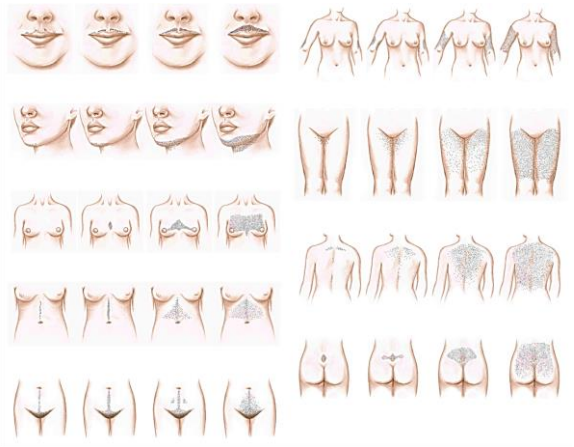

Figure 1. The Ferriman-Gallwey score for hirsutism involves assigning scores of 1 to 4 to nine different body areas. A total score of less than 8 is considered normal, a score of 8 to 15 indicates mild hirsutism, and a score greater than 15 suggests moderate to severe hirsutism. A score of 0 indicates the absence of terminal hair.

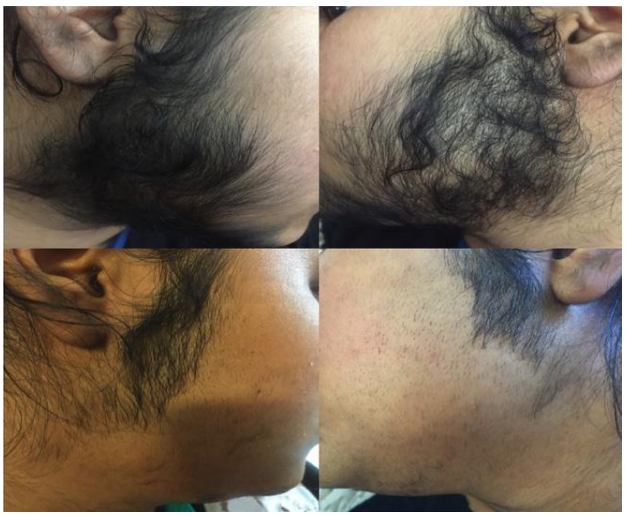

Figure 2. Unwanted hair growth, which is a common aesthetic issue.

Furthermore, the diagnosis of hirsutism is based on the quantification of the issue and the definition of its etiology. Quantifying hirsutism can be achieved through physical examination using subjective and objective methods. Determining the most likely etiology is based on clinical history (onset age and rate of development), hormone profiles, and, in some cases, genetic analysis. Regardless of the degree of hirsutism, the most crucial clinical feature to observe is the rapid development of hair growth, consistent with tumoral causes or drug-related disturbances. Conversely, mild to moderate hirsutism around puberty or in young adulthood often has benign causes, most commonly represented by PCOS (Barrionuevo P, et al. (2018).

Androgen

Androgens are produced de novo from cholesterol in the ovarian theca cells and adrenal cortex (reticularis zones). Additionally, circulating androgen precursors can be metabolized into stronger androgens in peripheral tissues such as the liver, adipose tissue, and pilosebaceous unit (PSU). The synthesis of basic androgens is regulated through transcriptional changes in genes by luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. The increase in androgen production observed in women after the mid-cycle LH surge is regulated by cholesterol access to mitochondria through the activation of the steroidogenic acute regulatory protein (StAR) (Talaei A, et al. 2013)

Androgens are produced throughout the body in steroid-producing organs, such as the adrenal glands and ovaries, as well as in other tissues, including the skin. Several androgens are normally found in women, including dehydroepiandrosterone, dehydroepiandrosterone-sulfate, testosterone, dihydrotestosterone, and androstenedione. These androgens play a role in the development of several common skin conditions in women, including acne, hirsutism, and female pattern hair loss (FPHL), all of which are androgen-mediated skin disorders (Spritzer PM, et al. (2022).

The production of androgens in the ovaries and adrenal glands involves a relatively small number of enzymes, but the expression of steroidogenic enzymes generates various steroid precursors and end-active products. The adrenal reticularis zones and gonadal tissues specifically convert pregnenolone into sex steroid precursors through a single enzyme, P450c17, which exhibits dual 17α-hydroxylase activity. Furthermore, the reticularis zones have abundant cytochrome b5 that facilitates androgen production by P450c17. Therefore, most of the sex steroid biosynthetic pathways proceed through dehydroepiandrosterone (DHEA). The adrenal reticularis zones express more sulfotransferase than steroid sulfatase, resulting in increased DHEAS production. In women, the primary circulating androgens (in decreasing order of serum concentration) are DHEAS, DHEA, androstenedione, testosterone, and DHT. However, only T and DHT have a strong affinity and potency for the androgen receptor (AR), as DHEAS, DHEA, and androstenedione have little or no capacity to bind to AR and require conversion to testosterone to exert androgenic effects. Androstenedione is the most important precursor to testosterone,

while DHEA contributes only 5% to 13% of circulating testosterone in reproductive-age women (Talaei A, et al. 2013).

The Relationship between Hirsutism and Androgen Hormones

Hirsutism follows changes in the hair follicle cycle, particularly the elongation of the anagen phase, resulting in the transformation of vellus to terminal hair. These changes occur under the influence of androgens and are involved in the regulation of sexual hair growth. Clinically, hyperandrogenism has been shown to produce various symptoms in the activity of pilosebaceous units (PSU) in specific gendered skin areas, such as hirsutism, acne, and androgenic alopecia (Talaei A, et al. 2013).

TNFα serum

Tumor necrosis factor-alpha (TNFa), also known as cachectin, is a potent pro-inflammatory cytokine that plays a crucial role in the immune system during inflammation, cell proliferation, differentiation, and apoptosis. TNFa is a pleiotropic cytokine with significant functions in homeostasis and the pathogenesis of diseases.[18,19] TNFα is a cytokine that exhibits significant cytotoxic activity upon immune system stimulation, leading to tumor necrosis. The receptor for TNFα is part of the tumor necrosis factor receptor superfamily (TNFRSF), whose members have distinctive intracellular segments, transmembrane domains, and extracellular ligand-binding domains (Yilmaz B, Yildiz BO. 2019).

The Relationship between Hirsutism and Androgen Hormone Levels with TNFα Serum

Excessive androgen levels increase inflammation, as evidenced by the upregulation of androgen receptor (AR) and TNFα. These effects are mediated in a receptor-dependent manner. Inflammatory conditions involving TNFα in women often occur in polycystic ovary syndrome (PCOS). Elevated androgens are activated by the progesterone pathway and the limited dehydroepiandrosterone testosterone biosynthesis pathway. Testosterone induces TNFα secretion and modifies ovarian response by increasing androstenedione and slightly decreasing estradiol in women with PCOS and high androgen levels. It is this androgenic concentration that is capable of causing hirsutism (Yang S, et al. 2018; Zelová H, Hošek J. 2013).

CONCLUSION

Hirsutism occurs due to the interaction between androgen levels and the sensitivity of hair follicles to androgens. Hirsutism can arise from several conditions triggered by high concentrations of androgen hormones. Androgen hormones induce inflammatory effects through the presence of TNFα. Based on the literature review above, it can be concluded that hirsutism is associated with androgen hormone levels and serum TNFα.

REFERENCES

Bienenfeld A, Azarchi S, Lo Sicco K, Marchbein S, Shapiro J, Nagler AR. Androgens in women. (2019). J Am Acad Dermatol [Internet]. Jun;80(6):1497–506. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0190962218326744

Barrionuevo P, Nabhan M, Altayar O, Wang Z, Erwin PJ, Asi N, et al. (2018). Treatment Options for

Hirsutism: A Systematic Review and Network Meta-Analysis. J Clin Endocrinol Metab [Internet]. Apr 1;103(4):1258–64. Available from: https://academic.oup.com/jcem/article/103/4/1258/4924417

Barrault C, Garnier J, Pedretti N, Cordier-Dirikoc S, Ratineau E, Deguercy A, et al.(2015) Androgens induce sebaceous differentiation in sebocyte cells expressing a stable functional androgen receptor. J Steroid Biochem Mol Biol [Internet]. Aug;152:34–44. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0960076015001028

González F, Sia CL, Bearson DM, Blair HE.(2014). Hyperandrogenism Induces a Proinflammatory TNFα Response to Glucose Ingestion in a Receptor-Dependent Fashion. J Clin Endocrinol Metab [Internet]. May 1;99(5):E848–54. Availablefrom:https://academic.oup.com/jcem/article/99/5/E848/2537891

Hohl A, Ronsoni MF, Oliveira M de.(2014) Hirsutism: diagnosis and treatment. Arq Bras Endocrinol Metabol [Internet]. Mar;58(2):97–107. Available from:http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-27302014000200097&lng=en&tlng=en

Kini S, Ramalingam M. Hirsutism. (2018).Obstet Gynaecol Reprod Med [Internet]. May;28(5):129–35. Available from:https://linkinghub.elsevier.com/retrieve/pii/S1751721418300381

Kalliolias GD, Ivashkiv LB.(2016). TNF biology, pathogenic mechanisms and emerging therapeutic strategies. Nat Rev Rheumatol [Internet]. Jan 10;12(1):49–62. Available from:https://www.nature.com/articles/nrrheum.2015.169

Lizneva D, Gavrilova-Jordan L, Walker W, Azziz R.(2016) Androgen excess: Investigations and management. Best Pract Res Clin Obstet Gynaecol [Internet]. Nov;37:98–118. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1521693416300220

Mimoto MS, Oyler JL, Davis AM. (2018).Evaluation and Treatment of Hirsutism in Premenopausal Women. JAMA [Internet]. Apr 17;319(15):1613. Available from:http://jama.jamanetwork.com/article.aspx?doi=10.1001/jama.2018.2611

Oner G, Muderris II.(2013). Efficacy of omega-3 in the treatment of polycystic ovary syndrome. J Obstet Gynaecol (Lahore) [Internet]. Apr 3;33(3):289–91. Available from: http://www.tandfonline.com/doi/full/10.3109/01443615.2012.751360

Pasquali R, Gambineri A. (2014). Therapy Of Endocrine Disease: Treatment of hirsutism in the polycystic ovary syndrome. Eur J Endocrinol [Internet]. Feb;170(2):R75–90. Available from:https://academic.oup.com/ejendo/article/170/2/R75/6661664

Polat S, Karaburgu S, Unluhizarci K, Dündar M, Özkul Y, Arslan YK, et al. (2020). The role of androgen receptor CAG repeat polymorphism in androgen excess disorder and idiopathic hirsutism. J Endocrinol Invest [Internet].

Sep 12;43(9):1271–81. Availablefrom:http://link.springer.com/10.1007/s40618-020-01215-7

Somani N, Turvy D. (2014). Hirsutism: An Evidence-Based Treatment Update. Am J Clin Dermatol [Internet]. Jul 3;15(3):247–66. Available from:http://link.springer.com/10.1007/s40257-014-0078-4

Szczuko M, Zapałowska-Chwyć M, Drozd A, Maciejewska D, Starczewski A, Stachowska E. (2016). Effect of IGF-I and TNF- α on intensification of steroid pathways in women with PCOS phenotypes are not identical. Enhancement of progesterone pathway in women with PCOS increases the concentration of TNF- α. Gynecol Endocrinol [Internet]. Sep 1;32(9):714–7. Availablefrom:https://www.tandfonline.com/doi/full/10.3109/09513590.2016.1159672

Spritzer PM, Marchesan LB, Santos BR, Fighera TM. (2022). Hirsutism, Normal Androgens and Diagnosis of PCOS. Diagnostics [Internet]. Aug 9;12(8):1922. Available from: https://www.mdpi.com/2075-4418/12/8/1922

Talaei A, Adgi Z, Mohamadi Kelishadi M. Idiopathic Hirsutism and Insulin Resistance. Int J Endocrinol[Internet].2013;2013:15.Availablefrom:http://www.hindawi.com/journals/ije/2013/593197/

Thathapudi S, Kodati V, Erukkambattu J, Katragadda A, Addepally U, Hasan Q. (2014). Tumor Necrosis Factor-Alpha and Polycystic Ovarian Syndrome: A Clinical, Biochemical, and Molecular Genetic Study. Genet Test Mol Biomarkers [Internet]. Sep;18(9):605–9. Available from:http://www.liebertpub.com/doi/10.1089/gtmb.2014.0151

Unluhizarci K, Karaca Z, Kelestimur F. Hirsutism – From Diagnosis to Use of Antiandrogens. In 2013. p. 103–14. Available from:https://www.karger.com/Article/FullText/341822

Yilmaz B, Yildiz BO. (2019). Endocrinology of Hirsutism: From Androgens to Androgen Excess Disorders. In. p. 108–19. Available from:https://www.karger.com/Article/FullText/494907

Yang S, Wang J, Brand DD, Zheng SG. (2018). Role of TNF–TNF Receptor 2 Signal in Regulatory T Cells and Its Therapeutic Implications. Front Immunol [Internet]. Apr 19;9. Available from: http://journal.frontiersin.org/article/10.3389/fimmu.2018.00784/full

Zelová H, Hošek J. (2013). TNF-α signalling and inflammation: interactions between old acquaintances. Inflamm Res [Internet]. Jul 18;62(7):641–51. Available from: http://link.springer.com/10.1007/s00011-013-0633-0