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Influential Effects of Dihydrotestosterone (DHT) in Women's Health



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ABSTRACT

Androgen is the most important hormone of male physiology for the development of the reproductive and another essential physiological role. Though it is dominant over males, it also produces a significant role in women's health too. Their regulation and biosynthesis play an essential role in the general physiology of those hormones. Among the various types of androgenic hormones, Dihydrotestosterone is considered the most potent of all other androgen. The normal concentration of DHT never produces negative effects, but its imbalances may exhibit several physiological issues in both genders. When compared to men the effects are so unfamiliar to women and produce remarkable issues in their health and well-being.



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INTRODUCTION:

In the recent era, modified lifestyle changes and habitual changes have pushed this generation into the unrecoverable space where most of people from children to elders were affected with some kind of health issues such as metabolic disorders, psychological disorders, hormonal disorders, and so on. This disorder may also lead to immunocompromised conditions in which our system became weak and unable to produce immunity against even a simple microbial infection. Among several disorders, hormonal disorder serves as one of the most prevalent disease conditions. Hormones are chemical signal-producing agents, which control and influence each and every system of our body. Any imbalance in such an area cause several health complications. Among various imbalances, reproductive hormonal imbalances produce severe complications in this normal physiology as well as affect the reproductive life of an individual. The most common imbalance that affects the present generation is an androgenic imbalance. It affects both males and females, beyond the various types of androgens, dihydrotestosterone serves as the most important hormone which imparts imbalances due to various etiological condition. Though it may produce equal and significant effects on both gender but the problem faced by the women is more complicated when compared to men in psychological, physiological and sociological way. So in this article let's explore to the defined review about the androgens (DHT), it's biosynthesis, mechanism and its influential effects on women's health which were briefly established[1].

WHAT IS DHT?

DHT stands for dihydrotestosterone which is a category of male androgenic hormone that gets converted from the common androgenic hormone testosterone by the action of the enzyme 5 alpha-reductase[1]. Usually, these hormones are commonly dominated over males than females and produce various influential effects across both genders. Among various other androgenic hormones like dehydroepiandrosterone [DHEA], rostenedione, and testosterone[3] DHT serves as the most potent androgenic hormone and considered as pure androgen[4], because once it get converted from Testosterone, there is no other way for the conversion of DHT to any other estrogenic hormone whereas other androgens have the ability to converted into estrogenic hormone via several biosynthetic pathways.

Notably, these DHT are secreted (converted through[2] 5 alpha-reductase) only in glands in which it get utilized itself, some such examples were the prostate[4], seminal vesicle,

epididymis particularly in male, in females include ovaries and adrenals and commonly secreted in some visceral regions of the human body in both genders.

Beyond the enormous types of hormones, the need for the study of DHT serves as an essential phenomenon as its deficiency as well as the overproduction may highly produces noticeable effects nowadays that psychologically affect one's well-being, especially in women.

Testosterone and dihydrotestosterone vary slightly in both structural and physiological features. Structurally DHT lacks a single double bond in the ring A (first cyclic ring structure) of testosterone and so DHT serves as the most potent and has more fold affinity [7] towards the androgen receptor when compared to testosterone [6].

FUNCTIONS:

Being a metabolite of testosterone DHT produces and provides various functions towards human either in a favourable or an unfavourable way [1, 2],

➤ Functions in men: DHT as a pure androgen it serves as one of the most essential and important androgens which play both primary and secondary function in male physiology. Primary roles includes amplification of hormonal signals during embryonic development and also have a huge role in deciding the gender of the fetus [1]. Another primary role involves external virilization during puberty and sexual differentiation [6] of male genitalia during embryogenic development [2].

Secondary roles includes the development of secondary sexual characters such as growth of body and facial hair, maintenance, development and maturation of reproductive organs and so on [1].

Existing as an androgenic metabolite, DHT deficiency as well as over production may cause several health-related hazards. A few conditions of DHT deficiency are hypogonadism, Poor development of male characteristics and also affects fertility. Overproduction of DHT may leads to patterned baldness, benign prostatic hyperplasia, androgenic alopecia, prostatic cancer are the few common health issues[1, 7].

One of this ovoverproductionr deficiency of DHT may be due to the increased or decreased action of the enzyme 5 alpha-reductase on testosterone [2]. Which may also leads to imbalances of testosterone and produces testosterone-related complications.

➤ Functions in women: In women, being an androgen DHT's amount of concentration in circulation is too low when compared to men. But those little amount plays a significant role in their health. Similar to men, it even causes discomfort in both states of deficiency and overproduction.

The normal concentration of DHT explicit the normal physiology of women including hair growth in scalp, face, pubic and body ,healthy menstrual cycle from the period of menarche to the period of menopause[3].

Even the gender and the age of puberty is also determined by the concentration and Synthesis of DHT.

Deficiency may affect the above normal physiology. Overproduction may produce various health-related condition which may be discussed below.

BIOSYNTHESIS:

The synthesis and production of DHT depend upon the synthesis of the primary androgen testosterone. As it serves as the key element for the DHT synthesis. So testosterone synthesis is one of the important syntheses to be known before knowing about DHT synthesis. For both testosterone and DHT synthesis, cholesterol serves as the precursor [8].

Regulation of the synthesis depends upon the pituitary hormones. These hormones play an extensive role in production and regulation of each and every hormone in the human body.

PRECURSOR:

Cholesterol serves as the principal sterol of all higher animals, distributed in body tissues. It is an essential component of animal cell membranes and biosynthesized by all animal cells. Cholesterol acts as the precursor for the overall synthesis of reproductive hormones. The cholesterol for that synthesis is obtained either from de novo synthesis or from the already existing low-dense lipoprotein (LDL). From the cholesterol, the synthesis of androgen continues in two pathways called $\Delta 4$ and $\Delta 5$ pathways.

SITE OF SYNTHESIS:

As seen before both males and females have separate prime areas of synthesis with some common areas too. The primary site of synthesis for male are in the Leydig cells [6] of the testes and also in the adrenals (Zona reticularis and fasciculata) and some secondary sites

including the prostate, epididymis and some rare areas. In females, the synthesis takes place primarily in ovaries (small amount of theca cells of ovarian follicles), adrenals and placenta. The common areas of synthesis include skin, scalp, liver, brain and so on [3].

REGULATION:

Androgen synthesis are usually regulated by pituitary hormones such as Luteinizing hormone (LH) and Follicle-stimulating hormone (FSH) which are stimulated by the chief hormone Gonadotropin-releasing hormone (GnRH)[5].

Both LH and FSH are bound to high G-protein-coupled plasma membrane receptors. Where LH in Leydig cells [6] and FSH in Sertoli cells. After binding LH receptors gets aggregated and conformational changes were made to convert Guanosine Tri Phosphate (GTP) to cyclic Adenosine Mono Phosphate (cAMP), then the cAMP activates the protein kinase A which leads to protein phosphorylation and results in stimulation of steroidogenesis and androgen production .

SYNTHESIS OF ANDROGENS:

The synthesis takes place in the inner mitochondrial cells with the stimulation and help of the enzymes. At first, cholesterol is converted to pregnenolone by the enzyme cytochrome P450 which is a side chain cleavage enzyme (P450SCC) that forms androstenedione by two pathways [4],

- i. By progesterone (Δ^4)
- ii. By DHEA /17 – hydroxy pregnenolone pathway(Δ^5)

FSH regulation follows the same mechanism that resembles the LH regulation. The higher concentration of LH and FSH leads to desensitization of their respective receptors and affects the production of androgens [8].

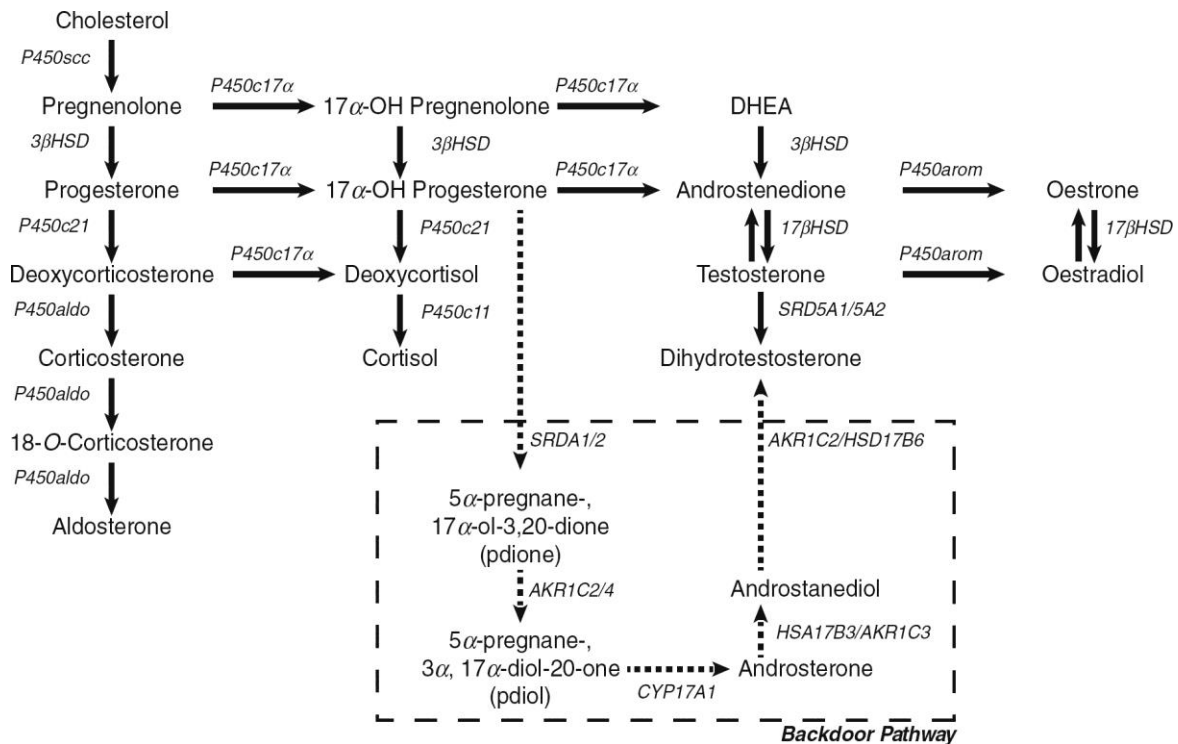


Figure:1 Synthesis of Androgens

CLASSIFICATION OF ANDROGENS(DHT):

With the previous knowledge of androgen, we know that DHT is the metabolized Androgen of testosterone by the action of 5α- reductase. Hence, similar to biosynthesis, the other pharmacological characteristics are also similar to both testosterone and DHT.

Androgens were classically categorized into two types they are

- (1) Natural androgen
- (2) Synthetic androgen

Among them, natural androgen is naturally synthesized by the human body and differentiated into potent and weak androgen. Androgens that are chiefly synthesized by testes such as testosterone and dihydrotestosterone are considered potent androgen whereas, androgen from adrenals including DHEA and and rostenedione were considered as weak ones.

Synthetic androgens are androgens that usually man-made and administered to balance androgenic deficiencies which include methyl testosterone, floyxymesterone, testosterone undeconate and various other forms are also available[8].

Biological actions were already described in the functions of androgens. The major targeted action of DHT are

- Sexual differentiation during gestational period
- Maturation while attaining puberty
- Improving masculine characters in male

MECHANISM OF ACTION:

Both leading androgens testosterone and dihydrotestosterone usually bind about 98% to plasma protein albumin and especially to Sex hormone binding hormone (SHBG)[6], the remaining serves as the free and unbound androgen that produces the targeted biological effect when bound to androgen receptor[4] (AR). Still, the bound hormones don't produce any biological effect on the system and remain unavailable for the action.

The free androgen (either TST or DHT) may easily get entered the plasma membrane through diffusion and reaches the cytoplasm where the AR is located and displaces the inhibitory heat shock proteins[6] (HSP) that were bounded androgen and AR undergoes dimerization and the produced dimer gets translated to nucleus itself and attached to the coactivator which leads to the interaction of the androgen response element, that stimulates the target gene activation to produce the desired biological effects via messenger RNA(mRNA) that are specified by the androgens. In the case of DHT entering the cell, the Testosterone is converted into DHT before entering into it.

EFFECTS OF ANDROGEN (DHT) ON WOMEN:

Basically, the word androgen is generally denoted to masculinity and are known to be secreted dominantly over men than women. Naturally female body synthesizes a little amount of androgen and males too have a tiny amount of female hormone. These tiny secretions maintains the balance in the endocrine system and also helps in various other functional development of body. The usual range of potent androgen in males ranges from

- Testosterone ⇒270-1070 ng/dl
- Dihydrotestosterone⇒14-77ng/dl

While in females,

- Testosterone ⇒15-70ng/dl
- Dihydrotestosterone ⇒4-22 ng/dl

This may vary on age.

Other androgens (weak) like DHEA, DHEAS and androstenedione were also present in women of minute quantity. The above-normal level of androgen in women never produces any abnormalities and the normal level regulates various functions in women's health as we have seen before. Once the imbalance of these androgen occurs it may produce either elevated or deficit levels that may provoke various issues in women's health. Some of the common and major issues were discussed below.

ANDROGEN MEDIATED HAIR LOSS (ALOPECIA):

Hair serves as one of the defining characteristics of mammals which is made up of protein, especially keratin. It also provides various functions according to the site of location such as thermo regulation, protection, facilitation for evaporation of perspiration, heat insulation and so on.

Hair types may be categorized into three types they are [12],

- Lanugo hair
- Vellus hair
- Terminal hair

Lanugo hair is the one in which hair is soft, fine and unpigmented which is generally present in the fetus and in some diseased condition. Vellus hair is a short fine and unpigmented or slightly pigmented that is generally considered as hair less and retained more by women. Whereas terminal hair is a long, coarse and densely pigmented hair that is commonly present in the scalp, eyebrows, eyelashes, pubic area and in some other areas [14]. These types of hair are generally retained equally by men and women in some cases men retains more compared to women in body hair ratio. Hair growth and development is a continuous cyclic processes, after the maturation each and every hair follicle, undergoes a set of three phases which is collectively called as hair growth cycle. The duration of each phase depends on the location of hair and individual nourishment and also includes several factors such as age, hormonal status and lifestyle. The three phases of the hair growth cycle are [7],

- Anagen phase (growth phase)
- Catagen phase (transition phase)
- Telogen (shedding phase)

From the three phases, anagen is the phase in which the follicles enlarges and attain original shape and hair follicles enlarges and attains original shape and hair fiber is produced, hair growth in this phase is about 1-1.5 cm per month and retains usually up to 6years. This may differs according to genetic and other factors. The second phase is said to be catagen phase, which is the phase of transition stage where the growth stays in resting period, this phase may last upto two weeks in humans approximately. The final phase is said to be telogen phase, the phase that is also known to be the shedding phase which may last around 3-4 months. Some scientists have divided this into two as telogen and exogen phase if they considered telogen as the resting phase and exogen is said to be the shedding phase that may cause shedding of the existing hair which has white bulb-like keratin covering in the edge of the follicle and results in the growth of new hair. All these phases are essential for a healthy hair growth and maintenance. And all these cycles are based on one's health condition. If these three phases were well balanced then the hair growth is also well balanced if these phases are affected, then it may tend to hair loss. Usually, a healthy individual loses almost 50 – 100 hair per day and that's considered completely normal, but once it exceeds the above level then that condition is said to be hair loss. Hair loss may be of different types, but the loss is based only on these mechanisms such as hair loss from the roots and hair loss due to hair breakage these and may results in the state of hair thinning (by the conversion of terminal hair to vellus hair) following baldness if untreated[9].

Among the certain other reasons for hair loss such as genetics, nutritional deficiencies, malabsorption, increased Stress, drug-induced, disease-induced, and hair loss due to androgenic alopecia serves as the major reason for severe kind of hair loss in both genders. Generally, men have more hair fall compared to women but the impact of it may greatly affects the women than men on both psychological and sociological manner.

In females, during the period of menstruation, the level of estrogen synthesise gets reduced and progesterone level gets increased which leads to terminate the synthesis of Testosterone by ovaries temporarily which in turn, already synthesized testosterone are readily converted to dihydrotestosterone by the increased action of 5α – reductase. DHT is the metabolized

androgen that regulates and helps in the growth of the body but unluckily it also tend to cause inhibition of scalp hair growth by interfering with follicle signaling and leads to hair loss for few days after menstruation. But once a woman is affected by any of the medical condition that is related to hormonal imbalances, the short-term hair loss may get converted as a continual hair loss and even leads to permanent hair loss if left untreated. Hair loss is commonly termed by the word alopecia in the state of a chronic condition and can be classified into two different types they are [12],

- Cicatricial alopecia (scarring)
- Non-cicatricial alopecia (non-scarring)

Cicatricial alopecia indicates the destruction of hair follicles and leads to permanent hair loss that includes central centrifugal cicatricial alopecia, trichotillomania, tinea capitis, Alopecia areata (syphilis), and chronic cutaneous lupus erythematosus.

Non-cicatricial alopecia indicates the temporary condition in which hair regrowth is possible and non-scarring which includes androgenic alopecia, Alopecia areata, telogen effluvium, alopecia universalis and so on.

These are the basic category of alopecia among these androgenic alopecia is the most common issue faced by women who are affected by hormonal imbalances, such type of alopecia causes patterned baldness. If it affects male then it is male patterned baldness or it affects females it is female-patterned baldness. In female pattern baldness, the anterior hairline is preserved and thinning occurs primarily at the crown which resembles the Ludwig pattern [14]. In general cases, men with androgenic alopecia tend to loss the whole hair and become completely bald whereas in women the complete baldness is rare and takes time attain such conditions.

MECHANISM OF HAIR LOSS IN ANDROGENIC ALOPECIA:

The exact mechanism for androgenic alopecia is not completely known, some of the self-theories were proposed to depict the mechanism, but still seems to be unknown.

Recently some studies have found that dermal papilla (DP) cells are the cells that send signal to follicular epithelial cells, either for hair growth or hair by DHT[11] (thus DPcells may be sensitive to DHT). Another theory is that hair loss and baldness due to increased pressure on hair follicles caused by thickening of the scalp [10]. Thickening usually occurs on ageing but

androgens are responsible for early and rapid thickening and also increased conversion of DHT may fastens the erosion of subcutaneous fat under the scalp (which retard scalp thickening) that leads to hair loss.

Management of androgenic alopecia is somewhat developed using androgen blockers, vasodilators, 5 α – reductase blockers and so on. For the exact treatment of androgenic alopecia the exact mechanism must be known so it needs more researches further.

HIRSUTISM:

Hirsutism is a condition, in which the women experience increased body hair growth resembling male patterns. Similar to alopecia, hirsutism is more dependent on Androgen production, it is one of the symptoms of any of the hormonal conditions. Usually, Hirsutism is mostly due to Polycystic ovarian syndrome which secrete more amount of androgen and hyperandrogenism which may be of ovarian or adrenal origin with tumor or without it [13]. Other causes for Hirsutism are hypothyroidism, hyperprolactinemia, congenital adrenal hyperplasia, idiopathic hirsutism, androgen-secreting tumors, acromegaly, Cushing syndrome and drug-induced and some other rare condition [14].

PATHOGENESIS:

The hirsutism is exactly defined as the conversion of the vellus hair to terminal hair throughout the body. Pathogenesis may differ according to the condition affected but the mechanism may not differ. The major mechanism is due to the sensitivity of the body hair follicle to the androgens that convert Vellus hair follicle to the terminal hair. In some cases some normal women have excessive body hair which is due to genetics or misconception as hirsutism women and other women who have hirsutism with normal level of androgen is due to peripheral Androgen activity. Hirsutism may also occur in some women who are in menopausal and premenopausal stage and continue to few years after Menopause due to estrogen depletion in ovaries [13]. Hirsutism is the common clinical condition which could affect almost 5 to 10% of women who are treated in the dermatological out- patient department in each and every Hospital [15].

CLINICAL FEATURES AND MANAGEMENT:

Clinical features of a hirsutism women may have increased hair growth of terminal hair in areas such as the chin, sides of the face, upper lip, sternum, upper abdomen, shoulder, upper

back and some rare areas. It is clinically manifested by Ferriman and Gallewey scale [13]. Treatment and management by physical methods include epilation methods such as waxing, plucking, shaving and so. These are the simplest method, but they have its own side effects such as Folliculitis, inflammation, dermatitis etc., These methods are temporary and other such method includes electrolysis, laser treatment, which are complex in nature. Pharmacological methods using various drugs the used to manage hirsutism such as oral contraceptives, GnRH agonist adrenal suppression glucocorticoids, 5-RA inhibitors and doesn't receptor blockers etc., are used to treat and manage Hirsutism[15].

ACNE VULGARIS:

Acne is considered one of the skin conditions that affects most of the adults psychologically nowadays. Acne is a skin problem that affects not only adults and also to women who are in various stages of menopausal and premenopausal period. One of the significant factors of acne is due to an elevated level of dihydro testosterone. It is a condition that affects not only a single gender or a single group of people, it affects both gender but, it is more common among women when compared to men in all age groups. Acne which is generally referred as acne vulgaris is a common and chronic disorder of pilosebaceous unit [16]. It is the most common disorder of the period of adolescence is estimated to be 70% to 87 %. Gender and genetics are an important factor for the prevalence of acne one study of 200 patients with post-adolescent acne found that 50% of a patient reported at least one first degree family relative with acne.

PATHOGENESIS OF ACNE:

- 1) Excessive sebum production by androgen-mediated stimulation of the sebaceous gland
- 2) Abnormal keratinization of follicles leads to plugging and comedone formation.
- 3) Propionibacterium acne colonisation
- 4) Inflammation of follicles and surrounding dermis [16].

ADULT FEMALE ACNE:

Though the acne which is caused over the period of adolescence is quite normal due to hormonal changes for the maturation that doesn't affect it anyway. But women even on the adult age are affected by these acne is generally termed as Adult female acne (AFA) [17]. Women between the ages of 25 to 45 are generally affected by AFA. The aggravating factors that trigger AFA include obesity, diet, exposure to radiation, sleeping disorders, unhealthy lifestyle modification including smoking, alcohol consumption etc., cosmetics medication, stress, endocrine deficiency disorder, excessive washing of the skin, deficiency of the epidermal barrier and so on.

POLYCYSTIC OVARIAN SYNDROME:

Polycystic ovarian syndrome (PCOS) is hormonal disorder that affects women's in the reproductive years [19]. PCOS is a condition in which Small sacs of fluids may develop along the outer edge of ovaries. These are termed as cyst. These cyst may contain fluid filled immatured eggs which are unable to release in a particular period of time which may result in irregularities of the menstrual cycle, decreased, and various other symptoms associated with it. The exact cause of PCOS is not exactly established [18]. And also there is no specific treatment is introduced for it. The treatment and management are only based on the individual symptoms. So still there is no exact drug or cure for their disorder. Relationship between androgen and PCOS: Even though there are no exact causes of PCOS. Recently some evidence-based theories were formulated, that hyperandrogenism serves as one of the aggravating reasons for PCOS [18]. All potent and weak androgens became imbalanced during this condition and gets elevated. The elevation and stimulation is due to insulin resistance hyper insulinemia, decreased SHBG and some other rare condition PCOS patients with hyper androgenicity. Is of two types, one is adrenal hyper androgenism and other is ovarian Hyperandrogenism[19]. In adrenal hyperandrogenism, the elevated androgen wouldn't exert any effect on metabolic disorder and only 20-30 percent of patients are affected by it. While ovarian hyperandrogenism causes the most metabolic issues and affects more patients with PCOS [20].

EFFECTS OF ANDROGENS IN POLYCYSTIC OVARIES:

Elevated androgen level cause various effects on polycystic ovaries including,

- Apoptosis-through various signaling pathways and affects the development of oocytes. Androgens either directly or indirectly induce apoptosis in oocytes.
- Autophagy-abnormal autophagy may produce cell death that influences the quality and development of oocytes.
- Mitochondrial dysfunction may lead to mitophagy and autophagy provoked cell death.
- Endoplasmic reticulum stress - stress in the endoplasmic reticulum due to Hyperandrogenism lead to increased activation of unfold protein response and disturbs various cellular function[18].

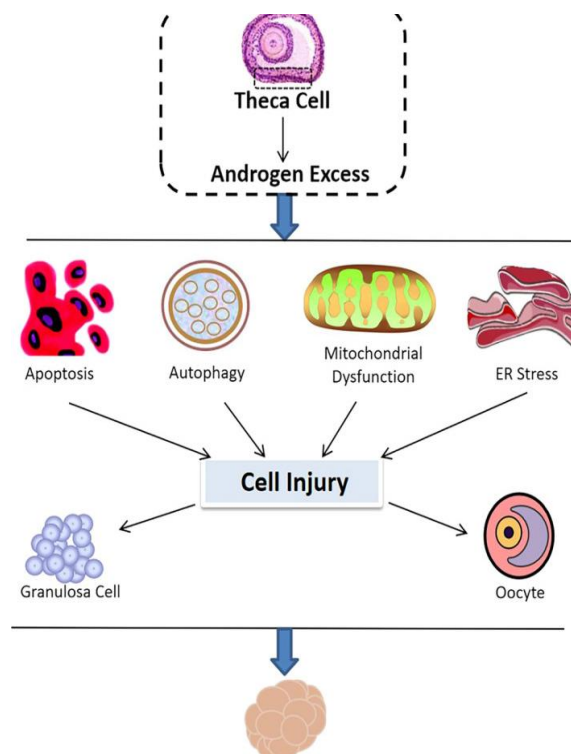


Figure:2 Effects of androgen in cellular activities of PCOS.

COMPLICATIONS:

Excessive androgen in PCOS not only affect the reproductive life such as decreased fertility, premature delivery, and Gestational diabetes and also causes various complication in another metabolic system including obesity, diabetes[20], cardiovascular disorders, Kidney diseases,

neurodegenerative disorders and other physiological conditions including hirsutism, alopecia, acne and psychological conditions such as Stress[5], depression, anxiety etc.,

Though there is no specific treatment recognized, but the condition should be managed symptomatically to avoid life-threatening condition such as cancers.

CONCLUSION:

The major effects of Dihydrotestosterone (Androgen) were discussed above. Several researches were already performed and still performing under progress even though for that condition further research should be done in order to find the exact mechanism to treat them efficiently and support women and Society to overcome those imbalances and improve the quality of One's life.

REFERENCES:

1. DHT (Dihydrotestosterone). Cleveland Clin 20,2022.<http://my.clevelandclinic.org>.
2. Elizabeth Boskey. Ph.D. What is Dihydrotestosterone (DHT)? Verywell health. Jan 2023.<http://www.verywellhealth.com>.
3. Vittorio E. Bianchi, Elena Bresciani, Ramona Meanti, Laura Rizzi, Robert J.Omeljaniuk. The role of androgens in women's health and wellbeing. *Pharmacologia Research*, 2021;105758.
4. Ronald S Swerdloff, Robert E Dudley, Stephanie T page, Christina Wang, Wael A Salameh. Dihydrotestosterone: Biochemistry, Physiology and clinical implications of Elevated Blood levels. *Endocr Rev.*, 2017;38(3):220-54.
5. Bettina Weber, Sabina Lewicka, Michael Deuschle, Michael Colla,Isabella Heuser. Testosterone, Androstenedione and dihydrotestosterone concentration are elevated in female patients with major depression. *Psychoneuroendocrinology*, 2000;25(8):765-71.
6. MH Eileen Tan, Jun Li, Eu-long Yong. Androgen receptor: Structure, role in prostate cancer and drug discovery. *Acta Pharmacologia Sinica (APS)*, 2015;36:3-23.
7. Daniel Murrell M.D-By Tim Newman.Everything you need to know about DHT.Medical News Today.28/07/2017.<http://www.medicalnewstoday.com>.
8. Handelsman DJ. Androgen Physiology, Pharmacology, Use and Misuse. [Updated 2020 Oct 5]. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext [Internet]. South Dartmouth (MA): MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279000>
9. DHT and Hair Loss: Men Vs Women, divi. Feb 14 2023.<http://www.diviofficial.com>.
10. Emin Juncay Ustuner, MD Ankara. Causes of androgenic alopecia: Crux of the Matter. *Plast Reconstr surg Glob Open*, 2013;1(7):e64.
11. Driskell RR, Clavel C, Rendl M, Watt FM. Hair follicle dermal papilla cells at a glance. *J Cell Sci.*, 2011;124(8):1179-82.
12. Qi,ji, and Lui's A Garza. An overview of alopecia. *Cold Spring Harbor Perspectives in medicine*, 2014;4 (3): A013.
13. Silonie Sachdeva. Hirsutism : Evaluation and treatment. *Indian Journal of Dermatology*, 2010;1(2):115-140.
14. Eric Matheson, MD, MS and Jennifer Bain MD. Hirsutism in women. *American Family Physicians*, 2019;100 (3):168-75.
15. Jon Mihalidis MD, Racha Demessopian MD, Pamela Taxel MD. Endocrine evaluation of Hirsutism. *International Journal of Women's Dermatology*, 2017;3(1):S6 -S10.

16. Tobechei.Ebede, Emily L.Arch and Diane Berson. Hormonal treatment of Acne in women. *J Clin Aesthet*, 2009;2(12):16-22.
17. Edileia Bagatin, Thais Helena Proenca de freitas, Maria Cecilia Rivitti Machado, Beatriz Medeiros Ribeiro. Adult female acne: an guide to clinical practice. *An Bras Dermatol*, 2019 ;94(1):62-75.
18. Wenting Ye, Tingling xie, Yali song. The role of androgen and its related signals in PCOS. *Journal of Cellular and Molecular alarm*, 2020;2(1):E10- E23.
19. Valentina Rodriguez Paris and Michael J. Bertoletto. The Mechanism of Androgen Actions in PCOS Etiology. *Medical Sciences, MDPI*, 2019;7(9):89.
20. Catherine G.Baptiste, Marie-Claude Battista,Andreanne Trottier and Jean -Patrice Baillargeon. Insulin and Hyperandrogenism in women with Polycystic ovarian syndrome. *Steroid Biochem Mol Biol.*, 2010;122(1-3):42-52.