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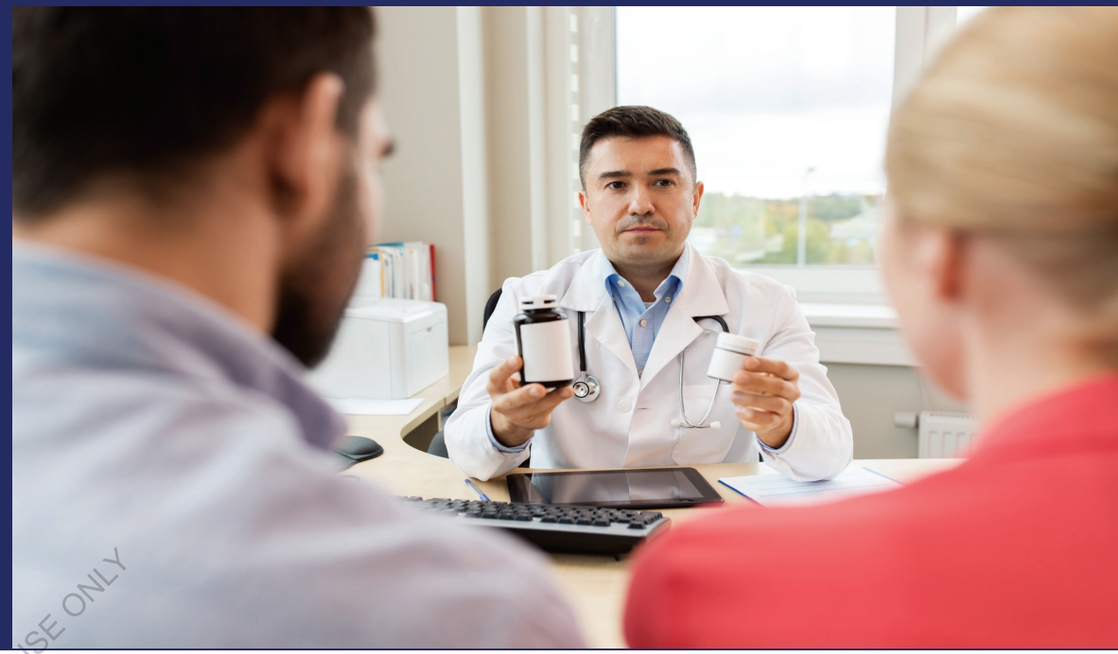
Androgens are important steroid hormones that control how the male phenotype is expressed, including the establishment and maintenance of spermatogenesis as well as the external development of secondary sex traits. The development of male reproductive organs such as the epididymis, vas deferens, seminal vesicle, prostate, and penis is greatly influenced by androgens. Additionally, males require androgens during puberty, masculine sexuality, and reproduction. Spermatogenesis requires a lot of intratesticular testosterone, which is released by the Leydig cells. The majority of the androgen-binding protein that binds intratesticular testosterone is released into the seminiferous tubules. The androgen receptor is specifically coupled to testosterone inside the Sertoli cells, where activation of the receptor causes the spermatogenic process to begin and be maintained as well as the suppression of germ cell apoptosis. All male reproductive organs include the androgen receptor, which can be activated by either testosterone or its more potent metabolite, dihydrotestosterone. Male sexual development in males may be aberrant as a result of severe androgen receptor abnormalities.



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Male Androgens: Physiology, Pharmacology, and Related Disorders

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Abstract:

Androgens are important steroid hormones that control how the male phenotype is expressed, including the establishment and maintenance of spermatogenesis as well as the external development of secondary sex traits. The development of male reproductive organs such as the epididymis, vas deferens, seminal vesicle, prostate, and penis is greatly influenced by androgens. Additionally, males require androgens during puberty, Masculine sexuality, and reproduction. Spermatogenesis requires a lot of intratesticular testosterone, which is released by the Leydig cells.

The majority of the androgen-binding protein that binds intratesticular testosterone is released into the seminiferous tubules. The androgen receptor is specifically coupled to testosterone inside the Sertoli cells, where activation of the receptor causes the spermatogenic process to begin and be maintained as well as the suppression of germ cell apoptosis. All male reproductive organs include the androgen receptor, which can be activated by either testosterone or its more potent metabolite, dihydrotestosterone. Male sexual development in males may be aberrant as a result of severe androgen receptor abnormalities. Male infertility may be brought on by more modest modulations. Since exogenously administered testosterone and its metabolite estrogen will suppress both GnRH production by the hypothalamus and Luteinizing hormone production by the pituitary gland and subsequently suppress testicular testosterone production, treating an infertile man with testosterone does improve spermatogenesis. Additionally, the testis requires significant quantities of testosterone, which cannot be produced by giving androgens to patients orally or intravenously. Deficient spermatogenesis will arise from Leydig cell suppression of testosterone production, as is evident in males who use anabolic-androgenic steroids.

1. Introduction

A substance that may generate and sustain masculine traits in reproductive tissues—specifically the genital tract, secondary sexual traits, and fertility—as well as support the anabolic status of somatic tissues is known as an androgen, sometimes known as the male sex hormone. The main androgens in the blood of mature male mammals are testosterone and its powerful metabolite, dihydrotestosterone (DHT). Leydig cells, which are found in the interstitium of the testis between the seminiferous tubules, produce the majority of the testosterone, which has a distinctive four-ring C18 steroid structure.Leydig cell secretion raises the local concentration of testosterone in the testis to extremely high levels while also maintaining circulating levels of testosterone that have the typical androgenic effects on distant androgen-sensitive target tissues. The primary mechanism by which androgens exert their traditional biological effects is through binding to the androgen receptor, a member of the steroid nuclear receptor superfamily that is encoded by a single gene on the X chromosome. The androgen receptor then controls the transcription of a variety of androgen-responsive target genes, resulting in a distinctive pattern of gene expression. A biochemical and pharmacological definition of androgen as a substance that successfully competes with testosterone binding to the androgen receptor **[1]** to stimulate post-receptor functions in isolated cells or cell-free systems has been added to this physiological definition of androgen in the whole animal. Additionally, non-genomic androgen action mechanisms involving quick, membrane-mediated non-transcriptional reactions in the cytoplasm have been discovered but not fully characterized **[2].**Clinically, testosterone is utilized at physiologic dosages for androgen replacement therapy, while testosterone or synthetic androgens based on their structural makeup are also used at generally larger doses for pharmacologic androgen therapy. Restoring a physiological pattern of androgen exposure to all

tissues is the mainobjective of androgen replacement therapy. Such treatment is typically limited to the main androgen in nature, testosterone, and aims at replicating physiological levels of circulating testosterone, the full range of endogenous androgen effects on tissues (including activation of pre-receptor androgens), and the natural history of efficacy and safety. Pharmacologic androgen therapy takes advantage of the anabolic or other effects of androgens on bone, muscle, and other tissues as hormonal drugs that aim to change the course of the underlying disorder. Its effectiveness, safety, and relative cost-effectiveness are assessed similarly to other therapeutic agents. Grasping and using androgen pharmacology to its fullest potential requires a grasp of the physiology of testosterone **[3].**

2. Androgens Source

The most frequent androgens are dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S), androstenedione (A), androstenediol (Δ^5**-diol**), and dihydrotestosterone (DHT), among others. DHT and testosterone are the two that are the most powerful.While much of DHEA-S action may come from its peripheral conversion to DHEA, some in vitro investigations demonstrate that DHEA-S is androgenic in and of itself **[4].** The adrenal gland and the ovary secrete androgens in non-gestational females**[5,6].**While the ovary and adrenal both release the other hormones, the adrenal secretes DHEA and DHEA-S in the majority **[7-9].** Pituitary hormones influence the secretion of androgens. The adrenocorticotropic hormone (ACTH) and likely another component or factor that may only increase androgen, stimulate the production of androgen in the adrenal glands. Since a decrease in prolactin levels following the removal of pituitary prolactinomas or bromocriptine has resulted in a decrease of DHEA-S, prolactin has also been regarded as an adrenal androgen-stimulating agent **[10,11].**With no discernible change in cortisol, testosterone (T) and dihydrotestosterone (DHT) are present. Acute elevation of prolactin has no influence on androgen levels, and hyperprolactinemia is not always accompanied by elevated androgen levels **[10,12].** The mechanism underlying the rise in adrenal DHEA-S serum levels caused by estrogens is unclear **[13].** Although it has been hypothesized that the *zona reticularis* of the adrenal produces androgens principally, it has also been discovered that the *zona fasiculata* and reticular also contain significant amounts of DHEA-S, T, DHT, and A**[14].**

2.1 Dihydrotestosterone (DHT)

The strongest androgen is dihydrotestosterone. About half of the testosterone's free fraction is found in comparison **[15].** However, we have demonstrated that ovarian

and adrenal vein levels of DHT are significantly greater than peripheral levels in both hirsute and normal people, suggesting that DHT is released directly by the ovaries and adrenals **[6].**The adrenal's ability to secrete DHT may be substantiated, DHT is present in the adrenal glands, where it undergoes a chemical conversion to androstanediol, which is then eliminated in the urine. Thus, the excretion of androstanediol in the urine may be a reflection of the cellular level activity of dihydrotestosterone (DHT) **[16].**The ovaries and the adrenals each contribute about 50% to the peripheral plasma levels of DHT, and these levels do not fluctuate appreciably throughout the menstrual cycle.DHT levels rise during puberty and fall following menopause **[9].**

2.2 Testosterone (T)

Testosterone is the second most powerful androgen. Over 98% of the T that is in the blood is bound, primarily to Testosterone-estradiol binding globulin (TeBG). Both the adrenals and the ovaries secrete around 50% or less of the circulating testosterone **[5].** Similar to cortisol, peripheral T levels demonstrate a small diurnal fluctuation. With the exception of the periovulatory phase, when the ovary contributes more, the adrenals and ovaries roughly equal each other in their contribution to peripheral T levels. T levels rise after puberty and fall following menopause **[9].**

2.3 Androstenedione (A)

With the exception of the periovulatory period, when the ovarian contribution increases, the majority of this steroid is directly released by the ovaries and adrenals in roughly equal proportions.10% is primarily created peripherally from DHEA. The diurnal change of androstenedione levels is similar to that of cortisol. Levels fluctuate during puberty and following menopause**[9].** A is predominantly linked to albumin when it travels through the bloodstream, its TeBG binding is weaker than testosterone.

2.4 Dehydroepiandrosterone (DHEA)

About 10% to 25% of DHEA is produced by the ovary, 60% to 70% by the adrenals, and the remaining 30% is produced by the hydrolysis of DHEA-S sulfate. **[8].** Albumin and globulin bind the majority of the DHEA that is circulating. The ovarian portion of DHEA production rises during the periovulatory phase. DHEA rises during puberty and falls during menopause. Cortisol's diurnal variation is comparable.The two main precursors of urinary 17-ketosteroids (17-KS) are DHEA and DHEA-S **[17].**

2.5 Dehydroepiandrosterone Sulfate (DHEA-S)

The adrenal glands create dehydroepiandrosterone sulfate almost exclusively through direct secretion or conversion from DHEA. The levels fluctuate considerably less than those of DHEA**[7],** but exhibit fluctuations throughout the course of the reproductive cycle and during the course of the day. Puberty causes an increase in DHEA-S production, which then declines following menopause **[9].**

2.6 Androstenediol (Δ^5-diol)

The main sources of androstenediol, a weak androgen, are the adrenal glands and peripheral conversion **[8].** It primarily binds to globulin and only slightly to albumin. After menopause, the peripheral level drops **[9].**

3. Testosterone and male sexual development

Between the 7th and 12th week of pregnancy, male sexual development begins. By expressing the sex region of the Y chromosome (SRY), a gene complex found on the short arm of the Y chromosome, the undifferentiated gonads transform into fetal testis**[18].** Anti-Muellerian Hormone (AMH) and testosterone are both produced by the fetal testis. The epididymis, vas deferens, and seminal vesicle all develop as a result of the Wolffian ducts' development, which requires testosterone. The Muellerian ducts will regress as a result of AMH activity. During the first trimester of pregnancy, the number of gonocytes per tubule will grow thrice under the influence of intratesticular testosterone.Additionally, the prostate, penis, and scrotum all develop as a result of testosterone. However, the enzyme 5-alpha reductase transforms testosterone into the more powerful metabolite DHT in these tissues. Because the enzyme is not present in the testes, 5-alpha reductase inhibitors do not significantly affect spermatogenesis. Male pseudohermaphroditismand pseudovaginal perineoscrotal hypospadias.Inadequate virilization of the male external genitalia, are symptoms of people with low 5-alpha reductase activity**[19].**Both testosterone and DHT are necessary for penile development. While testosterone supplementation in adults will not cause extra penile growth, the androgen receptor (AR) in the penis disappears after puberty **[20].** The hormone aromatase, which is found in adipose tissue, the prostate, and bone, can also convert testosterone into estradiol. Although aromatase is also present inside the testis, it is unclear what function estrogens serve in the tubular compartment. It has been proposed that estrogens have an impact on the Sertoli cells' ability to produce and secrete Inhibin-B. Additionally, Leydig cell, Sertoli cell, and germ cell growth and function are probably influenced by estrogenic action **[21].** The pituitary hormone luteinizing hormone (LH) regulates the synthesis of testosterone. Serum testosterone concentrations reach adult levels

shortly after birth and remain there for several months. After then, testosterone levels are low until adolescence, preventing male virilization. Gonadotrophins are first produced during puberty, which is triggered by GnRH secretion from the brain and results in the creation of testosterone, male sexual characteristics, and spermatogenesis. Sperm development and testosterone after puberty, the follicle-stimulating hormone (FSH) triggers the beginning of spermatogenesis **[22].** Only the surface of Sertoli cells contains the FSH receptor. FSH is required for Sertoli cell proliferation during fetal life. Although there is conflicting evidence on the function of FSH in human spermatogenesis, a dual action of both FSH and intratesticular testosterone appears necessary for full quantitative and qualitative spermatogenesis **[23].** The Sertoli cells' FSH reactivity decreases as they mature and changes to enhanced responsiveness to androgens **[24].** In order to maintain the spermatogenic process and prevent germ-cell death, testosterone is required **[25].** Testosterone concentrations in the seminiferous tubules of the testes are 25–100 times higher than those in the blood. Reduced spermatozoa in the ejaculate and hypospermatogenesis are effects of gonadotrophin suppression **[26].** But if intratesticular testosterone is completely inhibited, meiosis is completely stopped up to the spermatid level **[27,28].** By expressing the androgen receptor (AR) and affecting the tubular through the Sertoli cells, testosterone appears to operate indirectly on the germ cells. Numerous paracrine substances, including peptide growth factor, cytokines, activins, and many more, are present inside the tubular compartments. It is still unclear whether and how testosterone controls or affects these intercellular activators that change cells **[29].** Animal studies have shown that the function of the epididymis is likewise androgen-dependent **[30].** The tubular system allows significant amounts of testosterone to reach the epididymis. While DHT is necessary for the epididymis to function in adulthood, testosterone is necessary for its growth from the Wolffian ducts. Androgens increase the synthesis

of most epididymal proteins. The epididymis eventually loses its capacity to support the maturation of sperm under androgen deprivation **[31].**Together with its metabolite estradiol, testosterone suppresses the production of gonadotrophins as well as GnRH. The Sertoli cells' Inhibin-B serves as the FSH negative feedback hormone. The Leydig cells in the interstitial compartment of the testis produce testosterone, which is primarily bound to the Sertoli cell-produced androgen binding protein (ABP). Given the limited storage space inside the seminiferous tubules, it was hypothesized that ABP is necessary for sustaining high amounts of testosterone inside the tubular compartment.Additionally, the testes do not have 5-alpha reductase, which prevents the production of DHT. The majority of male reproductive organs require substantially lower levels of testosterone for optimal development and function because DHT is far more effective in binding to the AR. High intratesticular testosterone levels have been hypothesized to make up for the testis' lack of 5-alpha reductase and assure AR expression **[32].**The testosterone receptor,the androgen receptor, which is found in the cytoplasm and nucleus of the target cells, is the mechanism through which testosterone exerts its action. In response to androgen binding, numerous proteins will be transcribed from DNA and have various intercellular altering functions. By increasing the number of cells with the AR as well as the number of ARs in each cell, testosterone in the fetal testis will increase the number of androgen receptors **[20].** The elevation of AR expression brought on by FSH-receptor binding will enhance tubular fluid and ABP synthesis**[24].**The AR gene has eight exons and is located on the X chromosome (Xq 11–12). Male sexual development caused by errors and mutations in the AR gene may result in testicular feminization or poor virilization. Male infertility and milder forms of androgen resistance may be brought on by less severe mutations of the AR gene **[33].** The transactivation domain of the gene's exon 1 is a trinucleotide tract (cytosine-adenine-guanine, CAG) of variable length.

Patients with spinobulbar muscular atrophy, also known as Kennedy disease, have varying lengths of elevated CAG triplet repeats. Gynecomastia, muscle atrophy, paralysis, and endocrine abnormalities are the hallmarks of this X chromosome-linked neurodegenerative illness **[34].** It was hypothesized that the length of the CAG repeats of exon 1 of the AR gene was negatively connected with sperm production because individuals with this condition exhibit late onset androgen resistance along with gynecomastia and testicular shrinkage **[35].** The length of the CAG repeats and male infertility were not consistently correlated in most studies, despite some researchers finding a slight association in males with idiopathic oligozoospermia **[36,37].** Perhaps only a small subset of infertile males that excludes other causes of male infertility exhibits this association.

4. Adrenal androgens

Adrenal androgens (AAs) are steroid hormones with little androgenic activity that are typically released by the fetal adrenal zone and the zona reticularis of the adrenal cortex. They are androstenedione (A4), androstenediol (A5), dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), and 11-hydroxy androstenedione (11-OHA4).More DHEA and DHEAS are released than the other adrenal androgens combined. Despite having limited androgenic activity, these steroids serve as a source of circulating precursors that can then be converted peripherally to more potent androgens and estrogens, such as testosterone (T) and estradiol (E), respectively. The amount of T that the adrenal glands produce is quite little. Although adrenal androgens do not seem to have a significant function in the fully androgenized adult man, both sexes prior to puberty appear to be affected by them. Contrary to adult men, girls, women, and prepubertal boys may have deleterious effects from AA hypersecretion**[38].**

5. Main Biosynthetic Pathway of Adrenal Steroids

Cholesterol serves as the source of all steroid hormones in humans. The main source of adrenal cholesterol is plasma lipoproteins. About 80% of the cholesterol transported to the adrenal gland is in low-density lipoproteins (LDL). The tissue of the adrenal gland contains unique cell surface LDL receptors. Acetyl-coenzyme A is used in the gland for its own synthesis. When stimulation occurs, a small pool of free cholesterol within the adrenal is ready for an immediate reaction. Acute stimulation increases plasma lipoprotein absorption, cholesterol production within the gland, and hydrolysis of stored cholesteryl esters to free cholesterol (39). Additionally, there is proof that the HDL receptor, SR-B1, in the adrenal may metabolize high-density lipoprotein HDL cholesterol **[37].**The steroid acute regulatory (STAR) protein transports cholesterol from the outer mitochondrial membrane of steroidogenic cells to the inner mitochondrial membrane, where it enters the steroidogenic pathway through the activity of the enzyme cholesterol esterase. The conversion of cholesterol to pregnenolone, the initial stage in steroid production and the main way that ACTH affects the adrenals, occurs after this transfer. The cholesterol side-chain cleavage enzyme, also known as P450scc, is needed to convert cholesterol into pregnenolone. It is produced by the CYP11A gene, which is found on chromosome 15 in mitochondria. As a result of this cleavage, the C27 cholesterol molecule is transformed into molecules with 21 carbons (C21). Molecular oxygen and two electrons are needed for these reactions. The electrons are given by nicotinamide adenine dinucleotide phosphate (NADPH) to the flavoprotein adrenodoxin reductase, then to the iron-sulfur protein adrenodoxin, and lastly to the P450scc. The enzyme P450 reductase is involved in electron transport to microsomal cytochrome P450.The cyclopentanoperhydrophenanthrene ring structure, which consists of three cyclohexane rings and one cyclopentane ring, is the source of the steroid hormones

made by the adrenal cortex. All steroid synthesis in the human body, including that of the adrenal, depends on P450scc. Although its expression is necessary for the production of C19 steroids (DHEA, DHEA-S, and A4), it is the presence of downstream enzymes that decides whether these cells generate C21 corticosteroids or C19 steroids. It is present in all zones of the adrenal cortex**(Figure 1).**

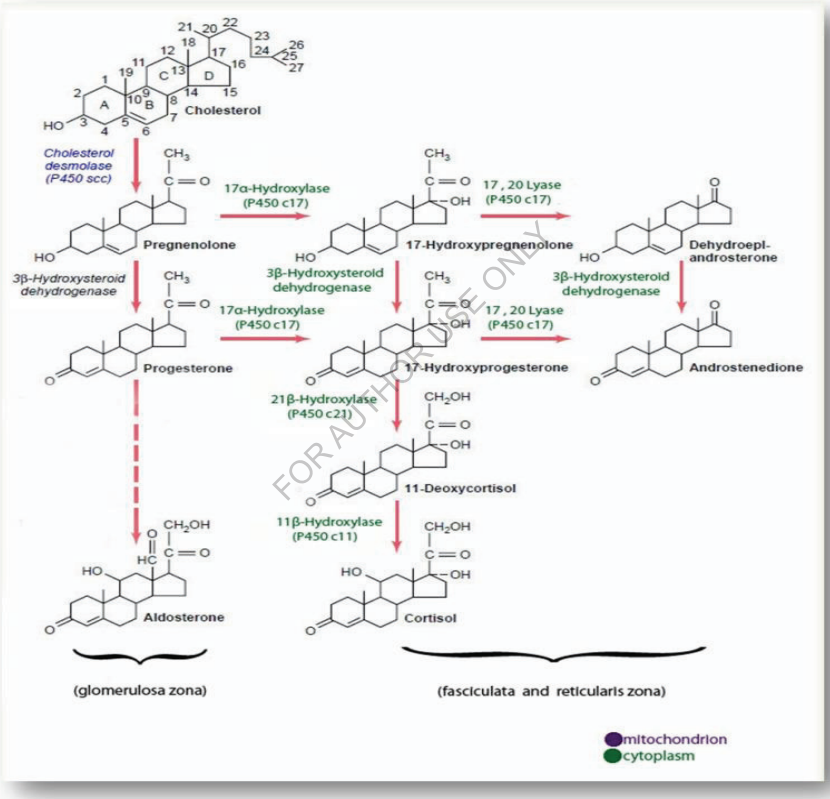


Figure 1: Adrenal androgen biosynthetic pathway.

6. Circulation and Metabolism

The adrenal cortex releases adrenal androgens in an unbound form. Steroids that are bound have no biological effect. Albumin is where androstenedione, DHEA, and DHEAS bond most. Approximately 3% of adrenal androgens are attached to sex hormone-binding globulin (SHBG), whereas about 90% of them are bound to albumin. While albumin has a low affinity and high capacity for steroids, binding globulins have a high affinity and low capacity. After entering the bloodstream, adrenal androgens might go by two distinct routes. They either undergo peripheral conversion to their more powerful derivatives, T and dihydrotestosterone (DHT), or they undergo breakdown and inactivation. In many tissues, including the liver and kidney, adrenal androgens and their metabolites are inactivated or broken down **[40].** The conjugation of androgens to glucuronate or sulfate residues results in hydrophilic glucuronides or sulfates, which are eliminated in the urine, respectively. Peripheral tissues convert DHEA, DHEAS, and A4 to the powerful androgens T and DHT. The major conversions of A4 to T and T to DHT are carried out, respectively, by the enzymes 17-hydroxysteroid dehydrogenase (17-HSD) and 5-reductase. The hair follicles, sebaceous glands, prostate, external genitalia, and adipose tissue are important peripheral sites of androgen conversion **[41].** These androgens' metabolites are either conjugated as glucuronides or sulfates or eliminated in the urine. Through the actions of the enzymes 17-HSD and aromatase, respectively, active absorption of androgens and in situ estrogen production take place in peripheral adipose tissue **[42].** In contrast to men, in whom the testis is primarily responsible for producing T, peripheral conversion considerably increases the concentration of T in the blood in women. In peripheral tissues, estrogens are synthesized primarily by three enzyme complexes **[43]:**

1- Aromatase, which converts androstenedione into estrone.2- Estrone sulfatase (E1-STS) is the enzyme that catalyzes the conversion of estrone sulfate into estrone.3- The enzyme estradiol-17-hydroxysteroid dehydrogenase (17-HSD) Type 1 is in charge of converting estrone into estradiol, the physiologically active form of estrogen.

7. Peripheral Metabolism of Androgens

The main circulating androgen in men is testosterone, which is released by the testes in response to luteinizing hormone (LH). Consideration of its peripheral metabolism is necessary to comprehend its action. The prohormone for the synthesis of two classes of active metabolites that regulate numerous processes related to androgen activity is testosterone. Dihydrotestosterone, the intracellular mediator of many of testosterone effects, can be produced when testosterone undergoes irreversible decrease **[44].** On the other hand, peripheral tissues in both sexes can convert circulating testosterone to estradiol. Adipose tissue is likely the most significant of the various peripheral tissues where this aromatization, or the conversion of testosterone to estrogen, occurs. In some circumstances, the estradiol produced may cooperate with androgens to affect physiological processes, but it may also function independently or produce results that are the opposite of those produced by androgens **[45].** Thus, the combined effects of testosterone itself and its active androgen and estrogen metabolites lead to the physiological effects of circulating testosterone.The involvement of the main adrenal androgen, androstenedione, and its conversion to the weak estrogen estrone must be taken into account when discussing the quantitative elements of androgen-estrogen dynamics. Be added as well. The common 17β-Hydroxysteroid dehydrogenases can reversibly interconvert androstenedione and testosterone, as well as estrone and estradiol. In healthy young males, there is an average daily production of estradiol, of which (35-40%) is formed by the aromatization of circulating testosterone, (50%) is produced by the weak estrogen estrone, and (10-15%) is secreted by the testes directly into the plasma. Direct secretion of estradiol into the plasma, on the other hand, increases when plasma LH is high for any cause **[46].**

8. Normal Androgen Action

The Leydig cells secrete testosterone, which is found in the testis at high quantities (about 100 times plasma levels). Although specific androgen binding proteins have been found in the testis and epididymis of lower animals, where they appear to transport testosterone through Wolffian duct-derived structures, these proteins have not been found in higher primates or in man **[47].** The two proteins albumin and testosterone-binding globulin serve as the main binding sites for testosterone in the plasma. The unbound or free hormones and the protein-bound steroid are in a dynamic equilibrium **[48].** Only the free fraction, it is believed, can penetrate cells and have actions attributed to androgens. Even while there may be more to the entry of androgens (and other steroids) into target cells than just passive diffusion, the existence of distinct transport mechanisms that operate at physiological concentrations has not yet been conclusively proven **[49].**Men's androgen has several important roles, including controlling the release of gonadotropins, starting and maintaining spermatogenesis, creating the male phenotype during sexual differentiation, and triggering sexual development during puberty. The 5 a-reductase enzyme in the cell can convert testosterone (T) into dihydrotestosterone (D). Then, in the cytoplasm (R), T or D binds to a particular androgen receptor protein.Before the hormone receptor complexes (TR or DR) may diffuse into the nucleus, it is then hypothesized that they go through some sort of alteration in the cytoplasm. With reconstituted cell-free systems, this "activation" or "transformation" of the steroid-receptor complex has been thoroughly studied in vitro. For the binding of steroid-receptor complexes to nuclei in these systems, temperature increases or changes in the ionic strength of cytosol receptor preparations appear to be necessary **[49].** It is unclear whether this activation includes a significant physical alteration in the receptor, such as subunit dissociation **[49].**Before triggering a biological response, steroid receptor

complexes inside the nucleus interact with acceptor sites. Numerous studies are being conducted, however it is not yet obvious how particular these nuclear acceptor sites (such as chromatin, nuclear proteins, or DNA) are or how many there are. The enhanced transcription of particular subsets of structural genes, as well as the arrival of particular messenger RNA and fresh proteins in the cell's cytoplasm, are all effects of the nuclear interaction **[49].**According to the available data, the dihydrotestosterone-receptor complex is in charge of external virilization during embryogenesis and the majority of androgen action during sexual maturation and adult sexual life, whereas the testosterone-receptor complex controls gonadotropin secretion, spermatogenesis, and Wolffian stimulation during sexual differentiation. It is unclear why some androgen effects appear to be mediated by testosterone while others appear to be mediated by dihydrotestosterone. It could be caused by an imperceptible change in receptor affinity, the brief presence of a particular protein that binds testosterone during development, or a phenomena involving the metabolism of testosterone and the local concentration in the genital tract. The exact processes by which estrogens enhance or inhibit androgen activity are still unknown. However, modest increases in estradiol may raise the number of androgen receptors in the prostate and hence boost androgen action in the case of prostatic development in aged males **[50].**

9. Normal Male Sexual Development

Up until around 40 days of gestation, the embryos of both sexes develop indistinguishably; it is only after this point that development diverges to result in the emergence of the male and female phenotypes. In most cases, a gene for testis development is located on the Y chromosome. This determinant might be similar to or closely related to the H-Y antigen, a cell surface antigen **[51].** The indifferent gonad is induced to develop into a testis in the presence of a Y chromosome (or in some cases, more particularly, in the presence of an H-Y antigen). In the chromosomal female without this beneficial influence, the neutral gonad develops into an ovary. The sort of gonad developed has a direct impact on the ultimate process, which converts gonadal sex into phenotypic sex. Undifferentiated internal and external genital anlage is transformed into male or female forms during the formation of phenotypic sex. The Mullerian and Wolffian ducts, which are present side by side in early embryos of both sexes, are the sources of the internal genitalia in each of the two sexes **[52].** The Mullerian ducts are created from the Wolffian ducts, which are the excretory channels of the mesonephric kidney. The epididymis, vas deferens, and seminal vesicle develop in the male from the Wolffion ducts, whereas the Mullerian ducts vanish. The Mullerian ducts give rise to the female's uterus, upper vagina, and fallopian tubes, whereas the Wolffian ducts regress. The urethra and external genitalia, on the other hand, grow from a single anlage in both sexes. The urethra and a section of the vagina are both born from the urogenital sinus, which also gives rise to the prostate and prostatic urethra in males and the urethra in females. The glans penis in males and the clitoris in females both originate from the genital tubercle. The vaginal folds transform into the labia minora or the shaft of the penis, while the urogenital swelling becomes the scrotum or the labia majora.The development follows female lines when the

testis is absent, as it does in a healthy female embryo or a male embryo that has been castrated before the start of phenotypic differentiation. Therefore, the fetal gonad's hormone has the favorable effect of masculinizing the fetus, whereas the gonad is not necessary for female development. Ordinarily, the development of the sexual phenotype follows the chromosomal sex pattern. That is, chromosomal sex dictates gonadal sex, which then dictates phenotypic sex. The actions of three hormones are responsible for determining how the male phenotype develops. The fetal testis produces the secretory substances Mullerian regression factor and testosterone, two of the three. The Mullerian regression factor is a poorly understood peptide hormone that suppresses the Mullerian ducts, preventing the uterus and fallopian tubes from developing in the male **[53].** There are two ways that testosterone encourages urogenital tract virilization. The epididymis, vas deferens, and seminal vesicle are formed by directly stimulating the Wolffian ducts. Before these tissues gain the ability to produce dihydrotestosterone, the Wolffian duct in the human male embryo has finished differentiating **[54].** Testosterone functions as a prohormone for the third fetal hormone, dihydrotestosterone, in the remaining tissues of the male urogenital tract. Before molecular differentiation of these tissues occurs, dihydrotestosterone is created by 5 a-reduction of testosterone inside the lower urogenital tract and urogenital sinus **[54].**The male urethra and prostate are formed as a result of its action in the urogenital sinus, and the genital tubercle experiences swelling and folds that lead to midline fusion, extension, and enlargement, which result in the male external genitalia. As a result, androgen's main role throughout fetal development is to encourage the development of the reproductive accessory organs in males. By the middle of the second trimester, the male phenotype has largely developed. The external genitalia of the two sexes, however, are the same size at the time of the

male urethra's completion **[55].** Testes descend and the male external genitalia expand at different rates throughout the second half of pregnancy**(Figure 2).**

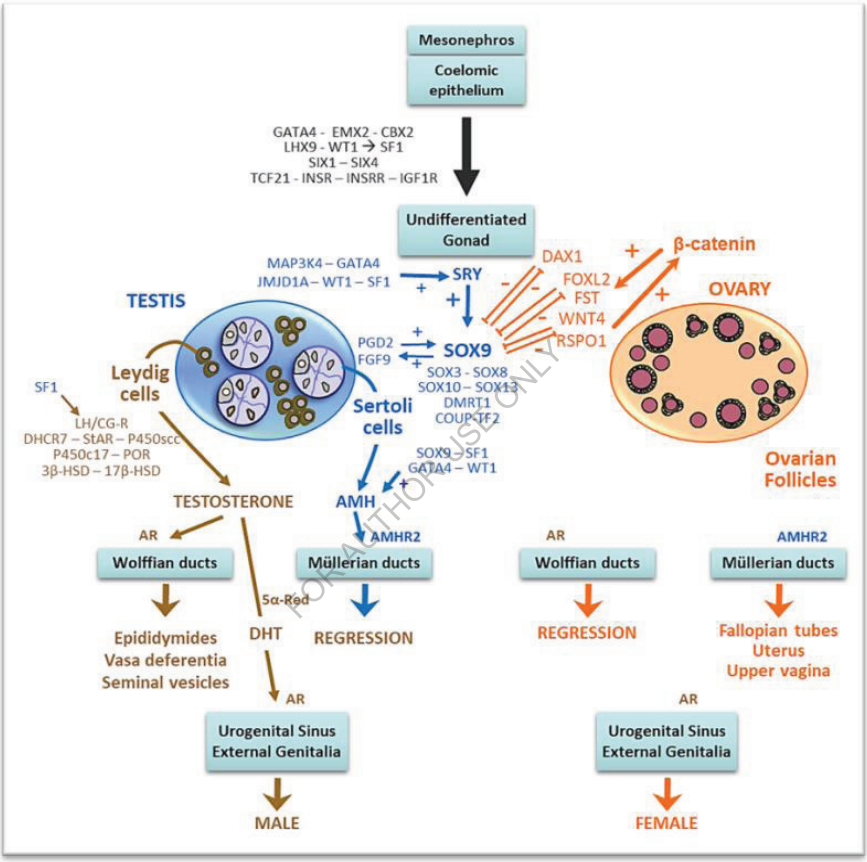


Figure2: Sex determination and differentiation.

10. Androgen Receptors

The development of a mature testis that can support spermatogenesis and the generation of testosterone that serves as the foundation for male fertility depends on the androgen receptor. It is also necessary for the differentiation of masculine sexuality and sexual maturation. The human androgen receptor is encoded by a single gene on the X chromosome, Xq11–12, which produces a protein with 919 amino acids **[1].** It is a traditional member of the large nuclear receptor superfamily **[56],** which also includes receptors for thyroid hormones, retinoic acid, vitamin D, and numerous orphan receptors, which are receptors for which the ligand was initially unknown **[57]**Although levels of expression and androgen sensitivity in non-reproductive tissues vary, androgen receptor expression is not restricted to reproductive organs and is widespread.Over half (535/919) of the AR's total length (535/919) is made up by the NTD (exon 1), which is a lengthily exon. In comparison to other steroid receptors, it has the least conserved sequence. It also features a flexible and movable tertiary structure with a transactivation domain (AF-1) that interacts with target genes and AR co-regulator proteins **[58].** Three homopolymeric repeat sequences (glutamine, glycine, and proline) are also present in its loose, naturally disordered structure **[59]** with the CAG triplet (glutamine) repeat polymorphism **[60]** being the most significant. Although linkage dysequilibrium between the glutamine and glycine repeat polymorphisms requires haplotype analysis for interpretation **[60],** the less variable glycine (typically 24 residues) and proline (9 residues) repeat polymorphisms have little apparent independent pathophysiological importance. The length of the glutamine repeat is inversely correlated with AR transcriptional efficiency in healthy individuals, where the glutamine repeat polymorphism has alleles with lengths ranging from 5 to 35 (population means 21). As a result, this polymorphism determines genetic

variations between individuals in the androgen sensitivity of their target tissues. It has been demonstrated experimentally that this genetic diversity affects the physiological responses to endogenous testosterone in the growth of the prostate and erythropoiesis **[61]** in well-designed investigations.In a number of potentially androgen-sensitive illnesses, the wider epidemiological implications of population diversity in the hereditary androgen sensitivity as characterized by the polyglutamine repeat have been investigated. Includes diseases of the reproductive system, hormone-dependent tumors in both sexes and non-gonadal diseases with notable gender inequalities in frequency. Male infertility **[62]** and prostate hypertrophy, cryptorchidism, and hypospadias are among the conditions that affect men, while polycystic ovary syndrome, premature ovarian failure, endometriosis, uterine leiomyoma, preeclampsia, and hormone-dependent cancers of the breast, ovary, and uterus are among the conditions that affect women.Studies have also looked at the dangers of being overweight and having cardiovascular disease, as well as the dangers of having mental and behavioral illnesses such as dementia, psychosis, migraines, and personality disorders **[62].** The results, however, remain mostly contradictory, suggesting methodological constraints, particularly in recruiting, participation, and publication bias as well as multiple hypothesis testing, all of which tend to exaggerate spurious connections, as in many large-scale genetic association studies **[63].**Remarkably, the neurodegenerative condition known as Spinal Bulbar Muscular Atrophy (SBMA, also known as Kennedy's syndrome), is caused by the abnormal extension of the polyglutamine (CAG triplet) repeat to lengths of over 37. One of numerous late-onset neurodegenerative polyglutamine repeat illnesses is a type of slow-progressing, deadly motor neuron disease. Before being diagnosed in middle age, these men often have normal reproductive function, including fertility and virilization. However, the high length of the polyglutamine repeat does indicate modest androgen resistance.Furthermore,

SBMA represents a toxic gain-of-function involving pathological protein aggregates of the mutant AR **[64],** just like other genetic polyglutamine repeat neurodegenerative diseases do with other proteins, because complete androgen receptor inactivation in humans and other mammals does not result in motor neuron disease and female carriers are protected from symptomatic neurodegeneration. Surprisingly, transgenic animal models of SBMA reveal that genetic or pharmacological injection of IGF-I may decrease disease progression as well as testosterone deprivation by medical castration using a GnRH agonist. However, the first significant clinical trial of the GnRH analog leuprolide failed to show neuromuscular improvement in swallowing and additional research on a few treatment targets and subgroups is necessary **[65].**

11. Receptor Disorders

11.1 Female Phenotype- Testicular Feminization

Since the early 1800s, when clinical accounts of this medical "curiosity" were first published, the syndrome of testicular feminization has been recognized as a unique entity. A careful pedigree analysis conducted in 1937 by Petterson and Bonnier yielded significant information about the pathophysiology of the disorder. They concluded that affected people "must" be genetic males, that the defect could be caused by either an X-linked recessive defect or a sex-limited autosomal dominant mutation, and that the syndrome might be caused by failure of male induction in an embryo in which the fundamental trend is toward the female phenotype.Morris coined the phrase "testicular feminization" for the first time in 1953 **[66].** According to estimates, the condition affects 1 in 2,000 to 1 in 64,00 male births, making it the most prevalent form of family male pseudo hermaphroditism**[67].** One in five intersex patients, excluding those with gonadal dysgenesis, according to some authors **[68].** To put it another way, testicular feminization, which affects around 11% of these individuals, is believed to be the third most common cause of primary amenorrhea, behind gonadal dysgenesis and congenital vaginal absence. The primary clinical characteristics of the disorder's full form are relatively consistent**[67].**The physician sees phenotypic females who have primary amenorrhea (postpubertal) or an inguinal hernia (prepubertal). Females generally have different habits and body fat distribution patterns, and they also develop their breasts around the time of predicted puberty. Many of the patients look distinctly feminine. Typically absent or sparse are pubic and axillary hair. The facial hair is nonexistent, and the hair on her scalp is typical for a lady. The clitoris is a typical size, and the external genitalia are unmistakably female. The vagina may be short or blind-ending, nonexistent, or very basic. Except for the gonads, all internal genitalia are gone. The testicles can be found in the labia majora, along the

inguinal canal, or in the abdomen. Occasionally, traces of Mullerian or Wolffian duct origin can be seen in the fibrous bands that protrude from the testis or the paratesticular fascia. Spermatogenesis is usually absent, which sets cryptorchid testes from other causes apart from normal testes in terms of histology. The karyotype is 46, XY **[69],** and there have typically been other family members who have been similarly impacted. The gene for the ailment is X-1 inked, as has been shown in the best-studied animal model of the condition, the Tfm mouse. A third of patients have unfavorable family histories and are thought to be novel mutations, similar to other diseases with decreased reproductive fitness. Androgen resistance is evident in the hormone profile of patients with testicular feminization. Testicular production rates and plasma testosterone levels are normal or higher than those of normal men. Due to the main impairment in androgen action and the accompanying lower bulk of androgen target tissues that metabolize testosterone, observations of decreased dihydrotestosterone production in these patients are likely secondary **[70].** With more frequent secretory episodes, raised mean plasma LH **[71],** and faulty feedback regulation caused by resistance to testosterone action at the hypothalamic-pituitary level are all plausible secondary causes of the increased testosterone production rate. Both increased testicular estrogen synthesis and increased blood levels of estradiol in the spermatic vein are likely related to increased LH levels. Estradiol production is often approximately twice normal and testosterone production is typically about 50% higher than normal, while the amount of estradiol produced directly by the testes is typically seven to eight times higher than usual **[72].** Thus, the development of female secondary sex traits at the anticipated time of puberty as well as the construction of a female phenotype during embryogenesis are caused by androgen resistance combined with increased estradiol production. Less than 10% of people who have testicular feminization have an incomplete or partial form of the condition. Except for some degree of

external genital ambiguity and the development of modest virilization as well as feminization at puberty, patients with incomplete testicular feminization resemble patients with testicular feminization **[73].** Numerous examples of incomplete male pseudohermaphroditism have been labeled with this designation, and many of these patients clearly lack androgen resistance. However, some of the individuals described under this category have a unique phenotype, and it may be justifiable to separate them into separate androgen resistance syndromes**[74].**As with patients with the full illness, those who are affected have the habits and outward look of women and typically present with primary amenorrhea. Karyotype 46 is an XY. The testes are identical histologically to those in their entire state and can be found in the abdomen or inguinal canals. The partial union of the labia scrotal folds and the varied degree of clitoromegaly on the external genitalia make them stand out. The vagina is short and has a blind end. Variable feminization and partial virilization may both occur at the time of expected puberty. All mullerian duct derivatives are absent after laparotomy, however the existence of wolffian duct structures is a defining characteristic that distinguishes the phenotypic from the full form of the condition (together with the partial virilization of the external genitalia). The Wolffian duct structures are masculine, however they are less developed than those of typical men. The family history is typically not helpful. However, the occurrence of two afflicted half-siblings with the same mother and a different father supports X-linked inheritance in at least one of the families tested sufficiently to rule out a deficiency in testosterone production. There hasn't been any clear evidence of a pedigree where testicular feminization in its complete and imperfect forms coexist in the same family.The endocrine findings are comparable to those in the disorder's full form **[74].** Dihydrotestosterone synthesis in cultured cells and fresh tissue slices **[74]** from one patient who has undergone extensive research was normal. Only lately has the nature of the androgen resistance been

clarified. Initial studies of particular high-affinity dihydrotestosterone binding in people with the full condition revealed a significant androgen receptor deficiency, which is comparable to the impairment shown in the Tfm mice. Other laboratories supported these findings in the human disorder and expanded them to include partial receptor deficit in one patient with the disorder's incomplete form **[75].** Although it was previously believed that the androgen receptor was almost entirely absent in testicular feminization, at least one family with the disorder's typical complete form of the disorder was found to have receptor positivity without any discernible abnormalities in nuclear localization or binding **[76].** Recent research has shown that testicular feminization is caused by two different types of androgen receptor defects **[77].**Under the typical conditions of the monolayer binding experiment, some patients with both complete and imperfect types of testicular feminization were shown to only exhibit partial receptor deficit (about half-normal levels of binding). Studies of affinities, specificities, turnover, nuclear localization, and thermolability were conducted in an effort to find evidence of qualitative anomalies in the quantifiable receptor. When the binding reaction was carried out at a high temperature (42°C), dihydrotestosterone binding (Bmax or the amount of receptor) fell by more than 80%, which was the only parameter that was discovered to be wrong in these testicular feminization patients.Thermolability has shown to be a sensitive indicator of structural problems in enzymes and other proteins in different systems. When the assay temperature was reduced to 37°C, the thermal inactivation was quickly reversed, indicating that the binding protein's tertiary structure was temporarily altered by the high temperature. Three sets of sibling patients have this temperature-sensitive receptor. X-linked inheritance is suggested by the family research. Thus, either a receptor that does not bind or one that is in an unstable state can cause the syndrome of testicular feminization. Only patients with the complete form of the condition have been demonstrated to have a

total absence of binding, despite the unstable receptor being linked to both the complete and incomplete forms of the disorder. It is unknown if the qualitative anomaly is allelic to the receptor-negative mutation.Both the complete and incomplete forms of testicular feminization require various approaches to treatment. If the testes are present in the inguinal area or the labia majora and cause discomfort or if there is accompanying hernia formation, castration is recommended for patients who have normal female external genitalia (the complete form). Testicular tumors rarely form before the end of adolescence in patients with intra-abdominal or otherwise asymptomatic testes, and affected individuals often go through a normal pubertal growth spurt and feminize at the usual time of puberty **[78],**Castration is frequently postponed until beyond adolescence. The growth of malignancies in the undescended testes is the most significant consequence in the untreated patient. Although it is unknown if tumor formation is more frequent than in cryptorchidism due to other factors, many of these tumors behave like genuine cancers, hence the testes should be removed once secondary sex development is finished **[79].**Any prepubertal patient with clitoromegaly or posterior labial fusion should have gonad surgery before the anticipated period of puberty because patients with the incomplete disease virilize (as well as feminize) at puberty. Replacement estrogens should be administered during postpubertal castration or at the age of typical puberty in castrated prepuberty patients. The blind-ending vagina typically has enough depth to allow for intercourse and will typically go deeper with more intercourses. As is done for patients with congenital absence of the vagina, operational or nonoperative procedures may be performed to augment depth in those people in whom there is insufficient vaginal depth to allow intercourse. These patients exhibit plainly feminine behavior and viewpoint, according to studies on psychosexual function, and are capable of carrying out the duties of a typical adoptive mother **[80].**

11.2 Male Phenotype

11.2.1 Reifenstein syndrome

Numerous incomplete male pseudohermaphroditism X-linked recessive variants have been identified, where the male phenotype predominates. This covers the syndromes mentioned by Gilbert-Dreyfus **[81],** Lubs **[82],** Reifenstein **[83,84],** and their coworkers. Initially, it was believed that each of these ailments was a separate nosological entity, but three very broad pedigrees have been recorded in which affected members of the same family have phenotypes that vary and combine the deficiencies mentioned.Our interpretation is that these disorders likely represent different manifestations of a single mutation and can be referred to as "Reifenstein syndrome" because all of these pedigrees are compatible with X-linkage **[85].** The spectrum of faulty virilization includes persons with pseudo-vagina development and more serious problems such as hypospadias, starting with a male with gynecomastia and azoospermia. The most typical presentation is a male with azoospermia, gynecomastia, and perineoscrotal hypospadias that appears during or after puberty. The growth of pubic and axillary hair throughout puberty is distinct from the limited growth of chest and facial hair. The voice is frequently pre-pubertal, and the temporal recession of the hairline is minor. The testicles are smaller than normal in cryptorchidism, though often larger than in Klinefelter syndrome. Leydig cells seem normal, the tubules contain Sertoli cells as well as germinal cells, and however, the germinal cells typically do not mature past the first spermatocyte. The one exception to this rule is a recent family with normal sperm densities but reduced ejaculate volume, in which a biopsy revealed normal spermatogenesis **[86].** Since infertility is a common finding in people with Reifenstein syndrome, it is possible that it is caused by anatomical changes in the ejaculatory system in addition to defective spermatogenesis. Some people with

Reifenstein syndrome have defects in Wolffian duct-derived structures, such as absence or severe hypoplasia of the vas deferens. Despite the possibility of ambiguous genitalia at birth, the majority of patients are reared as men. Most people seem to have clearly male psychological development. Plasma levels of LH and testosterone are increased **[85].** Testicular feminization is known to cause an increase in the frequency and size of LH secretory episodes.Increased synthesis of testosterone and estradiol, akin to testicular feminization, has been seen in quantitative analyses of androgen and estrogen dynamics. The total amount of estradiol generated and the amount released by the testes in the few patients tested actually exceeded the mean value of these measures in patients with complete testicular feminization. Despite this, there is not a significant amount of feminization at puberty. This is most likely a result of imperfect androgen resistance, which results in a less severe imbalance of the two hormones within the cell. Cultured fibroblasts from the affected patients have been employed in studies aimed at determining the molecular causes of androgen resistance.Patients with normal familial illness had partially inadequate levels of dihydrotestosterone binding **[75].** The use of changes in receptor affinities, specificities, or turnover to show qualitative aberrations in the remaining dihydrotestosterone binding was ineffective. The receptor in these patients' cells was not thermolabile, in contrast to the testicular feminization patients who lacked receptors **[77].** We can infer that the inheritance is X-linked because it has been demonstrated that the mutation involves a protein that is known to be X-linked. Surgically correcting the cryptorchidism and hypospadias is necessary. Gynecomastia, which is thought to be caused by a combination of elevated estrogen production and androgen resistance, can be unsightly. Surgery is the only treatment for gynecomastia that has proven effective**(Figure 3).**

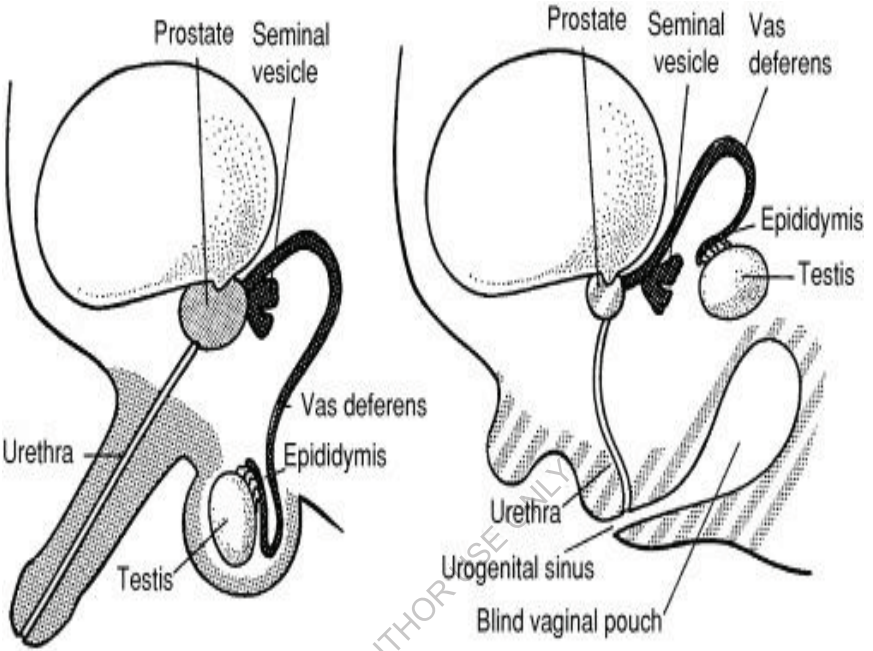


Figure 3: Male pseudohermaphroditism refers to a condition that affects 46, XY individuals with differentiated testes who exhibit varying degrees of feminization. A form of male pseudohermaphroditism in which 46,XY males show ambiguous genitalia at birth, including perineal hypospadias and a blind perineal pouch, and develop masculinization at puberty. The name of the disorder stems from the finding of a blind-ending perineal opening resembling a vagina and a severehypospadias penis with the urethra opening onto the perineum.

11.2.2 Infertile Male Syndrome

Unlike the other various types of androgen resistance, the second major category of receptor abnormalities with a male phenotype has just lately been discovered

[87];additionally, it is not a form of male pseudohermaphroditism. But it might turn out that this type of androgen resistance is the most typical. There were certain males with an X-linked condition of gynecomastia and infertility when analyzing the varied presentation of the Reifenstein syndrome. Thus, it was assumed that similar, little-affected patients might be discovered. Few of these patients have been found, though. However, when diagnosed only based on infertility, people without a favorable family history or gynecomastia were discovered to have androgen resistance. These 46, XY males have infertility brought on by azoospermia or oligospermia and androgen-estrogen dynamics comparable to those found in patients with the other receptor problems mentioned above **[87].** These men do not show hypospadias or discernible abnormalities of Wolffian duct structures. In comparison to normal men, testosterone production rates and mean plasma concentrations were around twice as high. Two of the first three individuals whose plasma LH levels were carefully examined had increased levels as well. Less than half of normal levels of high-affinity dihydrotestosterone binding are found, which is similar to what is seen in patients with Reifenstein syndrome **[87].** Similar to patients with Reifenstein syndrome, none of the current methods of evaluation show that the androgen receptor in the cells of these patients is qualitatively aberrant. With increased temperature, the receptor level does not consistently decrease. The prevalence of this type of androgen resistance in the sizable population of infertile males is the main unresolved question surrounding it. About % of all marriages end in childlessness by choice. At least 30% of these couples have a husband who can be blamed for the problems. Infertility affects up to 5% of married males. Despite claims that approximately 80% of the cases in the Iorge series of consecutive patients with male infertility have a recognized etiologic component **[88],** a close analysis of the categorization suggests that this is implausible. For instance, 39% of instances are said to have varicocele as the

cause. However, more than half of varicocele patients had sperm densities under 10 million, and their responses to varicocelectomy in terms of pregnancy may be similar to what would be expected in a control group. Therefore, it is probably acceptable to assume that at least 25% of males who have infertility lack a known cause.According to Walsh, one method for attempting to determine the proportion of infertile men who are androgen resistant would be to seek for patients who have elevated plasma levels of both LH and testosterone. In one study **[89],** 2% of males with hypospermatogenesis had elevated plasma testosterone levels.

12. Increased Androgen Production

Depending on gender and the stage of puberty, hyperandrogenism also presents a range of clinical manifestations. Hyperandrogenic prepubescent boys may exhibit virilization. Penile enlargement, excessive hair growth in androgen-dependent areas, and voice deepening are all signs of virilization. Hyperandrogenism in prepubescent girls can cause clitoromegaly, acne, and hirsutism. Whether an adult male's excess testosterone comes from exogenous or endogenous sources determines how it will affect him. Males with elevated levels of adrenal androgen don't typically experience an increase in muscle size or hair growth. Increased levels of adrenal androgens in adult females can cause virilization, acne, hirsutism, monthly abnormalities, infertility, and hirsutism.

12.1 Adrenal

12.1.1 Adrenal Tumors.

Adrenal virilizing tumors frequently develop prior to puberty or during menopause. Hormonal irregularities, virilization, and hirsutism all develop quickly in premenopausal women. These tumors primarily produce DHEA and DHEA-S,**[90]** although a few have been noted to produce exclusively testosterone; in these cases, the level of urine 17-KS or serum DHEA-S is normal**[91],** hCG may have an impact on tumors that produce testosterone. Following the use of dexamethasone, androgen levels typically do not decline, but they occasionally might. .Serum DHEA levels are often greater than 20 ng/ml, DHEA-S levels are greater than 9000 ng/ml, and testosterone levels are greater than 2 ng/ml in patients with these malignancies**[90].** Hirsutism is seen in Cushing's syndrome individuals with adrenal adenomas or carcinomas and hypercortisolism, and it can be accompanied with levels of 17-KS that vary from abnormally low to elevated **[92].**

12.1.2 Congenital Adrenal Hyperplasia

Congenital adrenal hyperplasia (CAH) can cause hirsutism, virilization, and an increase in testosterone production. A lack of the enzyme 21-hydroxylase results in elevated levels of T and 17-hydroxyprogesterone (17-P). Increased T and deoxycortisol (CpS) are signs of an 11-hydroxylase shortage, but a rise in 17-hydroxypregnenolone, DHEA, and DHEA-S is a sign of a 3-beta (ß) dehydrogenase deficiency. The diagnosis of CAH in females is now nearly invariably made at birth when the presence of ambiguous genitalia raises suspicion. However, in a small number of cases, this enzymatic deficiency is moderate and may not be noticed until puberty, when symptoms including hirsutism, irregular bleeding, amenorrhea, and virilization may develop. This condition is frequently known as acquired, delayed-onset, or attenuated adrenal hyperplasia and may not share the same genetic makeup as CAH **[93].**

12.1.3 Adrenal Hyperfunction

There is a lot of data to back up the idea that the adrenal can still be the source of excessive androgen production even in the absence of adrenal tumors or congenital adrenal hyperplasia.

12.2 Testicles

Some male pseudohermaphrodites who have completely feminized testicles or a genetic abnormality that prevents proper fetal virilization have a female phenotype before adolescence and are raised as Such Androgen levels rise during puberty, and hair growth in these people is mistaken for hirsutism **[94].**

12.3 Pituitary

Adrenal hyperplasia caused by Cushing's disease results in higher levels of androgens and corticosteroids. Acromegaly has been associated with hirsutism, and it has been proposed that synthesis of excess testosterone is influenced by other pituitary trophic hormones. Patients with hirsutism have been found to have

hyperprolactinemia, although a cause-and-effect connection has not yet been proved.

12.4 Iatrogenic (Drugs)

Hirsutism may result from androgens used to treat endometriosis. In addition to causing hirsutism and acne, danazol is an androgenic substance. Similar reports of acne and hirsutism have been made in relation to nor-testosterone derivatives like norethindrone and Noretynodrel **[95].** However, because of their suppressive action on LH, they typically have an antiandrogenic effect. Chronic ACTH administration may promote the production of adrenal androgen, which might result in hirsutism.

13. Late-onset hypogonadism

An aging-related syndrome called late-onset hypogonadism includes signs and symptoms of hypogonadism, a deficiency in serum androgen levels, and a decrease in genomic sensitivity to androgens. It is characterized by negative effects on multiple organ systems and a decreased quality of life. Characteristics of late-onset hypogonadism clinically numerous generalized, non-specific symptoms that could be related to low testosterone are frequently found in aging males. Reduced bone mineral density, decreased muscle mass and strength, abdominal obesity, decreased libido, erectile dysfunction, decreased body hair and skin changes, reduced hematopoiesis, depressed mood, impaired cognitive function, and decreased general well-being are all signs of late-onset hypogonadism **[96,97].**The word "andropause" refers to this decline, and while the cause of the decline in steroids differs from that seen during menopause in women, both circumstances have definite symptoms that are related to the decline in hormones at this time. For instance, a fall in bioactive androgens with age in men has been linked to decreased libido, exhaustion, loss of muscle mass, osteoporosis, melancholy, and/or cognitive dysfunctions. There is currently a lot of interest in the use of androgen-based therapies to alleviate some of these symptoms due to the aging population and the strong impact that androgens have on physiological and psychological function. Additionally, some younger populations use finasteride along with or instead of other medicines to change steroid metabolism, such as illicit anabolic androgenic steroids (AAS), which are synthetic androgens. The possibility for steroid-based treatments to raise the risk for prostate diseases and psychological side effects is a severe worry that restricts their usage in males **(Figure 4,5).**

13.1Loss of bone

Both in males and in women, the likelihood of hip fractures increases gradually with age. Every year, four to five men in the USA who are 65 or older break a hip**[98].** Only roughly 40% of these elderly men will be able to return to their prior level of everyday functioning, and 20% of them will pass away within the first six months. Reduced bone mineral density, also known as osteopenia or osteoporosis, which in aging men along with sarcopenia is believed to be caused, at least in part, by testosterone insufficiency, is the primary cause of hip fracture in the elderly. **[96,97].**Numerous studies have shown that as men age, their bone mineral density decreases, with trabecular bone losing more density than cortical bone. Recent research has demonstrated that there is a distinct association between bioavailable testosterone and bone mineral density, despite the fact that correlations between total testosterone and bone mineral density are often modest in aged men. Additionally, castration for prostate cancer, whether surgical or pharmaceutical, has been demonstrated to increase the risk of osteoporotic fractures, which are a kind of acquired hypogonadism and are preceded by a sharp fall in bone mineral density **[99].**Although the exact methods by which testosterone may affect bone mineral density are unknown, one option is a direct impact on androgen receptors or on cytokines or growth factors that are linked to them. It is likely that testosterone's aromatization into estradiol is the mechanism by which it has an indirect but significant influence. Aged men with lower plasma levels of the testosterone substrate experience less aromatization into estradiol, which has an impact on bone mineral density. Increased mechanical stress brought on by anabolic effects on muscle, calciotropic hormones, or renal processing of calcium, phosphorus, and vitamin D is other contributing factors **[100].**

13.2 Adverse Impact on body composition and muscular status

Men's muscles weaken and shrink as they age, and the central and upper regions of their bodies accumulate more adipose tissue. Sarcopenia, a term used to describe the condition of age-related muscle weakness, is linked to decreased functional performance, greater physical disability, increased reliance, and a higher risk of falling. In addition to the pathogenic effects of chronic disease and malnutrition, other potential causative causes include decreasing plasma levels of anabolic substances, decreased muscle protein synthesis, and nervous system aging. Additionally, findings from the New Mexico Aging Process Study have demonstrated that muscle strength and total and free plasma testosterone levels are significantly correlated in older, reasonably healthy men **[101].** Age, plasma testosterone levels, and body composition in men have been found to be significantly correlated. Obesity is linked to decreased testosterone plasma levels and a low testosterone/estradiol ratio. The distribution of adipose tissue and testosterone levels have also been linked, with testosterone levels being negatively correlated with visceral (or intra-abdominal) adiposity, which was essentially independent of the aging process.Men's increased visceral adipose tissue with age causes the portal vein to outflow more free fatty acids. This worsens insulin metabolism and lowers insulin sensitivity while also raising plasma triglycerides and lowering high-density lipoprotein cholesterol. It is hypothesized that these metabolic consequences raise the risk of type 2 diabetes, cardiovascular disease, and death. Recent cross-sectional investigations revealed that testosterone levels and muscle strength metrics of the upper and lower extremities, including leg extensor strength and isometric hand grip strength, are positively correlated in aging males. The doors test, which assesses the functionality of the upper limbs, as well as the 6-meter walk, "get-up-and-go" test, and five-chair sit/stand test, which assess the functionality of the bottom extremities, were functional characteristics

that were positively linked with testosterone. Additionally, "activities of daily life" and testosterone were found to have a strong association with male nursing home residents. A higher degree of reliance was linked to low testosterone levels **[104].** Some studies of testosterone supplementation in patients with andropause or hypogonadism reveal improvements in muscle and the distribution of body fat.These connections and findings imply that testosterone influences the status of muscles and the composition of the body, either directly or indirectly. The nitrogen-retention action of testosterone has been proposed as a crucial mediator, despite the fact that the mechanism is unknown.

13.3 Erectile dysfunction and a decline in libido

Libido is a subjective state that is poorly understood and is influenced by social, psychological, and biological factors. Men's libido issues significantly rise with age; according to a recent study, the prevalence of libido issues among men over 50 has increased by three times. Men's health and lifestyle characteristics such as alcohol usage, poor health, stress, and negative past sexual encounters are predictors of libido issues **[103].**Along with these contributing factors, the decline in plasma testosterone levels with age is sometimes blamed for the rise in libido issues among aging men. For proper sexual function, there seems to be a minimum level of testosterone that must be present; quantities over that have no noticeable effects. Therefore, reduced libido may be common in older men whose plasma testosterone levels are below this cutoff level **[104].** Additionally, it was shown that a drop in bioavailable testosterone in men was linked to a drop in sexual desire and arousal (but not total testosterone) **[105].**It is well known that erectile function decreases as people age. The incidence increased from 12.4 new cases per 1,000 men in the age group 40-49 years per 1,000 men in the age group 60-69 years in the Massachusetts Male Aging Study. Low levels of education, diabetes, heart disease, and hypertension all showed significant correlations with erectile

dysfunction. It is anticipated that there would be more than 600,000 new cases of erectile dysfunction per year in the USA alone **[106].** Numerous studies have attempted to show a link between erectile dysfunction and the known drop in plasma testosterone with aging. For instance, erectile dysfunction and serum total testosterone did not correlate in the Massachusetts Male Aging Study **[107].**Erectile dysfunction and bioavailable testosterone were not clearly correlated in a different research of older men **[108].** It is complicated how testosterone affects erectile function: whereas erections brought on by visual cues or fantasies are partially androgen-dependent, spontaneous erections are androgen-dependent **[109].** Despite the fact that testosterone is necessary for healthy erections (perhaps as a result of its capacity to boost nitric oxide release in the corpus cavernosum), the information at hand points out that hypogonadism is rarely a significant contributor to erectile dysfunction in older men. Only about 7–15% of men with erectile dysfunction are the main contributors to the hypogonadism issue, according to studies **[110].**These people with erectile dysfunction would definitely benefit from testosterone therapy.

13.4Decrease in hematopoiesis

Mammals' reticulocyte count, blood hemoglobin levels, and bone marrow erythropoietic activity are known to be stimulated by endogenous androgens, whereas castration has the reverse effect. Anemia may arise from the 10–20% reduction in blood hemoglobin content brought on by testosterone deprivation **[111].** Hemoglobin levels and red blood cell counts are often lower in young hypogonadal males than in age-matched controls, and healthy older men may also have lower hemoglobin levels than typical young men. The main androgen involvement in the mechanism of normal hematopoiesis is thought to involve direct stimulation of renal production of erythropoietin by testosterone. Moreover, the latter may also act directly on erythropoietic stem cells **[112].**

13.5 Depressed mood

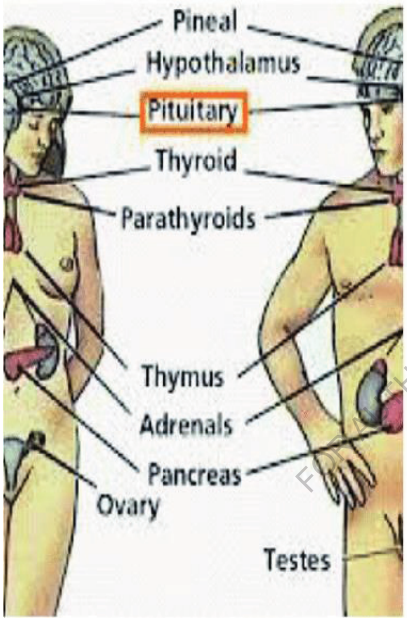
A correlation between testosterone levels and mood has been proposed in various research, and it appears that the prevalence of low mood in males rises with age **[113].** In older men, testosterone levels and depressive symptoms have an antagonistic relationship **[114].** A well-controlled study indicated that hypogonadal men experience greater depression than normal men **[115],** but the Rancho Bernardo Study discovered a strong link between age-related declines in bioavailable testosterone and higher depression scores. Additionally, bioavailable testosterone levels in a subgroup of patients with verified clinical depression were 17% lower than in men in a healthy state **[116].**

13.6Memory Loss and cognitive impairment

Studies in a mouse model have shown that the SAMP8 strain's age-related decline in plasma testosterone levels is linked to memory and learning capacity degradation **[117].** Numerous studies on aging men have examined the relationship between testosterone and cognition (tasks such as spatial attention, visual perception, object recognition, and visual memory), and it seems that there is, on average, a U-shaped association. This suggests that low testosterone plasma levels, both normal and supraphysiological, are linked to poor cognitive function **[118].** Therefore, it is reasonable to assume that plasma testosterone levels within the normal range will result in the best cognitive function.

Physical:

- Decreased body hair
- Decreased muscle strength and mass
- Development of breast tissue
- Hot flashes, sweats
- Sleep disturbances and fatigue
- Osteoporosis/ height loss



Symptoms of Testosterone Deficiency Among Men

Cardiometabolic:

- Increased body mass and abdominal obesity
- Metabolic syndrome
- Insulin resistance and type 2 diabetes

Sexual:

- Delayed puberty
- Hypogonadism (small testes)
- Decreased frequency of sexual thoughts and desire, and sexual activity
- Decreased or absent morning/nighttime erections
- Erectile Dysfunction and/or infertility

Psychological:

- Changes in mood
- Greater lability
- Anger, irritability, sadness, depression
- Overall sense of poor well-being and health
- Poor cognitive function
- Reduced concentration, spacail performance, and verbal memory

Figure 4:the effects of loss of androgens among men (**Late-onset hypogonadism**).

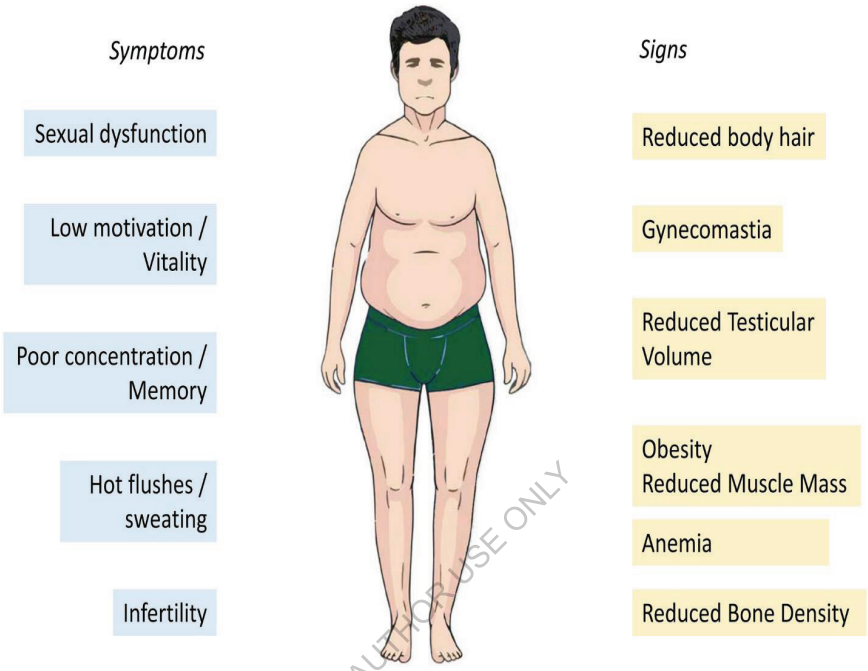


Figure 5: Symptoms and signs frequently associated with adult-onset hypogonadism.

14. Methods Used in the Diagnosis of Hyperandrogenism

There are five techniques for diagnosing hyperandrogenism: (1) measurement of the androgen production rate (2) measurement of the levels in the veins of the adrenal gland (3) measurement of the androgens' urine metabolites (4) measurement of the levels in the peripheral serum; and (5) measurement of the levels in the saliva. Only study uses production rate measurements, which are nearly invariably higher in hirsute patients **[119].** All of the hirsute patients who were investigated showed higher production rates of A and T. Although not frequently done, measuring adrenal venous levels can assist identify the origin of malignancies that are thought to be present. Measurements of peripheral blood levels and urine metabolites are the two most popular techniques.

14.1Measurement of Peripheral Serum Levels

With the development of the serum androgen assay and the introduction of the radioimmunoassay, elevated levels can be found in the majority of hirsute patients. In more than 90% of hirsute patients, Rosenfield discovered signs of hyperandrogenism by measuring total serum T, free T, and the 170H index. Givens measured T, A, and 170H progesterone before and after ACTH stimulation and found values that were comparable **[120].**

14.1.1 Serum Testosterone

RIA is a method used to measure total testosterone **[121]**Additionally, it should be noted that, absent chromatography or the use of a particular antibody, a lab that reports total testosterone frequently measures not just testosterone but also dihydrotestosterone, androstenediol, and androstanediol. For the sample collection, many writers have suggested different times: (1) daily from 8 to 10 a.m. (2) hourly; and (3) every 15 minutes According to several researchers, testosterone levels are increased in 30% to 82% of hirsute people. Both the ovaries and the adrenals may be the source of extra T. **[5].**

14.1.2 Serum-Free Testosterone

Total testosterone is thought to be a poorer predictor of androgenicity than free testosterone **[122]** Dialysis determination of the actual concentration of free testosterone is a time-consuming and technically challenging process that does not lend itself to routine therapeutic application. The free testosterone index is an estimation of free T made using a method Rosenfield described as indirect. This is a quantitative estimate that is based on the total testosterone and the percentage of these compounds that are TeBG-free at a 1:20 plasma dilution. In 75% to 100% of hirsute patients, increased free T levels have been found Moll discovered a strong association between the free testosterone index and free testosterone as determined by dialysis.

14.1.3 Serum Dihydrotestosterone

DHT may be separated from other androgens using chromatography **[123]** DHT levels have been discovered to be high in 30% to 91% of hirsutism patients. It is more usually of adrenal origin in the majority of cases **[123]**

14.1.4 Serum Androstenedione

Androstenedione is frequently raised in people with hyperandrogenism but is rarely elevated alone, as determined by RIA and chromatography. Of hirsute patients, androstenedione levels range from 47% to 100% **[123].** Excessive androstenedione can come from adrenal glands in hirsutism **[5].**

14.1.5 Serum DHEA

RIA is used to quantify serum DHEA after chromatography **[121]** Up to 53% of patients had increased serum DHEA, which is predominantly due to an excess of adrenal androgens.

14.1.6 Serum DHEA-S

RIAP8 is used to measure serum DHEA-S. It mostly represents the production of adrenal androgens, similar to DHEA. This determination is preferred over serum DHEA because it requires no chromatography and is considerably simpler to carry out. Since DHEA-S changes far less in the serum than DHEA does, it offers more dependable and consistent proof of hyperandrogenemia. Up to 76% of patients had high levels **[124].**

14.1.7 Serum Androstenediol

Since diol is rarely high on its own, we have not found it to be very helpful in the evaluation of hirsute patients. It has been noted to be high in 47% of hirsutism patients **[124].**

14.1.8 Serum 17B -Hydroxysteroids

This technique measures the sum of all androgens, including testosterone, dihydrotestosterone, androstenediol, and androstanediol, that have an affinity for TeBG. The approach is only somewhat beneficial because hirsute patients' values could be normal **[125].**

14.1.9 Serum Free 17B-Hydroxysteroid Index

Similar to the free testosterone index, this index also determines the level of free 170H androgens using an indirect technique. It was noted that 70% of hirsute patients had increased levels **[126].**

14.2 Measurements in Urine

14.2.1 Urinary Androstanediol

The main metabolite of androstenedione, testosterone, and dihydrotestosterone is androstenediol. More than 80% of hirsute patients have high levels **[127].**

14.2.2 Urinary Testosterone Glucuronide

In hirsute patients, urine testosterone glucuronide excretion typically falls within the normal range **[127]**

14.2.3 Urinary Total 17-Ketosteroids (17-KS)

This was the procedure that was most frequently used to determine hyperandrogenism prior to the development of the radioimmunoassay. The urine metabolites of each androgen are examined in this extremely basic assay**[128].** Only about 50% of the androgens' metabolites are represented; the remainder are eliminated in feces. Only about 25% of hirsute patients have increased urinary 17-KS. Due to the fact that serum DHEA-S accounts for around 85% of the daily urinary excretion of 17-KS, it is recommended that the measurement of urinary 17-KS be abandoned in favor of serum DHEA-S.Excretion of above 50 mg of 17-KS in a 24-hour period is indicative of an adrenal tumor. A tumor is still a possibility at levels between 25 and 50 mg/24 hours, which point to an adrenal androgen surplus and possibly congenital adrenal hyperplasia (CAH).

14.2.4 Urinary Fractionated 17 -Ketosteroids

The use of fractionated urinary 17-KS, androsterone, epiandrosterone, and DHEA should also be discontinued because it may show evidence of hyperandrogenism in many more patients than can be seen by measuring total urinary 17-KS**[129]** but in much fewer patients than can be seen by serum measurements.

14.3 Measurements in Saliva

The levels of serum-free T have been reported to correlate well with measurements of androgens in saliva**[130].**

15. Methods for Determining the Source of Hyperandrogenism

The various techniques can be divided into two primary categories: (1) tests for suppression and stimulation, and (2) catheterization of the adrenal veins. There is considerable debate over the main glandular source of the excess androgens in hyperandrogenism. Part of the issue is caused by variations in the approaches taken to identify the source. When a tumor is suspected, the dynamic tests are not reliable.

15.1 Suppression and Stimulation Tests

15.1.1Adrenal Suppression

Dexamethasone, prednisone, or other corticosteroids can be used to suppress the adrenal glands. Widespread usage of dexamethasone (DEX). It has been contested if DEX is a particular adrenal-suppressing substance. Two requirements must be met for an adrenal suppression test to be considered valid: (1) ovarian function must not be inhibited, and (2) the adrenal function must be repressed to the fullest extent possible.

The second necessary condition for a successful DEX suppression test is adequate adrenal suppression. Different interpretations may result from differences in the criteria that were utilized. The following are the criteria we employ: (1) The serum DHEA-S level should fall below 400 ng/ml as a sign of adrenal androgen suppression, a level seen in patients who had bilateral adrenalectomy **[131]** and those who had long-term adrenal suppression, and (2) Cortisol levels should fall below 40 ng/ml as a sign of adrenal corticosteroid suppression **[7]**For the majority of individuals, a satisfactory suppression requires a protracted adrenal suppression of at least 2 weeks duration. The majority of research have used shorter durations, which could partially account for reported inconsistencies in the assessment of the etiology of hyperandrogenism. In order to identify an adrenal source of androgens, Kirschner employed the 50% suppressibility of plasma T and A 200 following

DEX as a criteria. After DEX, mean plasma T and A levels were 50% suppressed in several of the individuals identified by catheterization criteria as having an ovarian source of androgens.

15.1.1.1 A Method of Adrenal Suppression

The procedure we utilize to identify the source using dexamethasone suppression, as originally explained by Abraham, is as follows.For three days in a row, antecubital venipuncture is used to draw 15 ccs of blood during the early morning (8 to 10 A.M.). Then, DEX is ingested for 14 straight days in 4 split doses at a rate corresponding to body weight. Blood is taken again over the course of the final three days of DEX therapy. Until all samples are obtained, the serum from each sample is kept frozen. By combining equal quantities from each sample in a separate vial, the mean of the steroid levels from the three samples before to DEX injection (= control value) may be determined. Only the pooled sample's androgen levels are measured. These are the levels of control. To determine the mean of the post-dexamethasone (post-DE X) steroid levels, equal quantities from the serum of the past 3 days of DEX are also pooled. When hirsute patients are assessed individually, the upper limit (mean + 2 sm of the normal peripheral value, etc.) of the mean control level of a steroid is regarded as elevated, While the post-DE X mean level is deemed elevated if it exceeds the maximum level seen after treatment with DEX. If, after DEX treatment, cortisol levels are greater than 40 ng/ml and DHEA-S levels are greater than 400 ng/ml, the DEX suppression is deemed insufficient. In such cases, the test is redone using an overnight dosage of 1.0 mg of DEX. Cushing's syndrome must be ruled out if cortisol is still not sufficiently suppressed; if cortisol is suppressed but DHEA-S is not, a one-month suppression is performed.

16. Source of Individual Androgens

When DHEA-S and cortisol levels are sufficiently suppressed, each androgen's source is assessed as follows: (1) the adrenals are thought to be the source of excess androgen if the mean peripheral androgen level is increased during the control period and lowered to normal after DEX treatment. (2) If the difference between the control and post-DEX levels is normal and the peripheral level of androgen is raised during the control period but not suppressed to normal levels after the administration of DEX.(3) When the difference between the control and post-DEX levels is more than normal and the peripheral level of androgen is elevated during the control period while being partially repressed by elevated post-DEX levels. (4) The diagnosis of pilosebaceous unit hypersensitivity is made if the peripheral levels are normal.

17. Source of Hyperandrogenism

One of the following three kinds of hyperandrogenism is thought to exist when one or more of the measured androgens are tested at increased peripheral levels (hyperandrogenism):(1) Adrenal hyperandrogenism if the adrenals are the exclusive source of increased androgens. (2) Hyperandrogenism of the ovaries, if all increased androgens, are ovarian in origin. (3) Mixed hyperandrogenism, which occurs when some increased androgens are ovarian- and adrenal-derived. This category also includes situations where the same high androgen is the result of many causes.

17.1 Ovarian Stimulation

The results of an hCG (human chorionic gonadotropin)-stimulated ovarian stimulation test are inconsistent, not necessarily indicative of clear-cut ovarian hyperandrogenism, and they do not considerably add to the knowledge gained from an adrenal suppression test. According to Toaff, hCG stimulation verified the findings of testing for adrenal suppression. The release of androgen from adrenal tumors may be stimulated by hCG**[132].**

17.2 Adrenal Stimulation

Although they have been employed, ACTH-stimulated tests for the adrenal glands have not generally been well received. Givens employed this test to pinpoint the cause of hyperandrogenism and discovered that 50% of the patients had androstenedione hyperresponsiveness to ACTH. DEX suppressibility may not be predicted by the results of ACTH stimulation. Since it is known that ovarian neoplasms may respond to ACTH, its activation in the presence of malignancies may be deceptive **[133].**

17.3Adrenal and Ovarian Vein Catheterization

This approach is especially crucial if a virilizing malignancy is suspected. The most precise way for identifying the cause of hyper androgenetic has been backed by several researchers, who recommend using adrenal and ovarian vein catheterization. Adrenal infarction and groin bleeding, where the catheter is placed into the femoral vein, are uncommon complications. In our experience, this technique has gone without incident; nevertheless, the following issues cast doubt on the accuracy of the data collected: (1) The catheterization of a vessel occasionally encounters technical issues; Blood flow from pelvic tributaries to the vein may dilute the levels of steroids in the ovarian vein, and (3) since adrenal production is episodic, isolated measurements may be vulnerable to significant error. Due to these factors, I believe that adrenal and ovarian vein catheterization should only be utilized in situations where an adrenal or ovarian tumor is suspected, not as a routine part of hirsutism assessment.

18. Androgen Pharmacology

18.1 Indications to Use Androgen Therapy

Depending on the dosage, androgen type, and intended treatment outcomes, androgen therapy can be categorized as a physiologic replacement or pharmacologic therapy. The goal of androgen replacement therapy is to raise tissue androgen exposure to levels that are comparable to those of eugonadal men in androgen-deficient men who have pathological hypogonadism (reproductive system disorders). Androgen replacement treatment strives to restore the whole spectrum of androgen effects while imitating the efficacy and safety experience of eugonadal men of similar age. It uses the naturally occurring androgen testosterone and a dose that is limited to one that keeps blood testosterone levels within the eugonadal range. Because androgen shortage, whether brought on by castration **[134],** or a biological condition, has a negligible impact on life expectancy, androgen replacement therapy is unlikely to extend it. Pharmacologic androgen therapy is an approach that use androgens without limitations on type or amount in order to create androgen effects on muscle, bone, brain, or other tissues. Regardless of their androgen status, androgens are employed therapeutically in this type of pharmacological treatment to target their hormonal medicines' anabolic or other effects on muscle, bone, and other tissues in a variety of non-reproductive illnesses. Such pharmaceutical androgen therapy is not limited to physiological replacement doses or their equal, nor is it restricted to the use of natural androgens like testosterone. Rather, it is evaluated similarly to any other hormonal or xenobiotic non-hormonal therapeutic medication on its efficacy, safety, and relative cost-effectiveness for that particular application. As more specialized treatments are developed, many prior applications of pharmacologic androgen therapy are now regarded as second-line therapies **[135].** For instance, improved

first-line drug treatments for endometriosis, osteoporosis, and advanced breast cancer have similarly relegated androgen therapy to a last resort while newer mechanism-based agents in development for hereditary angioedema may displace 17-alkylated androgens **[136].** Erythropoietin has also largely replaced androgen therapy for anemia caused by marrow or renal failure. Pharmacological androgen therapy, however, continues to be a viable, affordable option with a well-proven efficacy and safety profile in many clinical settings.

18.2 Androgen Replacement Therapy

Men with pathological problems of their reproductive system, including the hypothalamus, pituitary, and testis, are typically treated with testosterone. These conditions can cause Leydig cells to become destroyed or pituitary luteinizing hormone (LH) release to become reduced, both of which can result in a persistent testosterone shortage. The main objective of androgen replacement treatment is to allow androgen-deficient men, whose reproductive systems are unable to secrete enough testosterone to levels similar with those of eugonadal men, to regain a physiological pattern of net tissue androgen exposure.When endogenous testosterone synthesis is compromised due to pathological abnormalities of the reproductive system, replacement therapy uses solely the natural androgen, testosterone, with the goal of restoring the complete spectrum of androgen effects. Synthetic androgens are inappropriate since they cannot be converted to estrogens or the more powerful 5 reduced metabolites. By simulating the complete range of endogenous natural androgen effects on tissues, such replacement therapy aims to reflect the efficacy and safety experience of eugonadal men of a similar age. The known prevalence of Klinefelter's syndrome, which accounts for 25–35% of men needing androgen replacement therapy, is used to estimate the prevalence of male hypogonadism requiring such treatment. Androgen deficiency is a clinical diagnostic characterized by a typical presentation and a pathological underpinning

in illnesses of the hypothalamus, pituitary, or testis. The severity, chronicity, and stage of life at presentation all influence the clinical characteristics of androgen insufficiency **[137].** With the exception of defective spermatogenesis, androgen replacement treatment can treat the majority of clinical symptoms of androgen insufficiency. When spermatogenesis must be induced in gonadotropin-deficient males, therapy with pulsatile GnRH or gonadotropins can be used to replace pituitary gonadotropin output. Pharmaceutical hCG can be given two to three times a week for several months **[138].** It was first isolated from pregnant urine.It is yet to be established whether testosterone replacement therapy is beneficial for men who have partial, subclinical, or compensated androgen deficiency conditions. However, significant clinical benefits from testosterone replacement therapy have yet to be proven. Biochemical features of Leydig cell dysfunction, such as persistently elevated LH with low to normal levels of testosterone constituting a high LH/testosterone ratio, may indicate mild androgen deficiency. A form of androgen replacement therapy, hormonal male contraception uses testosterone alone, in combination with a progestin, or with a GnRH antagonist to reduce spermatogenesis by blocking gonadotropin secretion **[139].**

18.3 Testosterone Treatment for Male Ageing

Many observational and short-term interventional controlled clinical trials have lately been conducted on the possibility of using androgen therapy to slow down the aging process in men. According to population-based cross-sectional and longitudinal studies, testosterone levels in the blood drop by up to 1% annually after midlife. This age-related decline is sped up by the presence of concurrent chronic disease **[140],** linked to drops in tissue androgen levels, and associated with a number of co-morbidities of male aging. Low blood testosterone levels are linked to higher all-cause and/or cardiovascular mortality, according to numerous cross-sectional and longitudinal observational studies that have been compiled in

numerous meta-analyses. However, bias in the non-randomized design, which allowed for preferential treatment of healthy men with testosterone, may explain those findings **[142].** An observational research of elder war veterans found that testosterone treatment was related with higher survival **[141].** It is still likely that these decreases in blood testosterone may be a result rather than a cause of the higher mortality, although observational studies cannot attribute causality.

To tackle this problem, interventional trials have remained undersized and short-lived. The only consistent changes so far seen in well-controlled studies of at least 3 months duration have been small increases in lean (muscle) and decreases in fat mass. However, high-quality, randomized placebo-controlled clinical trials using testosterone, DHT or hCG, or synthetic androgens are required to determine whether androgen treatment ameliorates age-related changes in bodily function and improves quality of life.The most comprehensive evidence currently available from meta-analyses shows no or only sporadic benefits for bone, muscular, and sexual function and negative effects on cardiovascular disease/risk factors and polycythemia **[143].** In order to support a large-scale clinical study to balance possible benefits against risks of accelerating cardiovascular and prostate disease, the 2004 Institute of Medicine report **[144],** advised prioritizing the acquisition of more compelling, target-defining feasibility evidence.

18.4 Androgen Misuse and Abuse

Androgen abuse is the use of androgens for non-medical purposes, while androgen misuse is the medical prescription of androgens without a clear clinical indication and outside of an approved clinical trial. When there are no likely benefits, it is medically inappropriate to prescribe androgens for male infertility **[145],** or sexual dysfunction in men without androgen deficiency **[146],** or as a tonic for vague symptoms in older men ("male menopause," "andropause," "late-onset hypogonadism") or women **[147],** where safe and effective use has not been

established. Although there is no precise line defining overuse, systemic misuse of androgens is characterized by extensive marketing and promotion to delay aging in the lack of valid evidence. Androgens are perfect for deceitful marketing to the wealthy who worry about staying healthy as they age because of their myth of young virility.

19. Conclusion

Male reproductive system growth and development are influenced by androgens, the most active of which is testosterone. They are crucial for male sexual and reproductive function, bone and muscle development, and metabolism. Androgen deficiency refers to insufficient production of androgens, particularly testosterone, for optimal health. Deficiency can cause symptoms such as reduced sexual desire, hot flushes, breast development, lethargy, fatigue, depression, decreased muscle mass, increased body fat, weaker erections, ejaculate, hair loss, and increased risk of osteoporosis. It can result from medical conditions affecting the testes, pituitary gland, and hypothalamus.Androgens, such as dehydroepiandrosterone (DHEA), androstenedione (A), androstenediol (Δ^5-diol), and dihydrotestosterone (DHT), are the most common hormones. The adrenal gland and ovary secrete androgens, with pituitary hormones influencing the secretion. Prolactin, a prolactin-stimulating agent, is present without affecting androgen levels. The mechanism behind the rise in adrenal DHEA-S serum levels caused by estrogens is unclear. The zona reticularis of the adrenal produces androgens, but the zona fasiculata and reticular also contain significant amounts of DHEA-S, T, DHT, and A.Testosterone replacement therapy is used for proven androgen deficiency, but is not recommended for men trying to have a child. Regular doctor reviews are necessary, depending on age and risk factors for prostate cancer.It is crucial to measure the serum levels of cortisol, DHEA-S, and testosterone.Serum assays of free T and DHT are also advised. The least significant is A. and could be skipped. Serum DHEA-S measurements should take the place of urine 17-KS measurements.Finding the cause of hyperandrogenism improves treatment. The dexamethasone suppression test is recommended because it is instructive.Cyproterone acetate or ovarian and adrenal suppression can be used to treat hirsutism.Treatment options for anovulatory patients with hyperandrogenism

are varied. Treatment can be improved by determining the cause of hyperandrogenism.Androgen therapy is a pharmacologic treatment for male hypogonadism, using naturally occurring androgen testosterone and a dose to maintain eugonadal levels. It is evaluated for efficacy, safety, and cost-effectiveness. Low blood testosterone levels are linked to higher mortality, but no sporadic benefits for bone, muscle, sexual function, or cardiovascular disease. Androgen misuse and abuse are separate issues, with abuse involving non-medical use and misuse involving medical prescriptions without clear clinical indications.

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