Chapter

Testosterone: The Male Sex Hormone

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Abstract

Males primarily use testosterone as a sex hormone. Through its effects on the androgen receptor, it is released by the interstitial cells of the testes and is in charge of the male external genitalia development as well as the internal reproductive glands and ducts during adolescence and maturity. Additionally, testosterone is required for the descent of testes via the inguinal canal in the last 2 months of fetal development. When a Y chromosome and consequently the SRY gene are missing from an embryo, ovaries form. The Wolffian ducts do not mature because the fetal ovaries do not release enough testosterone. It is mostly used to treat male hypogonadism. Notably, this chapter addresses the following context: historical view of testosterone research, biosynthesis, secretion, metabolism, transport mechanism, biological actions, health benefit of testosterone, factors that promote and inhibit testosterone secretion, therapeutic implication as well as pathophysiology of testosterone secretion.

Keywords: testosterone, Leydig cell, sex hormone-binding globulin, GnRH, aromatase, cytochrome P450, 5-alpha reductase

1. Introduction

Testosterone as one of the major male hormone, is in charge of governing the development of male sex traits, spermatogenesis, and fertility [1]. The fetus first experiences the effects of testosterone. The initial 6 weeks of development result in identical male and female reproductive tissues. The Y chromosomes SRY (sex-related gene) drives the development of the testicles during week 7 of pregnancy. From sertoli cells in the testis cords, seminiferous tubules are produced (fetal testicles). The upper part of the vaginal canal, uterus, and fallopian tubes all regress as a result of a Müllerain inhibitory substance (MIS) secreted by the Sertoli cells (Müllerian structures normally present in women).

2. Historical view of testosterone research

Scientists of Ancient days knew that removal of the testicle would take away the vitality and aggression of men and beast. Historically, castration (removal of testes) was performed on male slaves who guarded Muslim harems. It was also used on some male singers during boyhood to preserve a high pitched voice. The testicles are male gonads, or sex gland, that produces sperm and secret androgens. The production of androgens by the testes is controlled by certain pituitary hormones called gonadotropins. Testosterone, or the male sex hormone, is the most significant and active hormone. Testosterone is mostly produced in the testes, although it is also produced in minor amounts in the adrenal glands and the female ovaries.

According to Freeman et al. [2], testosterone's origins and effects have been understood throughout human history.

In 1934, David et al. [3] was the first to isolate testosterone molecule and its structure and this won him a Noble Prize in 1935.

In 1938, the beneficial effect of testosterone on impaired glucose tolerance was discovered by Kenyon [4].

In 1939, a famous Scientist called Heinrich Schumann found it to improve intermittent claudication and reduce angina pectoris, as well as confirming it to cure gangrene [5].

In 1945, another scientist called Waldman [6] showed its function to stop angina pectoris.

Hamwi [7] demonstrated in 1951 that testosterone can enhance nitrogen balance and boost lean muscle hypertrophy.

In 1960s, another scientist discovered it can lower cholesterol as confirmed by Hartgens and Kuipers [8].

In 1962, scientists called Katz and Katz [9] normalized the abnormal electrocardiograms of 2000 cardiac patients with synthetic testosterone.

It can help with diabetic retinopathy, according to a 1963 research by Lawrence et al. [10].

According to Kim et al. [11], scientists first discovered that testosterone can reduce diabetic patients' need for insulin and their body fat percentage in 1964.

The Columbia University Department of Medicine stated in May 1994 that low levels of free testosterone are a risk factor and directly correspond with the severity of coronary artery disease in men [12].

2.1 Biosynthesis of testosterone

The 500 million Leydig cells, which account for about 5% of the mature testis' volume and are situated in the interstitial region of the testis between the seminiferous tubules, use an enzymatic process to convert cholesterol into testosterone. The most common method is the de novo synthesis of cholesterol from acetate, but preformed cholesterol can also be received from an external source, including circulating low-density lipoproteins, or intracellular cholesterol ester storage [13].

Two multifunctional cytochrome P450 complexes are required for the production of 17-hydroxylase/17,20 lyase (CYP17A1 or P450c17, which hydroxylates the C17 and C18 side chains) and cholesterol side-chain cleavage (CYP11A1 or P450scc, which produces C20 and C22 hydroxylation and C20,22 lyase activity) [13]. The regulation of 17,20 lyase activity, which is active in the gonads but inactive in the adrenals and is independent of 17-hydroxylase activity, is tissue-specific and a critical fork in the steroidogenic pathways. The enzyme cofactors that have the greatest impact

on the directionality of the route flux are cytochrome b5 and the membrane-bound flavoprotein P450 oxidoreductase (POR), which serves a variety of functions as a reductase. One protein with several functions houses both functions [14]. Adrenal androgens do, however, make a far bigger proportionate contribution to the circulating testosterone in women than it does to the testosterone circulating in men [15]. Additionally, it has been reported that the weak adrenal androgen precursor DHEA can be used to produce some extragonadal testosterone and dihydrotestosterone [16]. In the mitochondria of Leydig cells, LH regulates the rate-limiting conversion of cholesterol to pregnenolone, which in turn regulates the release of testicular testosterone. The inner mitochondrial membrane is home to the cytochrome P450 cholesterol side-chain cleavage enzyme complex, which mediates this process. Proteins like sterol carrier protein 2 [17] control the transfer of cholesterol to mitochondrial steroidogenic enzymes. This facilitates the transfer of cholesterol from the cytoplasm to the mitochondria along with steroidogenic acute regulatory protein [18] and translocator protein [19], which control cholesterol transport across the mitochondrial membrane. The following enzyme activity is present in the endoplasmic reticulum of the Leydig cell. Despite the fact that the precise physical process that leads to such high intratesticular testosterone and related steroid concentrations in the testis is still unknown, the high testicular testosterone production rate produces both high local concentrations of testosterone (up to 1 g/g tissue, which is roughly 100 times higher than blood concentrations) and rapid turnover of testosterone (200 times per day) [20].

2.2 Secretion of testosterone

In order to maintain male virilization, testosterone is secreted intermittently during the first trimester of intrauterine life (coinciding with the differentiation of the masculine genital tract), as the perinatal androgen surge (with as-yet-undetermined physiologic significance), and continuously after puberty. The sudden increases in testosterone output from the testicles, which rise roughly 30-fold over levels found in prepubertal toddlers, women, or castrate men, are what caused the dramatic physical changes associated with male puberty. After middle age, circulating testosterone levels gradually decline and gonadotrophin and sex hormone-binding globulin (SHBG) levels rise [21], with these tendencies being missing until late old age in men who remain in great health [22], but exaggerated by the presence of chronic illness [23]. Additionally, there are temporal trends, such as an increase in obesity prevalence [24] and variations in testosterone immunoassays due to artifactual methods that differ from standard mass spectrometry-based assessments [25].

Leydig cell attrition and malfunction, as well as atherosclerosis of testicular arteries, are all functionally responsible for these age-related alterations brought on by the chronic disease accumulation [26]. Meanwhile, the ageing of the hypothalamic-pituitary-testicular complex gradually functions abnormally on several levels, which together cause men to age with reduced levels of circulating testosterone [26]. Testosterone leaves the testis by diffusing into the bloodstream across cell membranes, similar to other lipophilic steroids synthesized by steroidogenic tissues. Smaller amounts also get to the fluid in the tubules and lymphatics. After puberty, males synthesize over 95% of the testosterone found in their blood by testicular secretion; the remaining 5% is created through extragonadal conversion of precursors such dehydroepiandrosterone and androstenedione, which have relatively low intrinsic androgenic potencies. The liver, kidney, muscle, and adipose tissue are only a

few extragonadal tissues that can convert these weak androgens, which are primarily produced by the adrenal cortex, into bioactive sex steroids.

Endogenous adrenal androgens play a much smaller role in men's direct virilization than they do in women. Moreover, androgen-sensitive prostate cancer is not significantly affected biologically by remaining androgens in the blood and tissues following pharmacological or surgical castration. Although peripheral interconversion of adrenal androgen precursors and direct gonadal secretion account for roughly equal amounts of blood testosterone, adrenal androgens are proportionally more responsible for the significantly lower levels of circulating testosterone (5% of men) in children and women [15]. Exogenous dehydroepiandrosterone cannot produce enough blood testosterone to replace male androgens at physiologic replacement dosages of 50 mg/day when supplied orally to humans [27]. It also does not elicit dose-dependent increases in circulating estradiol in males.

Calculating the pace at which hormones are produced can be done using the metabolic clearance rate, mean blood levels of testosterone, testicular arteriovenous differences, and testicular blood flow rate (from bolus injection or steady-state isotope infusion utilizing high-specific-activity tracers). These methods accurately estimate a testosterone production rate of 3–10 mg/day under steady-state settings using tritiated [28] or non-radioactive deuterated [29] tracers with interconversion rates of around 4% to dihydrotestosterone (DHT) [28] and 0.2% to estradiol (hours to days). The factors that these methods, which are oversimplified and focus on steady-state conditions, ignore include postural influences on hepatic blood flow, episodic variability in circulating testosterone levels over shorter time periods (minutes to hours), pulsatile LH secretion, and diurnal periodicity [30]. The primary elements that are known to affect the metabolic clearance rate of testosterone are circulating SHBG concentration, diurnal rhythm, and postural effects on hepatic blood flow [29]. Significant genetic [31] and environmental [29] factors have been proven to have an impact on testosterone levels. Variations in SHBG reduce the severity of these effects.

3. Mechanism of testosterone secretion

During puberty, the hypothalamic-pituitary-gonadal axis controls gonadotropin levels and gonad function. LH and follicle-stimulating hormone are also secreted by the anterior pituitary, which receives GnRH from the brain via the hypothalamohypophyseal portal system (FSH). Two gonadotropic hormones called LH and FSH act on gonad receptors while moving through the bloodstream. Through its effects on the Leydig cells, LH in particular promotes the generation of testosterone. By using negative feedback, testosterone controls its own secretion. High blood testosterone concentrations impair the anterior pituitary's ability to respond to GnRH stimuli and reduce hypothalamic GnRH release [1]. Throughout the reproductive lifetimes of males, the hypothalamus pulses GnRH every 1–3 h. From the onset of puberty, when levels start to rise, until the third decade of life, when levels peak and gradually start to fall, average plasma levels of FSH and LH stay largely constant in spite of this pulsatile release. Poor testosterone levels prior to puberty are an indication of low gonadotropin and GnRH production. The production of GnRH increases noticeably throughout puberty as a result of changes in the neuronal input to the hypothalamus and changes in brain activity.

Cholesterol is transformed into testosterone by Leydig cells in the testes. LH regulates the initial stage of this process. In this mechanism, androstenedione and

dehydroepiandrosterone (DHEA) are two crucial intermediates. Androstenedione turns into testosterone thanks to the enzyme 17-beta-hydroxysteroid dehydrogenase. Blood plasma proteins like albumin and sex hormone binding globulin, as well as a large portion of the testosterone present, are bonded to one another. This major source of protein-bound testosterone provides the body with an overabundance of testosterone hormones. Low blood levels of free testosterone cause tissue-level responses in the seminal vesicles, bone, muscle, and prostate gland. By converting testosterone, the enzyme 5-alpha-reductase produces dihydrotestosterone in cells. Both testosterone and dihydrotestosterone can interact with cell receptors and control how proteins are expressed. In the zona reticularis of the adrenal gland, both men and women produce androgens with weak effects. One example of a weak-acting androgen is dehydroepiandrosterone. Despite having a lesser affinity for testosterone receptors, if produced in high amounts, they can be converted to testosterone in the peripheral tissues [32].

3.1 Transport of testosterone

Because it binds to moving plasma proteins, the amount of testosterone that circulates in blood is higher than its solubility in water. Albumin, corticosteroid binding globulin, and 1 acid glycoprotein are low affinity proteins, whereas SHBG, a protein with high affinity but low capacity, is the most important binding protein. The circulating SHBG, a homodimer comprising two 373 amino acid long glycoprotein subunits, readily binds testosterone [33]. It has one highly-affinity steroid binding site, two N-linked and one O-linked glycosylation sites, and three glycosylation sites. The homodimer's two binding sites exhibit cooperative, dynamic binding affinities with subsequent androgen binding [34]. Although genetic variants can change SHBG's capacity to bind testosterone, acquired liver illness has little impact on this feature [35]. It is yet unclear if pregnancy or other long-term illnesses have an impact on it (when circulating levels increase). Humans but not rodents secrete SHBG into the circulation through the liver. Rodent Sertoli cells release testicular androgen-binding protein, or SHBG, into the seminiferous tubules of the testis [36]. Not the least of which is that the placenta may influence the increase in blood SHBG levels during pregnancy. The levels of circulating SHBG, a byproduct of hepatic secretion and a first-pass liver effect of oral medicines, including sex steroids, are significantly influenced by these effects. The levels of circulating SHBG (and consequently total testosterone) are typically increased (androgens, glucocorticoids) or decreased (first pass effects) as a result of producing supraphysiologic hormone concentrations at the liver, such as those caused by oral administration (first pass effects) or by high-dose parenteral androgen injections (estrogens, thyroxine).

Transdermal, depot implants, and parenteral (non-oral) distribution, which essentially maintain physiological circulating hormone concentrations, have no effect on blood SHBG levels [29], whereas endogenous sex steroids and these techniques do. Acute or chronic liver disease, androgen deficit, obesity, diseases that cause protein loss, non-alcoholic fatty liver disease, and, in rare circumstances, hereditary SHBG insufficiency, all have an impact on the level of SHBG in the blood [37, 38]. In a healthy state, SHBG binds 60–70% of the circulating testosterone, leaving 1–2% unbound or linked to lower affinity, high-capacity binding sites for the remainder (albumin, 1 acid glycoprotein, corticosteroid binding protein).

The physicochemical partitioning between the hydrophobic protein binding sites on circulating binding proteins, the hydrophilic aqueous extracellular fluid, and the

lipophilic cellular plasma membranes is the basis for the hypothesis that the transport of hydrophobic steroids into tissues occurs passively. The most physiologically active component of testosterone is thought to be the fraction that is weakly protein-bound but still mobile [39], whereas the majority of the moiety that is strongly coupled to SHBG just serves as an inert storage [34].

The free hormone hypothesis is based on the now-outdated pharmacological theory that drug-drug interactions result from the displacement of mutual protein binding. However, in molecular pharmacology, well-established physiological mechanisms like the activation of the drug transporter, the stimulation of the cytochrome P450 enzyme, and other mechanisms unrelated to binding to circulating proteins have long since supplanted this theory. The free fractions may alternatively be viewed of as the least active and transitory since they would have easier access to regions where testosterone is inactivated by degradative metabolism, ultimately stopping androgen action. This would undermine the assumption of the free hormone hypothesis.

So far, it has not been possible to determine the free or bioavailable fractions' overall biological significance. Additionally, evidence from experiments suggests that SHBG actively participates in cellular testosterone uptake through a number of SHBG membrane receptors, uptake processes, and signaling via G protein and cyclic AMP [40]. This is in contrast to the conventional view that SHBG is biologically inert. By facilitating receptor-mediated cellular uptake of SHBG laden with testosterone via endocytosis on cell surface membranes, megalin, a multivalent low-density lipoprotein endocytic receptor, may change tissue androgen activity. Due to its lack of a physiological basis and the scant and speculative empirical data backing it [41], the free hormone hypothesis [42] is thus refuted by broad, prospective clinical inquiry.

Therefore, the biological importance of fractionating circulating testosterone into these derived forms is unknown, and their therapeutic use may be deceptive. The time-consuming, manual techniques necessary for the direct estimation of free testosterone are also only available in research or specialist pathology institutions. They are expensive and lack any external quality control procedures or established reference ranges when they are given.

3.2 Metabolism of testosterone

A very little amount of released testosterone is activated to two bioactive metabolites, estradiol and DHT, by hepatic phase I and II metabolism, whereas the bulk is inactivated to inactive oxidized and conjugated metabolites for urine and/or biliary clearance [43]. The amplification pathway transforms 4% of the blood's testosterone into DHT, a more potent, pure androgen. When transactivating the androgen receptor, DHT has a higher binding affinity and a 3–10 times greater molar potency than testosterone [44]. The most potent natural androgen, DHT, is produced by the 5-reductase enzyme, which is derived from two distinct genes (I and II).

Type 1 5′-reductase is located in the liver, kidney, skin, and brain, whereas type 2 5′-reductase is typically strongly expressed in the prostate but also found in the skin (hair follicles) and liver at smaller levels.

Puberty causes marked virilization, including phallic growth, normal testis development and spermatogenesis, bone density, and, in rare cases, masculine gender reorientation, despite the fact that undermasculinization and congenital 5-reductase deficiency cause genetic males who may be raised as females to experience a specific type of genital ambiguity [1]. While the prostate is still developing, the usual prostate condition is sparse body hair without baldness [45]. The anomalous natural history

makes it evident that high levels of 5-reductase expression are necessary as a local androgen amplification mechanism for correct development of the tissues derived from the urogenital sinus. The development of azasteroid 5-reductase inhibitors was based on this mechanism of enhanced androgen activity [46].

Blocking the type 2 5′-reductase enzyme limits the inhibition of testosterone action to the prostate (and other urogenital sinus tissue derivatives) without obstructing extra-prostatic androgen action because it converts over 95% of testosterone entering the prostate into the more potent androgen DHT. However, type 2 5′-reductase mutations result in abnormalities of urogenital sinus derived tissues in both men and mice, whereas genetic inactivation of type 1 5′-reductase has no male phenotype in mice and no mutations of the human type 1 enzyme have been observed [47]. Whether this denotes an unanticipated type 1 enzyme phenotype or a critical role that has persisted throughout evolution, it is unknown.

Through the androgen action diversification pathway, the enzyme aromatase converts testosterone into estradiol to activate estrogen receptors [1]. Although aromatization only contributes 0.2% to testosterone output, because to the increased molar potency of estradiol, it may represent a significant mechanism for diversifying androgen effect in tissues where aromatase is expressed (approximately 100 times higher than testosterone). The diversification route is regulated by the cytochrome P450 enzyme CYP19 aromatase [48]. Extratesticular aromatization is responsible for producing around 80% of the estradiol that is present in eugonadal men.

Beginning in the 1970s, it was shown that the local conversion of testosterone to estradiol inside neural tissues played a key role in mediating testosterone action on the brain, including negative feedback as well as activational and organizational effects [49]. As a result, the biological importance of aromatization in male physiology was acknowledged for the first time [50]. Recent studies have demonstrated the importance of local aromatization in testosterone action by demonstrating that hereditary aromatase inactivation, which results in a complete lack of estrogen, produces substantial developmental abnormalities in the bone and other tissues of men and mice [51]. This illness and genetic changes in mice and men that inactivate ER share a number of commonalities [52]. Additionally, exogenous estrogen or other estrogen-like medicines significantly accelerated bone development in patients with aromatase insufficiency.

Male mice are unaffected by ER genetic inactivation, and no modifications in humans have been seen [53]. The expression of aromatases, which affects local tissue-specific androgen activity via aromatization in tissues like bone [54] and the brain [52], may have an impact on development and function. A mature liver and muscle are two more tissues that exhibit minimal to no aromatase expression. Despite the importance of aromatization in the physiology of male bones, recent research shows that androgens acting through androgen receptors have significant extra direct effects on bone.

Despite having lower levels of circulating estradiol than young women, men have higher bone density than young women [55], non-aromatizable androgens increase bone density in estrogen-deficient women [56], and androgen insensitive rats with non-functional androgen receptors do not maintain normal male bone density [57]. The effects of testosterone on bone and the brain cannot be fully described as a pro-hormone for local estradiol synthesis (and/or action via estrogen receptors and/or). Androgen receptor-mediated actions must be present for testosterone's entire range of effects on the brain and bone to be observed. Regarding the need for aromatization to offset testosterone's effects on male sexual function, conflicting information is available. Male sexual activity was not necessary for aromatization, according to a study

that generated estrogen deficiency using DHT and found [58]; however, a different study that produced estrogen deficiency using aromatase inhibitors showed partial dependence.

Therefore, more research is needed to completely understand how aromatization contributes to the maintenance of androgen activity in mature male animals. Notably, testosterone is metabolized to inactive metabolites in the liver, kidney, stomach, muscle, and adipose tissue. Phase I metabolism involves the majority of oxygen moieties being oxidized by hepatic oxidases, particularly those in the cytochrome P450 3A family. Hepatic conjugation to glucuronides during phase II metabolism produces compounds that are sufficiently hydrophilic for renal excretion. The UDP glucuronosyl transferase (UGT) enzymes UGT2B7, UGT2B15, and UGT2B17 catalyze the majority of the phase II metabolism (glucuronidation) of testosterone, with 2B17 being quantitatively the most important. A functional polymorphism of UGT 2B17, a deletion mutation that is several times more common in Asian than European populations, accounts for the concordant population difference in the testosterone to epitestosterone (T/E) ratio in a World AntiDoping Agency-approved urine screening test for testosterone doping in sport, which constitutes an ethnic differential, false negative in surveillance for exogenous testosterone doping [59].

Furthermore, increased blood levels of SHBG, decreased hepatic blood flow (from, for example, posture), or both can slow down the metabolic clearance rate of testosterone. The metabolic inactivation of testosterone could theoretically be impacted by medications that alter hepatic oxidase activity, however there aren't many empirical instances with a big enough effect on clinical practice. The brief duration of action and low oral bioavailability of testosterone when taken parenterally are both brought on by the liver's quick metabolic inactivation. Because of these limitations, oral

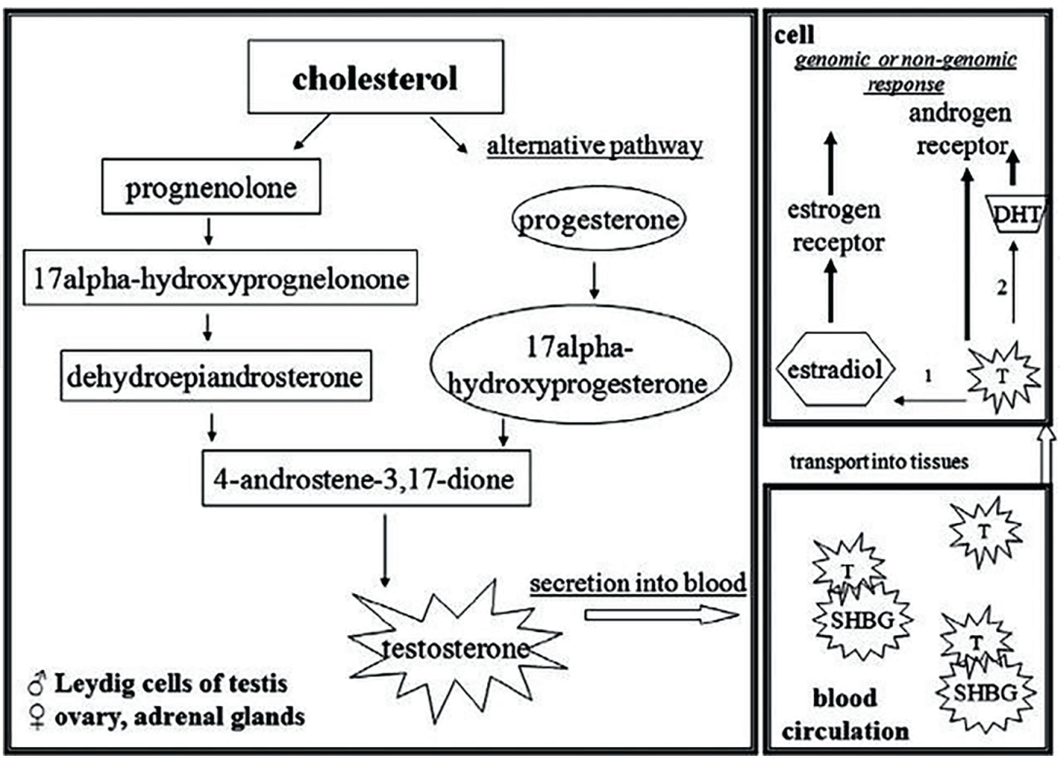

Figure 1
The metabolism of testosterone. *Desmolase activity converts cholesterol into the steroid hormone testosterone [60].*

administration methods including buccal, sublingual, and gut lymphatic must either prevent hepatic portal absorption or use synthetic androgens with substituents that prevent them from being inactivated by first pass hepatic metabolism [60] (**Figure 1**).

4. Biological actions of testosterone

The basic sexual processes of spermatogenesis, testicular descent, penis and testes enlargement, and heightened libido are all mediated by testosterone [1]. Around 7 months during the pregnancy, the testes begin to move into the scrotum and begin secreting enough testosterone. Testosterone injections can assist the testes descend via the inguinal canals in male neonates who are born with normal, undescended testes that do not descend by the time they are 4–6 months old. Additionally, testosterone controls the secondary characteristics of males that define their masculinity. Male hair patterns, vocal changes, and voice deepening are examples of secondary sex characteristics in men, in addition to anabolic effects like puberty growth spurts (testosterone increases tissue growth at the epiphyseal plate early on and eventually causes plate closure later in puberty) and skeletal muscle growth (testosterone stimulates protein synthesis) [32]. In addition to increasing erythropoiesis, testosterone causes men to have a greater hematocrit than women. As men age, their testicular size decreases, their libido declines, their muscular mass declines, their production of fat increases, and their erythropoiesis decreases, all of which may contribute to anemia. The biological actions of testosterone could be splitted into two pathway:

4.1 Non-genomic pathway of testosterone

Steroid hormones' non-genomic effects are those steroid-mediated processes that are quick to respond, utilize second messengers, and do not directly involve gene transcription (as seen by their susceptibility to transcriptional and protein synthesis inhibitors) (within seconds to minutes). Non-genomic actions are distinct from genomic mechanisms in that they bind the steroid to an androgen receptor on the cell membrane or establish a connection with a plasma membrane receptor connected to a Pertussis toxin (PTX)-sensitive G protein rather than the more typical androgen receptor found in the cell's cytoplasm before being translocated into the nucleus. In contrast to genomic effects, non-genomic actions of steroid hormones call for the hormone to be present continually. The non-genomic effects will diminish as soon as the hormone leaves the tissue [61–64].

- The most consistent non-genomic consequence of androgen exposure is a fast shift in [Ca2+], despite the fact that the evidence for non-genomic androgen action is sparse. It has been assumed that in order to trigger calcium modulation, which happens within seconds to minutes, the androgen must attach to a receptor on the cell's surface. It's interesting to note that not all cell types that show a rapid androgen Numerous cell types, including osteoblasts, macrophages, T-lymphocytes, endothelial cells, breast cancer cells, prostate cancer cells, androgens' ability to quickly modify the function of ion channels and [Ca2+]i has been noted [61–63].

- Androgens may mediate a range of non-genomic actions through their structural characteristics, independent of receptors, channels, or second messenger

pathways. It has been discovered that androgen metabolites can pick up extra charges from sulfate residues, which enables them to enter the lipid/protein complex of the cell membrane and reduce membrane flexibility. This in turn affects how ATP hydrolysis-related enzymes behave [62]. As well as other second messenger pathways, testosterone has been shown to quickly activate calcium pathways. Further proving that androgens are to blame for the downregulation of G activity, testosterone has been shown to decrease potassium input in Xenopus oocytes overexpressing G-protein inward rectifying potassium channels. Interestingly, the effects of T on potassium channel function were prevented by RNA interference-mediated downregulation of AR expression at low but not high T dosages [62].

- Androgens have instantaneous effects on biological systems, as is well documented. The neuroendocrine control of gonadotropin-releasing hormone is one area in particular where androgens and the reproductive system interact intimately (GnRH). It has long been understood that androgens inhibit the anterior pituitary's ability to secrete luteinizing hormone, which is directly controlled by the brain's release of GnRH. Despite the fact that androgens are known to affect the pituitary's sensitivity to GnRH, a new study strongly suggests a neuronal mechanism [1, 32].

- Despite the fact that the specific mechanism of action of androgen treatment is yet unknown, it has been shown that animal behavior changes swiftly in reaction to it. Researchers have shown that utilizing the female lordosis reflex as the end goal, androgens can quickly modify a female rodent's sexual receptivity. Rodents' sexual receptivity is found to be terminated by dihydrotestosterone and 3-Diol, and this effect is shown even when the hormone isn't operating [62].

- Androgens' impact on the central nervous system can be neurotoxic or neuroprotective. It has been determined that dihydrotestosterone can influence cellular development, differentiation, survival, or death through both genomic and non-genomic signaling pathways. When employed in culture, androgens such as T and DHT can protect neurons from damage brought on by beta-amyloid toxicity, kainic acid toxicity, and serum deprivation [62].

- It is clear that testosterone has a negative impact on the cardiovascular system since men are more likely than premenopausal women to have cardiovascular disease. However, numerous clinical and epidemiological studies did find a controversial connection between testosterone and cardiovascular disease. Additionally, an increasing amount of evidence points to the possibility that testosterone may exert its vasorelaxing properties immediately via non-genomic routes. These actions do not require the endothelium, but some studies do indicate an endothelial function. This has a major impact on the vascular smooth muscle[65, 66].

4.2 Genomic pathway of testosterone

The ligand activated receptor is a crucial transcription factor in the genomic route that controls the expression of genes involved in cell division, proliferation, metabolism, and apoptosis. However, the following highlights could be made of testosterone's genomic effects:

DOI: http://dx.doi.org/10.5772/intechopen.110657

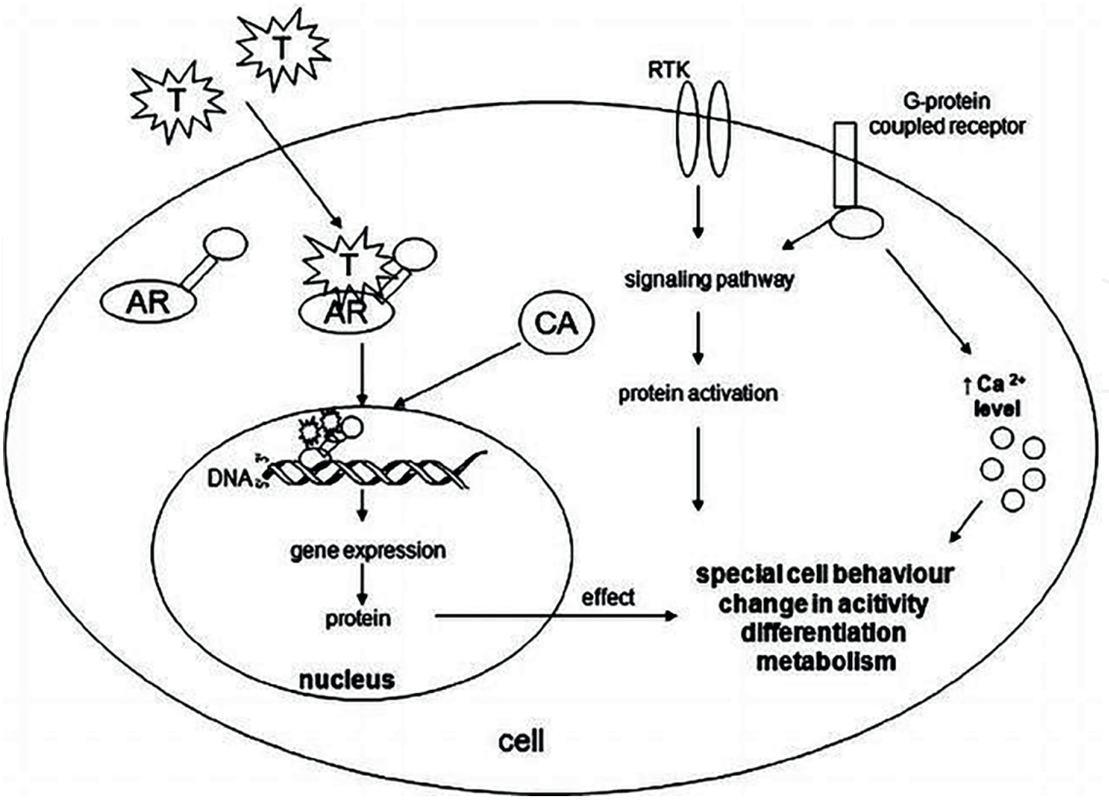

Figure 2.
Depicted the effects of testosterone on both genes and non-genes. Free bioactive testosterone interacts with the cytoplasmic androgen receptor (AR).

- Vascular calcification is the abnormal mineral deposition in the vascular system. Vascular calcification can be controlled. It can occur in the heart's valves and takes on a variety of shapes, such as medial and intimal calcification. Males who had low or high testosterone levels had a higher chance of developing vascular calcification [67].

- Maintaining healthy renal and heart function. A common symptom of Fabry disease, which is brought on by a lack of the lysosomal enzyme—galactosidase A, is cardiac and renal hypertrophy [68].

- Preservation of erectile abilities. It is important to highlight that decreased testosterone expression may, in turn, contribute to the ED vascular phenotype (**Figure 2**) [68].

5. Health benefits of high testosterone

Men with high testosterone levels have been shown to have longer, healthier lives as well as to preserve their sexual potency [69, 70]. Beyond fostering aggression, body and facial hair, and even pattern baldness, testosterone has many other functions as well. Additionally, studies have demonstrated that testosterone protects against autoimmune disease. Since testosterone is an anabolic, it encourages the development of new muscle. One of the main aspects of aging in both men and women is the loss of lean body mass. This loss is made up by testosterone [70]. The most significant study

about the link between high levels of testosterone and lowered risk of cardiovascular disease was published in May 1994 and found that low levels of free testosterone are a risk factor and directly correlate with the severity of coronary artery disease.

Lower levels of testosterone have been seen in males with dementia in several studies, which has prompted speculation that testosterone deficiency may contribute to the onset of dementia. However, other research has demonstrated that there is no distinction in testosterone levels between men with dementia and those without it. There is yet no conclusive proof that testosterone levels are correlated with a lower incidence of dementia. Therefore, it is doubtful that using testosterone can help lower your risk of developing dementia. In addition, there are dangers associated with hormone use that must be weighed against your own health.

5.1 Factors that promote and inhibit testosterone secretion

Certain elements can either increase or decrease testosterone levels. Since the building block for male sex hormones is the cholesterol molecule, a low-fat diet restricts the creation of testosterone. Additionally, testosterone is increased by rigorous exercise, but it can be decreased by overtraining [71]. Although severe stress or sadness can suppress testosterone, sexual activity also increases it. While many elderly men can still bear children, their sperm counts may be lower.

5.2 Therapeutics implications of testosterone

Male hypogonadism is mostly treated with androgen replacement therapy, which is the principal application of testosterone. The testosterone injectable preparation called testosterone undecanoate allows for injections every 12 weeks as opposed to every 2–3 weeks as is the case with testosterone esters like testosterone cypionate or enantate. This testosterone injectable preparation also delivers the most consistent blood levels of testosterone, within the physiological range. Short-acting medications lessen the possibility of mood swings or emotional instability by limiting variations in blood concentrations [72]. To administer the hormone, testosterone undecanoate can also be administered orally. Additionally, a patch or gel can be used to apply it transdermally.

Additionally, testosterone is used in the treatment of breast cancer in combination with an aromatase inhibitor to restrict estrogen conversion since it directly inhibits the development of mammary cells via the androgen receptor [73]. Despite the fact that oral administration of testosterone effectively increases absorption, gastrointestinal metabolism and significant first-pass hepatic metabolism make roughly 98% of the hormone inert [74]. When taken with food, testosterone undecanoate molecules are absorbed into chylomicrons, significantly bypassing the liver. The substance then travels through the intestinal lymphatic system and enters the peripheral circulation. However, pills with an oily testosterone composition.

Since low-fat meals have poor testosterone undecanoate absorption, the amount of fat in the meal has an impact [74]. Men who received four intramuscular injections of testosterone undecanoate at intervals of 6 weeks had serum testosterone levels that were consistently at or above the lower physiological limit; the upper physiological limit was only briefly surpassed after the third and fourth doses. The half-life and Cmax of testosterone under prolonged therapy were 70.2 days and 32.0 nmol/l, respectively. To achieve physiological values of serum testosterone in nearly all men, it appears that a 12-week injection interval following initial loading doses of testosterone undecanoate at 0 and 6 weeks is sufficient [72].

6. Pathophysiology of testosterone secretion

Overproduction, underproduction, receptor insensitivity, or poor testosterone metabolism are all examples of pathology connected to testosterone [75]. The more typical and extensively studied testosterone diseases include the ones listed below. The following disorders, such as polycystic ovarian syndrome (PCOS) [76], adrenal virilization/adrenal tumors, ovarian or testicular tumors, Cushing syndrome, and as a result of exogenous steroid use, can cause an overproduction of androgens. It's crucial to grasp the variations between testosterone and dehydroepiandrosterone (DHEA), in order to properly comprehend some of these illnesses. The ovaries, testes, and adrenals all create DHEA, which is a relatively mild androgen. DHEA is a precursor of a number of hormones, including estrogen and testosterone. The adrenal glands only contain DHEA in its sulfated form, or DHEAS. Unusual gonadotropin-releasing hormone (GnRH) secreted during polycystic ovarian syndrome increases LH secretion (PCOS). Women with PCOS who take LH have increased androgen produced by their ovarian theca cells, which results in hirsutism, a masculine escutcheon, acne, and androgenic alopecia. Usually, ovarian and adrenal tumors are accompanied by rapidly worsening androgenic symptoms (hirsutism, virilization). An ovarian tumor is most likely to be to blame when DHEAS is normal and testosterone levels are elevated.

When DHEAS is elevated and testosterone levels are typically normal, an adrenal tumor is most likely the cause. Age, some drugs, chemotherapy, problems with the hypothalamus-pituitary axis, intrinsic hypogonadism, cryptorchidism, orchitis, and genetic illnesses including Klinefelter and Kallmann syndrome can all cause reduced testosterone production [77]. The congenital disorder that results in primary hypogonadism most frequently is Klinefelter syndrome. In Klinefelter, inhibin levels fall and FSH levels rise as a result of seminiferous tubule dysgenesis and Sertoli cell loss. Aromatase is upregulated by FSH, which speeds up the process of turning androgens into estrogens [78]. Because there is no negative feedback when Leydig cells die in Klinefelter, testosterone levels fall and LH levels rise. The Kallmann syndrome, which is characterized by the inability of GnRH-producing neurons to migrate, manifests as a lack of GnRH [78]. LH, FSH, testosterone, and sperm levels fall as a result of low GnRH levels. Compared to other types of hypogonadotropic hypogonadism, Kallmann syndrome is the only one to have defects in the sense of smell (hyposmia or anosmia). Dihydrotestosterone is created from testosterone by an enzyme known as 5-alpha reductase [65]. Due to a shortage of dihydrotestosterone, males with 5-alpha reductase insufficiency may be born with ambiguous genitalia or with typical female or male genitalia. The internal male urogenital tract is present in these folks (anti-Mullerian hormone is still present). Teenagers with this enzyme deficit, who may have been raised as girls due to a lack of secondary male characteristics, begin to develop secondary male sex characteristics and experience primary amenorrhea at puberty [79]. Less DHT and a higher testosterone to DHT ratio will be present in these people, who will also have normal levels of LH and testosterone.

Patients with androgen insensitivity, as opposed to those with insufficient levels of the enzyme 5-alpha reductase, are less virilized due to the absence of functional androgen receptors. Similar to those who have a 5-alpha reductase impairment, these patients exhibit a 46 XY karyotype [66]. On the other hand, these patients have typical undescended testes and healthy external genitalia. During adolescence, they experience primary amenorrhea and the development of their breasts, but not the vocal changes or pubic or axillary hair growth associated with puberty. They will have a defective internal reproductive system and a blind vaginal pouch as a result of the Mullerian inhibitory

factor being created. These people will have very high levels of LH and testosterone. Several types of congenital adrenal hyperplasia (CAH) may have impaired testosterone metabolism as a secondary consequence [80]. In 95% of instances with typical CAH, which is caused by a lack of 21 hydroxylase, neonates first display ambiguous genitalia. Later, they experience vomiting, hypotension, acidosis, salt deficiency, and other symptoms. Hyperandrogenism results from a significant increase in 17-hydroxyprogesterone being diverted to adrenal androgen production. By dramatically raising GnRH production, which boosts LH and FSH levels, hyperandrogenism decreases the hypothalamic sensitivity to progesterone. The generation of gonadal steroids increases when LH and FSH levels rise (17-hydroxyprogesterone, DHEA, testosterone, LH, and FSH). The diagnosis is made by the adrenocorticotropic hormone stimulation test, which displays an excessive 17-hydroxyprogesterone response.

7. Concluding remarks

Both men and women produce testosterone, which is one of the most significant sex hormones. Leydig cells from men's testicles create the majority of it. In males, the adrenal cortex also releases it. The development of secondary sexual traits in males, such as increased muscle, bone mass, and body and facial hair, is widely acknowledged to be heavily influenced by testosterone. Maintaining sexual potency, on the other hand, is critical. Furthermore, testosterone has been found in studies to protect against autoimmune disorders.

Testosterone: The Male Sex Hormone
DOI: http://dx.doi.org/10.5772/intechopen.110657

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References

[1] Oyovwi Mega Obukohwo, Nwangwa Eze Kingsley, Rotu Arientare Rume and Emojevwe Victor (2022): The concept of male reproductive anatomy. 3-34. (Male Reproductive Anatomy by Wu, W., (Ed.). (2022). London, UK IntechOpen. DOI:10.5772/intechopen.94696

[2] Freeman ER, Bloom DA, McGuire EJ. A brief history of testosterone. The Journal of Urology. 2001;**165**(2):371-373

[3] David K, Dingemanse E, Freud J, Laqueur E. Über krystallinisches männliches Hormon aus Hoden (Testosteron), wirksamer als aus Harn oder aus Cholesterin bereitetes Androsteron. 1935:281-283

[4] Kenyon AT. The effect of testosterone propionate on the genitalia, prostate, secondary sex characters, and body weight in eunuchoidism. Endocrinology. 1938;**23**(2):121-134

[5] Møller J, Einfeldt H. Historical review. In: Testosterone Treatment of Cardiovascular Diseases. Berlin, Heidelberg: Springer; 1984. pp. 1-3

[6] Waldman S. The treatment of angina pectoris with testosterone propionate. The Journal of Clinical Endocrinology. 1945;**5**(7):305-317

[7] Hamwi GJ. Marfan's syndrome (arachnodactyly). The American Journal of Medicine. 1951;**11**(2):261-266

[8] Hartgens F, Kuipers H. Effects of androgenic-anabolic steroids in athletes. Sports Medicine. 2004;**34**(8):513-554

[9] Katz AM, Katz PB. Diseases of heart in works of Hippocrates. British Heart Journal. 1962;**24**:257-264

[10] Lawrence JH, Tobias CA, Linfoot JA, Born JL, Gottschalk A, Kling RP. Heavy particles, the Bragg curve and suppression of pituitary function in diabetic retinopathy. Diabetes. 1963;**12**(6):490-501

[11] Kim SH, Park JJ, Kim KH, Yang HJ, Kim DS, Lee CH, et al. Efficacy of testosterone replacement therapy for treating metabolic disturbances in late-onset hypogonadism: A systematic review and meta-analysis. International Urology and Nephrology. 2021;**53**(9):1733-1746

[12] Phillips GB, Pinkernell BH, Jing T-Y. The association of hypotestosteronemia with coronary artery disease in men. Arherosclerosis and Thrombosis. 1994;**14**(5):701-706

[13] Miller WL, Auchus RJ. The molecular biology, biochemistry, and physiology of human steroidogenesis and its disorders. Endocrine Reviews. 2011;**32**:81-151

[14] Peng HM, Im SC, Pearl NM, Turcu AF, Rege J, Waskell L, et al. Cytochrome b5 activates the 17,20-lyase activity of human cytochrome P450 17A1 by increasing the coupling of NADPH consumption to androgen production. Biochemistry. 2016;**55**:4356-4365

[15] Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: Changes with age, menopause, and oophorectomy. Journal of Clinical Endocrinology and Metabolism. 2005;**90**:3847-3853

[16] Labrie F. Adrenal androgens and intracrinology. Seminars in Reproductive Medicine. 2004;**22**:299-309

[17] Gallegos AM, Atshaves BP, Storey SM, Starodub O, Petrescu AD, Huang H, et al. Gene structure, intracellular localization,

and functional roles of sterol carrier protein-2. Progress in Lipid Research. 2001;**40**:498-563

[18] Miller WL. Disorders in the initial steps of steroid hormone synthesis. The Journal of Steroid Biochemistry and Molecular Biology. 1 Jan 2017;**165**:18-37

[19] Midzak A, Zirkin B, Papadopoulos V. Translocator protein: Pharmacology and steroidogenesis. Biochemical Society Transactions. 2015;**43**:572-578

[20] Jarow JP, Zirkin BR. The androgen microenvironment of the human testis and hormonal control of spermatogenesis. Annals of the New York Academy of Sciences. 2005;**1061**:208-220

[21] Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. Endocrine Reviews. 2005;**26**:833-876

[22] Sartorius G, Spasevska S, Idan A, Turner L, Forbes E, Zamojska A, et al. Serum testosterone, dihydrotestosterone and estradiol concentrations in older men self-reporting very good health: The healthy man study. Clinical Endocrinology. 2012;**77**:755-763

[23] Feldman HA, Longcope C, Derby CA, Johannes CB, Araujo AB, Coviello AD, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: Longitudinal results from the Massachusetts male aging study. Journal of Clinical Endocrinology and Metabolism. 2002;**87**:589-598

[24] Perheentupa A, Makinen J, Laatikainen T, Vierula M, Skakkebaek NE, Andersson AM, et al. A cohort effect on serum testosterone levels in Finnish men. European Journal of Endocrinology. 2013;**168**:227-233

[25] Sikaris K, McLachlan RI, Kazlauskas R, de Kretser D, Holden CA, Handelsman DJ. Reproductive hormone reference intervals for healthy fertile young men: Evaluation of automated platform assays. Journal of Clinical Endocrinology and Metabolism. 2005;**90**:5928-5936

[26] Veldhuis JD, Keenan DM, Liu PY, Iranmanesh A, Takahashi PY, Nehra AX. The aging male hypothalamic-pituitary-gonadal axis: Pulsatility and feedback. Molecular and Cellular Endocrinology. 2009;**299**:14-22

[27] Nair KS, Rizza RA, O'Brien P, Dhatariya K, Short KR, Nehra A, et al. DHEA in elderly women and DHEA or testosterone in elderly men. New England Journal of Medicine. 2006;**355**:1647-1659

[28] Santner S, Albertson B, Zhang GY, Zhang GH, Santulli M, Wang C, et al. Comparative rates of androgen production and metabolism in Caucasian and Chinese subjects. Journal of Clinical Endocrinology and Metabolism. 1998;**83**:2104-2109

[29] Wang C, Cunningham G, Dobs A, Iranmanesh A, Matsumoto AM, Snyder PJ, et al. Long-term testosterone gel (AndroGel) treatment maintains beneficial effects on sexual function and mood, lean and fat mass, and bone mineral density in hypogonadal men. Journal of Clinical Endocrinology and Metabolism. 2004;**89**:2085-2098

[30] Diver MJ, Imtiaz KE, Ahmad AM, Vora JP, Fraser WD. Diurnal rhythms of serum total, free and bioavailable testosterone and of SHBG in middle-aged men compared with those in young men. Clinical Endocrinology. 2003;**58**:710-717

[31] Jin G, Sun J, Kim ST, Feng J, Wang Z, Tao S, et al. Genome-wide association study identifies a new locus JMJD1C

at 10q21 that may influence serum androgen levels in men. Human Molecular Genetics. 2012;**21**:5222-5228

[32] Victor E, Osarugue I, Obukohwo OM, Kingsley NE, Obidike NA. Endocrine Functions of the Testes. In: Male Reproductive Anatomy. IntechOpen; 11 Nov 2021

[33] Hammond GL, Wu TS, Simard M. Evolving utility of sex hormone-binding globulin measurements in clinical medicine. Current Opinion in Endocrinology, Diabetes, and Obesity. 2012;**19**:183-189

[34] Goldman AL, Bhasin S, Wu FCW, Krishna M, Matsumoto AM, Jasuja R. A reappraisal of testosterone's binding in circulation: Physiological and clinical implications. Endocrine Reviews. 2017;**38**:302-324

[35] Wu TS, Hammond GL. Naturally occurring mutants inform SHBG structure and function. Molecular Endocrinology. 2014;**28**:1026-1038

[36] Selva DM, Hammond GL. Human sex hormone-binding globulin is expressed in testicular germ cells and not in sertoli cells. Hormone and Metabolic Research. 2006;**38**:230-235

[37] Sarkar M, VanWagner LB, Terry JG, Carr JJ, Rinella M, Schreiner PJ, et al. Sex hormone-binding globulin levels in young men are associated with nonalcoholic fatty liver disease in midlife. The American Journal of Gastroenterology. 2019;**114**:758-763

[38] Vos MJ, Mijnhout GS, Rondeel JM, Baron W, Groeneveld PH. Sex hormone binding globulin deficiency due to a homozygous missense mutation. Journal of Clinical Endocrinology and Metabolism. 2014;**99**:E1798-E1802

[39] Ekins R. Measurement of free hormones in blood. Endocrine Reviews. 1990;**11**:5-46

[40] Hamada A, Sissung T, Price DK, Danesi R, Chau CH, Sharifi N, et al. Effect of SLCO1B3 haplotype on testosterone transport and clinical outcome in caucasian patients with androgen-independent prostatic cancer. Clinical Cancer Research. 2008;**14**:3312-3318

[41] Hsu B, Cumming RG, Blyth FM, Naganathan V, Waite LM, Le Couteur DG, et al. Evaluating calculated free testosterone as a predictor of morbidity and mortality independent of testosterone for cross-sectional and 5-year longitudinal health outcomes in older men: The Concord Health and Ageing in Men Project. The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences. 2018;**73**:729-736

[42] Handelsman DJ. Free testosterone: Pumping up the tires or ending the free ride? Endocrine Reviews. 2017;**38**:297-301

[43] Van Eenoo P, Delbeke FT. Metabolism and excretion of anabolic steroids in doping control—New steroids and new insights. Journal of Steroid Biochemistry and Molecular Biology. 2006;**101**:161-178

[44] McRobb L, Handelsman DJ, Kazlauskas R, Wilkinson S, McLeod MD, Heather AK. Structure-activity relationships of synthetic progestins in a yeast-based in vitro androgen bioassay. Journal of Steroid Biochemistry and Molecular Biology. 2008;**110**:39-47

[45] Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5alpha-reductase-2

deficiency. Molecular and Cellular Endocrinology. 2002;**198**:51-59

[46] Steers WD. 5alpha-reductase activity in the prostate. Urology. 2001;**58**:17-24

[47] Zhu YS, Katz MD, Imperato-McGinley J. Natural potent androgens: Lessons from human genetic models. Baillieres Clinical Endocrinology and Metabolism. 1998;**12**:83-113

[48] Bulun SE, Takayama K, Suzuki T, Sasano H, Yilmaz B, Sebastian S. Organization of the human aromatase p450 (CYP19) gene. Seminars in Reproductive Medicine. 2004;**22**:5-9

[49] Naftolin F. Brain aromatization of androgens. Journal of Reproductive Medicine. 1994;**39**:257-261

[50] Roselli CF. Brain aromatase: Roles in reproduction and neuroprotection. Journal of Steroid Biochemistry and Molecular Biology. 2007;**106**:143-150

[51] Jones ME, Boon WC, Proietto J, Simpson ER. Of mice and men: The evolving phenotype of aromatase deficiency. Trends in Endocrinology and Metabolism. 2006;**17**:55-64

[52] Lubahn DB, Moyer JS, Golding TS, Couse JF, Korach KS, Smithies O. Alteration of reproductive function but not prenatal sexual development after insertional disruption of the mouse estrogen receptor gene. Proceedings of the National Academy of Sciences USA. 1993;**90**:11162-11166

[53] Couse JE, Mahato D, Eddy EM, Korach KS. Molecular mechanism of estrogen action in the male: Insights from the estrogen receptor null mice. Reproduction, Fertility, and Development. 2001;**13**:211-219

[54] Gennari L, Nuti R, Bilezikian JP. Aromatase activity and bone homeostasis in men. Journal of Clinical Endocrinology and Metabolism. 2004;**89**:5898-5907

[55] Vanderschueren D, Vandenput L, Boonen S, Lindberg MK, Bouillon R, Ohlsson C. Androgens and bone. Endocrine Reviews. 2004;**25**:389-425

[56] Need AG, Nordin BEC, Chatterton BE. Double-blind placebo-controlled trial of treatment of osteoporosis with the anabolic steroid nandrolone decanoate. Osteoporosis International. 1993;**3**(Suppl. 1):S218-S222

[57] Vandenput L, Swinnen JV, Boonen S, Van Herck E, Erben RG, Bouillon R, et al. Role of the androgen receptor in skeletal homeostasis: The androgen-resistant testicular feminized male mouse model. Journal of Bone and Mineral Research. 2004;**19**:1462-1470

[58] Sartorius GA, Ly LP, Handelsman DJ. Male sexual function can be maintained without aromatization: Randomized placebo-controlled trial of dihydrotestosterone (DHT) in healthy, older men for 24 months. The Journal of Sexual Medicine. 2014;**11**:2562-2570

[59] Jakobsson J, Ekstrom L, Inotsume N, Garle M, Lorentzon M, Ohlsson C, et al. Large differences in testosterone excretion in Korean and Swedish men are strongly associated with a UDP-glucuronosyl transferase 2B17 polymorphism. Journal of Clinical Endocrinology and Metabolism. 2006;**91**:687-693

[60] Kurz D. Current management of undescended testes. Current Treatment Options in Pediatrics. 2016;**2**(1):43-51. DOI: 10.1007/s40746-016-0039-7 Epub 2016 Jan 25. PMID: 27158583; PMCID: PMC4856300

[61] Perusquía M. Androgens and non-genomic vascular responses in hypertension. Biochemical Pharmacology. 1 Aug 2022:115200

[62] Foradori CD, Weiser MJ, Handa RJ. Non-genomic actions of androgens. Frontiers in Neuroendocrinology. 2008;**29**(2):169-181

[63] Lorigo M, Mariana M, Lemos MC, Cairrao E. Vascular mechanisms of testosterone: The non-genomic point of view. The Journal of Steroid Biochemistry and Molecular Biology. 2020;**196**:105496

[64] Dent JR, Fletcher DK, McGuigan MR. Evidence for a non-genomic action of testosterone in skeletal muscle which may improve athletic performance: Implications for the female athlete. Journal of Sports Science and Medicine. 2012;**11**(3):363

[65] Bozzola M, Bozzola E, Montalbano C, Stamati FA, Ferrara P, Villani A. Delayed puberty versus hypogonadism: A challenge for the pediatrician. Annals of Pediatric Endocrinology & Metabolism. 2018;**23**(2):57-61

[66] Zhang JR, Zhang PY, Sun LG. Mild androgen insensitivity syndrome: A case report. Zhonghua Nei Ke Za Zhi. 2018;**57**(8):600-602

[67] Woodward HJ, Zhu D, Hadoke PW, MacRae VE. Regulatory role of sex hormones in cardiovascular calcification. International Journal of Molecular Sciences. 2021;**22**(9):4620

[68] Lucas-Herald AK, Alves-Lopes R, Montezano AC, Ahmed SF, Touyz RM. Genomic and non-genomic effects of androgens in the cardiovascular system: Clinical implications. Clinical Science. 2017;**131**(13):1405-1418

[69] Rajfer J. Relationship between testosterone and erectile dysfunction. Reviews in Urology. 2000;**2**(2):122

[70] Cunningham GR, Stephens-Shields AJ, Rosen RC, Wang C, Bhasin S, Matsumoto AM, et al. Testosterone treatment and sexual function in older men with low testosterone levels. The Journal of Clinical Endocrinology & Metabolism. 2016;**101**(8):3096-3104

[71] Kraemer RR, Durand RJ, Acevedo EO, Johnson LG, Synovitz LB, Kraemer GR, et al. Effects of high-intensity exercise on leptin and testosterone concentrations in well-trained males. Endocrine. 2003;**21**(3):261-265

[72] Yassin AA, Haffejee M. Testosterone depot injection in male hypogonadism: A critical appraisal. Clinical Interventions in Aging. 2007;**2**(4):577-579

[73] Glaser RL, York AE, Dimitrakakis C. Subcutaneous testosterone-letrozole therapy before and concurrent with neoadjuvant breast chemotherapy: Clinical response andtherapeutic implications. Menopause. 2017;**24**(7):859-864

[74] Schnabel PG, Bagchus W, Lass H, Thomsen T, Geurts TB. The effect of food composition on serum testosterone levels after oral administration of Andriol Testocaps. Clinical Endocrinology (Oxford). 2007;**66**(4):579-585

[75] Nassar GN, Leslie SW. Physiology, testosterone. [Updated 2022 Jan 4]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Available from: https://www.ncbi.nlm.nih.gov/books/NBK526128/

[76] Walters KA, Bertoldo MJ, Handelsman DJ. Evidence from animal models on the pathogenesis of PCOS.

Best Practice & Research. Clinical Endocrinology & Metabolism. 2018;**32**(3):271-281

[77] Kalfa N, Gaspari L, Ollivier M, Philibert P, Bergougnoux A, Paris F, et al. Molecular genetics of hypospadias and cryptorchidism recent developments. Clinical Genetics. 2019;**95**(1):122-131

[78] Spaziani M, Mileno B, Rossi F, Granato S, Tahani N, Anzuini A, et al. Endocrine and metabolic evaluation of classic Klinefelter syndrome and high-grade aneuploidies of sexual chromosomes with male phenotype: Are they different clinical conditions? European Journal of Endocrinology. 2018;**178**(4):343-352 [PubMed]

[79] Hauser LJ, Jensen EL, Mirsky DM, Chan KH. Pediatric anosmia: A case series. International Journal of Pediatric Otorhinolaryngology. 2018;**110**:135-139

[80] Falhammar H, Filipsson Nyström H, Wedell A, Thoren M. Cardiovascular risk, metabolic profile, and body composition in adult males with congenital adrenal hyperplasia due to 21-hydroxylase deficiency. European Journal of Endocrinology. 2011;**164**(2):285