Chapter 2
Physiology of Male Hormones

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2.1 Introduction to Male Sex Hormones

The testicle has two primary functions: endocrine (production of hormones) and exocrine (sperm production) 85–90% of the interior volume testicular is made up of seminiferous tubules and their germinal epithelium, place of sperm production (10–20 million gametes per day), and only 10–15% is occupied by the interstitium, where testosterone is produced (Jockenhövel and Schubert 2007).

2.2 Hypothalamic and Pituitary Hormones

The testicular function is controlled by the so-called axis hypothalamus-pituitary-testicular (Fig. 2.1). The hypothalamus gonadotropin-releasing hormone (GnRH) is secreted in the hypothalamus and stimulates hormonal production of the follicle-stimulating hormone (FSH) and luteinizing hormone (LH) by the anterior lobe of the pituitary gland (the adenohypophysis) (Hayes et al. 2001).

Numerous neurotransmitters modulate GnRH secretion and rhythm (Fig. 2.1). Alpha-adrenergic impulses stimulate GnRH secretion. Norepinephrine and prostaglandins increase hypothalamic secretion. Beta-adrenergic and dopaminergic impulses have an inhibitory action on the GnRH secretion. Endorphins, testosterone, progesterone, and prolactin, secreted in stressful situations, decrease GnRH secretion. GnRH is released by the hypothalamus in a pulsatile manner, with peaks

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every 90–120 min. This type of release is essential for the stimulatory effect of gonadotropin secretion. Continued GnRH administration would curb the pituitary discharge. The amplitude and frequency of the GnRH pulses modulate FSH and LH levels secreted by the anterior pituitary and, subsequently, the gonadal function (Hayes et al. 2001; Morales et al. 2004).

Pituitary hormones stimulate testicular functions: exocrine and endocrine. On the other hand, and due to the negative feedback process, hormones produced in the testis exert inhibitory effects on FSH secretion and LH (Table 2.1).

Pituitary LH stimulates testosterone production by Leydig cells located in the testicular interstitium by binding to specific receptors. LH release is a process discontinuous and occurs, mainly, during the night and in a pulsatile way, at intervals of about 90 min. It corresponds to the pulsatile secretion of GnRH. The available levels of this hormone will determine the amount of secretion of testosterone. But in turn, testosterone levels exert a reciprocal effect by inhibiting the LH production in the pituitary gland through two mechanisms (Table 2.2) (Vignozzi et al. 2005; Vermeulen 2003):

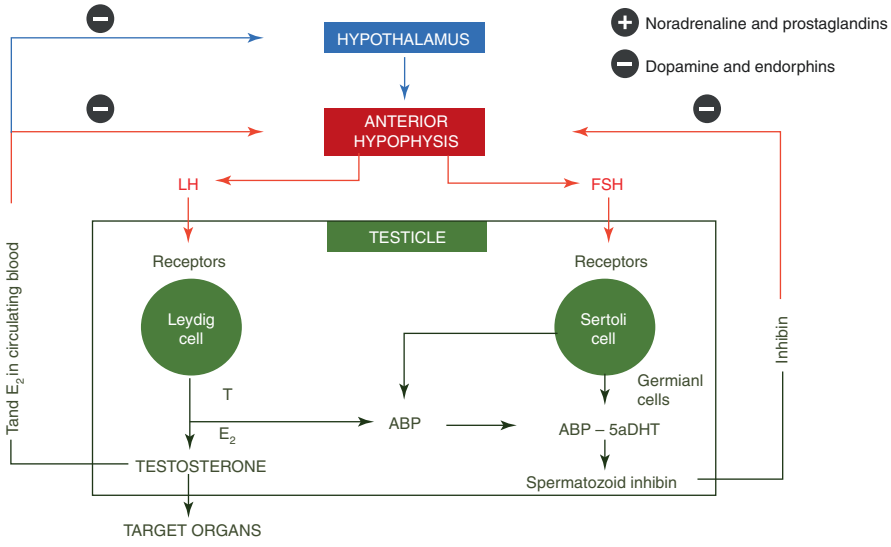

Fig. 2.1 Control of the hypothalamic-pituitary-testicular axis (*LH* luteinizing hormone, *FSH* follicle stimulant hormone, *ABD* androgen binding protein, *5a-DHT* dihydrotestosterone)

Table 2.1 Resume of the hypothalamic-pituitary-testicular axis

1. GnRH is secreted in the hypothalamus in regular amounts every 90–120 min.
2. The hypothalamus controls testicular function through GnRH by stimulating the pituitary hormones LH/FSH.
3. LH regulates and stimulates testosterone biosynthesis in Leydig cells, located in the testicular interstitium.
4. FSH stimulates spermatogenesis by acting on Sertoli cells, located in the seminiferous tubules.

Table 2.2 Hypothalamic-pituitary testicular retro-control

1. Testosterone has a weak negative feedback effect on the adenohypophysis, which results in a decrease in LH secretion. 2. On the other hand, testosterone directly inhibits GnRH secretion in the hypothalamus, causing a decrease in LH gonadotropin in the adenohypophysis, which will reduce the production of testosterone in the Leydig cells. Most of the inhibition of male hormone secretion is attributed to this feedback mechanism.	1. Testosterone exerts a depressant effect on the hypothalamic and pituitary production of gonadotropins (FSH and LH). 2. Estradiol exerts depressant effects on the hypothalamus and pituitary. 3. FSH stimulates the production of several proteins in Sertoli cells, such as inhibin, necessary for feedback control, which slows or suppresses FSH production.

A low testosterone concentration allows the hypothalamus to increase GnRH secretion, which stimulates the release of FSH and LH and thereby increases testosterone. In addition, the testicle can metabolize testosterone to estradiol through the flavouring enzymes present in the tubules and interstitium (Kaufman and Vermeulen 2005; Morley 2003). Estradiol, in physiological concentrations, also decreases the frequency and amplitude of the pulses of LH (Hayes et al. 2001).

2.3 Androgens

Male sex hormones or androgens induce the development of primary sexual characteristics in the embryo and secondary sexual characteristics in puberty. They are responsible for the general growth and protein synthesis that is reflected in the skeletal and muscular changes characteristic of the man. They are synthesized mainly in the Leydig cells of the testes, to a lesser extent in men's adrenal cortex and in women, in minute quantities, in the ovary. Like the rest of the steroid hormones, androgens are synthesized from cholesterol (Fig. 2.2).

The most important androgens are testosterone (Fig. 2.3), androstenedione, and dehydroepiandrosterone (DHEA), a precursor to the rest of the androgens and to estradiol.

The amount of testosterone is higher than the others, so it can be considered the most important testicular hormone. However, most of it is converted in the effector tissues into dihydrotestosterone (DHT), a more active hormone, as it has a greater affinity for the intracellular androgen receptor (AR) (Kelly and Jones 2013).

There is a considerable fraction of the testosterone produced that binds to albumin or sex hormone-binding globulins (SHBG) to be transported by the bloodstream, being its free concentration in serum minimal. In this way, it remains inactive until binding with its specific receptor (Heinlein and Chang 2002). The factors responsible for this transfer and how the cell causes the dissociation of the hormone-globulin complex are unknown. Still, it is believed to depend on the plasma concentration of the hormone (Heinlein and Chang 2002). Once in the cell,

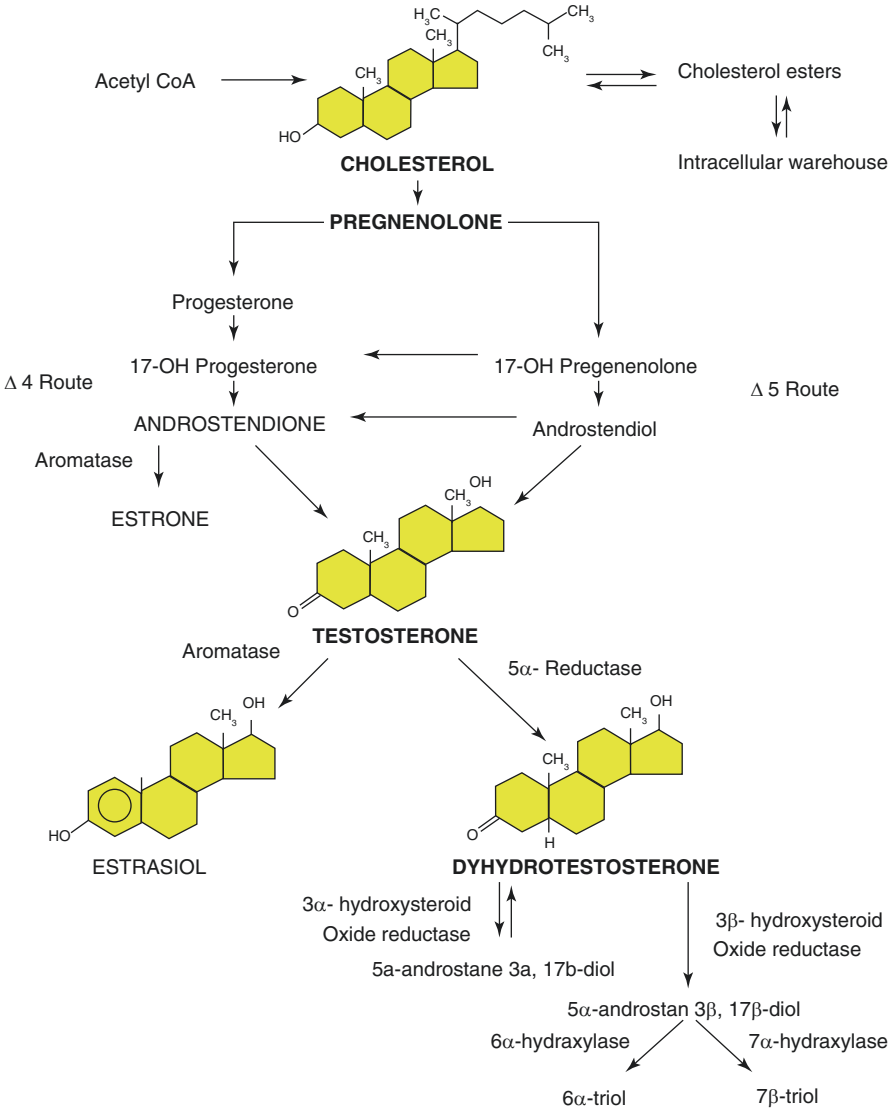

Fig. 2.2 Route of synthesis of sex hormones

the hormone binds to its receptor, located in the cytoplasm and/or in the nucleus, dimerization of the receptor is induced and its consequent activation.

AR, like those of other steroid receptors, is composed of several functional domains (Evans 1988) (Fig. 2.4):

1. The regulatory and binding domain of steroids is located in the C-terminal domain. It has several phosphorylation sites and is involved in the activation of the hormone-receptor complex.

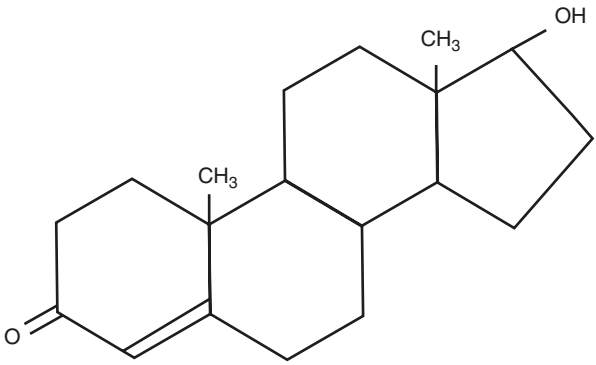

Fig. 2.3 Structure of testosterone

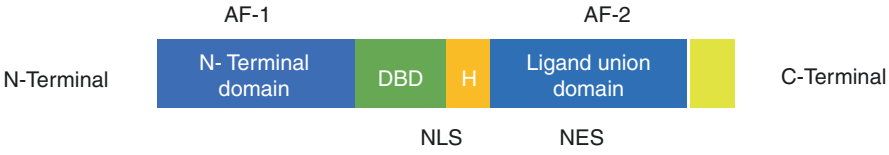

Fig. 2.4 Androgen receptors. Functional domains: A hypervariable N-terminal region, regulating transcriptional activity, a highly conserved central DNA-binding domain (DBD), a hinge region, and a long C-terminal, ligand-binding domain. Ligand-independent binding sites (AF-1, ligand-dependent (AF-2), nuclear signal localization (NLS), and nuclear signal export zone (NES) are also shown

2. The DNA-binding domain is found in the middle part and is essential for the activation of transcription. This portion is responsible for controlling which gene will be regulated by the receptor.
3. The hinge region is located between the two previous domains; it contains an important signal area for receptor movement into the nucleus after synthesis in the cytoplasm. It is a variable hydrophilic region in the different receptors.

The interaction of male sex hormones with the AR produces genomic effects, among which is the activation of the Mitogen-activated protein kinase (MAPK) and other transcription factors that induce the growth and proliferation of different cells (Geraldes et al. 2002).

There are also membrane ARs that induce non-genomic effects as they are not blocked by inhibitors of gene transcription (Gerhard and Ganz 1995; Farhat et al. 1996). Among other effects, there is an increase in the concentration of intracellular Ca^{+2} due to an increase in the formation of Inositol trisphosphate (IP3) (Estrada et al. 2000) or the phosphorylation of the Ras/Raf/extracellular signal-regulated kinase (ERK) 1/2 (Estrada et al. 2003). Through this non-genomic action, testosterone is capable of exerting a regulatory effect on vascular tone as it is capable of regulating the intracellular Ca^{+2} concentration. Likewise, testosterone can regulate the vasodilator effect of neurotransmitters, such as nitric oxide (NO) and Calcitonin gene-related peptide (CGRP) (Perusquía 2003; Isidoro et al. 2018).

2.4 Male Sex Hormones, Effects

At the sexual level, it plays a fundamental role in the development and maintenance of sexual characteristics and the male sex glands' development and functioning. As a "sex" hormone, androgens act on the central nervous system, stimulating and maintaining desire and sexual motivation.

It appears that testosterone is necessary for the normal functioning of the mechanism of ejaculation and maintenance of spontaneous erections. Its positive influence on erectile response is also known. Testosterone stimulates the activity the enzyme nitric oxide synthetase (NOS), which contributes to maintain adequate levels of nitric oxide (NO) in the smooth muscle of the corpora cavernosa of the penis. On the other hand, it has been proven that it favours the phosphodiesterase type 5 activity.

But testosterone and its metabolites are much more than a sex hormone; it performs numerous important physiological actions in the body, resulting essential for the overall health of men. Androgens play an important role in activating function cognitive; increase lean body mass; maintain bone mass (the hypogonadism is one of the main causes of osteoporosis in men); stimulate erythropoiesis; have a clear effect on lipids: improves the concentration of high-density lipoprotein (HDL) and decreases the concentration from low-density lipids (LDL); promotes cardiovascular health; even current evidence refers to an increase in life expectancy (Table 2.3).

2.5 Male Sex Hormones and Genitalia

The sex chromosomes determine if the primitive gonad is due to differentiate towards teste or ovary. Until the seventh week of gestation, the primitive gonad is common to both sexes. Subsequently, anatomical and physiological differentiation occurs that will determine the phenotype of female or male.

Testicular secretions determine the masculine character of the genitalia, both external and internal. Without this type of secretion, genetically the sex would be female, there would be no phenotypic differentiation towards male. The control of the formation of the male phenotype is due to the action of several hormones (Melmed and Jameson 2018):

1. Anti-Müllerian hormone, secreted by fetal testes, inhibits the development of Müllerian ducts (which would lead to the development of female internal genitalia).
2. Testosterone converts Wolf's ducts into the epididymis, the vessels deferens, and in the seminal vesicles.
3. DHT is later synthesized from fetal testosterone, induces the formation of the male urethra and prostate, and the fusion of the midline and elongation of the male external genitalia.

Table 2.3 Resume of the male sex hormone effects in different organs and systems

Target tissue	Active steroid	Effect
Wolff's duct	Stimulates growth and differentiation	Testosterone
External genitalia	Masculinization and growth	DHT
Urogenital sinus	Masculinization and growth	DHT
Bones	Closure of the epiphyses, anabolic effect	Estradiol/testosterone
Larynx	Growth and lengthening of the vocal cords	Testosterone/DHT
Skin	Stimulates fat production Stimulates hair growth Body and face Decreases hair growth (androgenic alopecia)	DTH
Kidneys	Stimulates the production of Erythropoietin	Testosterone/DHT
Liver	Induce enzymes, influence protein synthesis	Testosterone or DHT
Lipid metabolism	↑ HDL-cholesterol, ↓ LDL-cholesterol	Testosterone or DHT
Bone marrow	Stimulates erythropoiesis	Testosterone/DHT
Musculature	Anabolic effect	Testosterone
Testicle	Stimulates and maintains Spermatogenesis	DHT/estradiol
Prostate	Stimulates its growth and function	DHT/estradiol
Breast	Growth inhibition	Testosterone/DHT
Pituitary	Negative retro-control of the gonadotropin secretion	Testosterone/DHT
Hypothalamus	Negative retro-control of the GnRH secretion	DHT
Brain	Psychotropic effects, including on Libido	Testosterone/DHT/ Estradiol

Androgen deficiency during sexual differentiation, which occurs between weeks 9 and 14, gives rise to phenotypically intersex states, with the absence of masculinization and more or less ambiguous external genitalia. The deficits in later stages can condition abnormal development of the penis (micropenis) and abnormal testicular positioning. It is unknown how testosterone secretion is controlled in the embryo, although it seems that it can be regulated by LH and also receives influences from the placental choriogonadotropin hormone.

2.6 Testosterone at Puberty

In the prepubertal age, the levels of gonadotropins and sex hormones are low. At 6 or 7 years, the adrenarche begins, partly responsible for the growth of prepubertal and early armpit and pubic hair, but male sexual characteristics are not fully developed until puberty. Some of the organs involved in the appearance of puberty are:

1. The hypothalamic-pituitary axis.
2. The testes.

Table 2.4 Changes in puberty due to the effect of androgens

1. Thickening and pigmentation of penis and scrotum.
2. Growth of testes, penis, and scrotum.
3. Muscular development, especially in the pectoral and shoulders region.
4. Aggravation of the voice as a consequence of the elongation of the vocal cords.
5. Facilitation of the bone maturation and progressive closure of the growth cartilage.
6. Haematocrit Increase.
7. Decrease of HDL cholesterol.
8. Appearance and darkening of the axillary and pubic hair that already began in the adrenarche.
9. Psychological changes including libido increase and sexual function.
10. Maturation of the Leydig cells and beginning of the spermatogenesis.

3. The adrenal glands.
4. Other not well-known factors.

Anatomical and functional changes at puberty are predominantly a consequence of the effect of testicular androgens. These changes are summarized in Table 2.4. Complete maturation is achieved between 16 and 18 years, in 90% of cases, although the hair changes can continue until the second decade of life. If testosterone deficiency appears after birth but before puberty, virilization is poor or does not occur, this results in eunuchoid phenotypes and also a partial or total deficit of reproductive capacity (Melmed and Jameson 2018).

2.7 Testosterone in Adulthood

The effects of testosterone on adult men can be of three types:

1. Permanent and irreversible, which do not return even if there is a posterior androgenic deficiency (e.g., the severity of the voice).
2. Reversible, directly dependent on the continued secretion of androgens (e.g., influence on the production of erythropoietin, the maintenance of haemoglobin, as well as sexual function and libido).
3. Mixed (e.g., influence on spermatogenesis, consistency, and testicular size).

Over time, the sustained deficit of androgens gives rise to the manifestations known clinically as androgen deficiency syndrome in the adult male, whose predominant manifestations can be seen in Table 2.5.

2.8 Male Sex Hormones and the Cardiovascular System

Several population studies have shown a higher frequency of cardiovascular mortality in patients with low plasma testosterone levels. Studies reveal that patients with advanced cardiovascular disease have decreased plasma testosterone levels (Araujo

Table 2.5 Androgen deficiency syndrome in the adult male

1. Loss of libido
2. Erectile dysfunction.
3. Weakening of facial, axillary, and pubic hair.
4. Gynecomastia.
5. Hot flushes.
6. Decreased bone density, osteoporosis.
7. Decrease in muscle mass, body fat increase.
8. Normochromic normocytic anaemia due to erythropoietin deficiency

et al. 2005). In addition, cardiovascular diseases such as hypertension or atherosclerosis are more common in men during testosterone replacement therapy (Pongkan et al. 2016). Likewise, critical cardiovascular changes have been observed in men with prostate cancer who underwent androgen deprivation (Chou et al. 2015). All these data indicate that male sex hormones, specifically testosterone, has a fundamental role in cardiovascular health.

The basic organization of the blood vessel wall consists of three concentric layers:

1. The innermost layer, the tunica intima, is made up of one layer of endothelial cells (EC).
2. The middle layer, the tunica media, is made up of smooth muscle cells (SMC).
3. The adventitial layer, composed of collagen fibres, fibroblasts, and some sparse elastic and muscular fibres.

The tunica intima and the middle layer are separated by the internal elastic lamina, while the tunica media and the adventitial layer are separated by the external elastic lamina (Bohr et al. 1980).

The vasodilation effect of testosterone on coronary and peripheral circulation has been evaluated in animals and human trials and conclusion was that testosterone enhances the action of NO in the endothelium, inducing vasodilation (Vela Navarrete et al. 2009). The first experimental evidence was published by Yue et al. the study demonstrated the vasodilator effect of testosterone in the rabbit aorta and coronary arteries (Yue et al. 1995). Subsequently, numerous studies showed that testosterone acts as a direct vasodilator in human arteries through a non-genomic effect, independent of the ligand-dependent function of intracellular receptors and of protein transcription and synthesis (Rowell et al. 2009).

The biological actions of androgens are mainly mediated through binding to the AR, the classical genomic pathway. Androgen binding to the AR results in an AR conformational change that promotes the dissociation of chaperone proteins and facilitates receptor dimerization, nuclear transportation, phosphorylation, and deoxyribonucleic acid (DNA) binding. Upon the recruitment of co-regulators and general transcription factors, the transcription of target-genes is either induced or inhibited, leading ultimately to changes in androgen-target gene expression and cellular or biological structures and functions. This process usually takes hours before, resulting in biological changes in target cells (Cai et al. 2016).

The non-genomic effects of androgens are characterized by a rapid and reversible vasodilator effect on the vascular endothelium. The mechanism starts in the cell membrane when androgens binding to the AR on T lymphocytes, macrophages, or osteoblasts (Walker 2003), interacting between *G-protein coupled receptors* and *ion channels (*Pi et al. 2010*)*. Most of the studies highlight the non-genomic vasodilator effect produced by testosterone; however, more recent studies have been reported increased vasorelaxation of testosterone metabolites, specifically 5β-DHT, in experimental animal models. Thus 5β -DHT is a potent androgen with a strong affinity for the intracellular AR, whereas its 5-isomer (5-DHT), which does not bind to the AR, is totally devoid of androgenic properties but is highly efficacious in producing vasorelaxation (Perusquía and Stallone 2010).

Other studies on in vitro experimental studies have found that DHEA rapidly increased the expression of endothelial NOS (eNOS) and the activity of ERK 1/2 via the nongenomic pathway, which may increase NO secretion, leading to an increased flow-mediated dilation in vivo (Williams et al. 2004).

In addition to the direct vasodilator effect of androgens on the vascular endothelium, synthesis of different factors such as prostanoids, reactive oxygen species (ROS), or protein kinase C (PKC) have been implicated as important mechanisms that contribute to the regulation of vascular tone. In this way, the loss of gonadal function increases the production of prostanoids and decreases the bioavailability of NO, which can increase both systemic vascular resistance and vascular tone (Montaño et al. 2008).

Hypertension is a significant public health problem, being a direct cause of different cardiovascular diseases such as cerebrovascular disease, coronary heart disease, kidney disease, and peripheral vascular disease. Regarding the aetiology, genetic factors, age and sex, obesity, insulin resistance, alcohol, and high salt intake have been directly related to hypertension. Regarding the pathogenesis, arterial hypertension is characterized by alterations in vascular function and structure, including endothelial dysfunction, increased vasoconstrictor responses, and increased wall-vascular lumen ratio (Briones et al. 2003).

The vascular endothelium is considered an endocrine organ involved in vasoactive, metabolic, and immune processes. It is composed of endothelial cells which responses specifically to the physical and chemical conditions of the environment. The main *endothelium-derived vasoactive substances* are described in Table 2.6.

Androgens have been shown to regulate cell proliferation and function via either a classical genomic pathway or nongenomic pathway in endothelial cells from a variety of origins (Estrada et al. 2000). Androgen diffuses into the cell, directly

Table 2.6 Endothelial-derived vasoactive factors

Vasodilator factors	Vasoconstrictor factors
Nitric Oxide (NO) Endothelium-derived hyperpolarizing factor (EDHF) Prostacyclin (PGI_2) Acetylcholine Bradykinin	Endothelin (ET) Prostanoids (PGH_2, TXA_2, O_2) Angiotensin (AII)

activating a cascade of signalling creatine kinase and MAPK. The AR ligand may upregulate Vascular Endothelial Growth Factor (VEGF) and cyclins through the genomic pathway. Androgen may also induce eNOS synthesis. These mechanisms cause cell proliferation. The effects of androgens on endothelial cells proliferation and function may be a significant factor mediating the beneficial actions of androgens in the cardiovascular system in males and may explain findings that low levels of circulating androgens are associated with increased cardiovascular morbidity and mortality in males (Perusquía 2003).

2.9 Male Sed Hormones and muscular/Bone Metabolism

In the past decades, the importance of female and male sex hormones for skeletal muscle and bone health has become recognized. Although there are multiple sex hormones, those that have been studied the most are estrogen and testosterone. Both estrogen and testosterone are present in men and women, and both hormones exert direct and indirect effects on skeletal muscle and bone. Ageing results in a highly significant loss of testosterone in women and men. Men start losing testosterone continuously throughout life, at the beginning of their third decade. Indeed, many men are hypogonadal by the eighth decade, with free testosterone levels below 320 pg/dl, the accepted minimum (Elmlinger et al. 2003). Women become postmenopausal typically by the sixth decade, thus spending approximately one-third of their lifetime in an estrogen-deficient state (Davison et al. 2005). In young men and women, there are several conditions that cause sex hormone levels to drop to nearly undetectable levels, such as trauma, spinal injury, brain injury, and bed rest. There is emerging evidence that a sedentary lifestyle and associated obesity are associated with low sex hormone levels in men. The long-term consequences of low hormone levels at a young age have yet to be clearly defined. Due to sex hormones are markedly reduced with age and life expectancy is increased, there has been recent interest in restoring hormone levels to "normal" levels in ageing men and women. As expected, bringing testosterone levels above 320 pg/dl in hypogonadal older adults has an anabolic effect on skeletal muscle. Significant gains in muscle mass and strength have been realized; however, testosterone hormone replacement in older men is not without penalty. Likewise, providing estrogen to older women has an anabolic effect on bone and possibly muscle, but there may be negative consequences of giving estrogen to women in their 60–70 s decade.

2.10 Testosterone Effects on Skeletal Muscle in Men

The profound anabolic effect of testosterone on muscle becomes evident at puberty when male gain ≈ 35% more muscle mass than females. Testosterone stimulates myoblasts and increases the number of satellite cells, which promotes protein

synthesis. Once men are in their second decade, testosterone levels begin to decline, and this decrease is continuous throughout their lifetime. If serum levels of testosterone fall below 320 ng/dl, men are considered hypogonadal, a common state after 70 years. While testosterone values decline with natural ageing, many factors diminish testosterone levels at all ages, including obesity, inactivity, trauma, diet, disease, and drugs.

Skeletal muscle has many AR, and when receptors are stimulated, muscle protein synthesis occurs. AR is also responsive to Insulin-like Grow Factor-1 (IGF-1) and growth hormone, providing additional stimulation to increase muscle size. To illustrate the potent effect of testosterone, Bhasin S, et al., nearly obliterated endogenous testosterone production in normal young men with Gonadotropin-releasing hormone (GnRH); men became hypogonadal (testosterone values of 31 ng/dl) with GnRH and remained hypogonadal for 10 weeks. Before and after GnRH administration, the quantities of lean body mass and fat mass were measured. Muscle mass significantly decreased by ≈1 kg, and fat mass increased proportionately such that body weight was not different at the end of the study. This study illustrates the role of testosterone in the maintenance of standard body composition in men. In another group of men, GnRH was used to block endogenous testosterone production for 8 weeks. Various doses of testosterone were given back for the 8 weeks that GnRH was being given (Bhasin et al. 2001). Muscle mass and strength decreased in men on the low doses of testosterone but increased once testosterone levels reached a minimum of 320 pg/dl. Although none of the events were severe, the young men in this study experienced 55 adverse events, primarily prostate-specific antigen (PSA) above 4 μg/ml, hematocrit>54%, and leg oedema.

What happens when testosterone is given to older men who are already hypogonadal? Ferrando et al., addressed this issue and administered 100 mg of testosterone to six healthy men (average age: 67 year) who were hypogonadal (defined in this study as ≤480 ng/dl) to bring testosterone levels to within normal. Following 4 weeks of testosterone administration, knee extension, and flexion strength was significantly increased, and the fractional synthetic rate of quadriceps muscle protein synthesis was significantly elevated (Ferrando et al. 2002). Bhasin et al. administered graded doses of testosterone for 20 weeks to over 60 years old men (60–75 years) who were made hypogonadal following GnRH administration (Bhasin et al. 2005). The primary outcome measures were fat-free mass and maximum leg press strength. Muscle mass and strength increased in a dose-dependent manner ($r = 0.77$), the higher the dose of testosterone, the greater the increase in muscle size and strength. Decreases in fat mass also occurred and were inversely correlated with testosterone dose. The highest dose of testosterone increased muscle strength by nearly 50%, which has clear functional implications for the older man at risk for loss of independence. Unfortunately, there were 147 adverse events in this study, 12 of which were severe. Serious adverse events included haematocrit >54%, leg oedema with shortness of breath, urinary retention, prostate cancer, and haematuria with elevated PSA. Additional side effects of testosterone administration included a dramatic drop in HDL-cholesterol, which may have long-term cardiovascular consequences, and a general overall increase in PSA values (Bhasin et al. 2005).

In a recent evaluation on the safety of testosterone, Bhasin et al., concluded that "an AR modulator with anabolic properties that are free of dose-limiting adverse effects of testosterone" is needed. More recently, Sullivan et al., conducted a study in which strength training and testosterone were administered separately or together in frail old men. Testosterone was given weekly to 71 men for 12 weeks. Men trained at either 20% of one repetition maximum (1-RM) or at 80% of 1-RM. Those that performed the high-intensity strength training had a significant increase in strength of ≈25%. Men who trained at 80% of 1-RM and also received testosterone injections did not show an increase in strength over and above the strength increase shown by training alone (Sullivan et al. 2005).

2.11 Testosterone Effects on Bone in Men

A cross-sectional investigation of a large number of older men examined the relationship of declines in serum testosterone and estrogen on bone mass, fat-free mass, and muscle strength. Losses in bone mass were related to the age-related fall in endogenous testosterone and the decline in endogenous estrogen. As expected, low testosterone was correlated with poor muscle strength. Although testosterone was strongly related to muscle strength and bone, estrogen was also strongly associated with bone mineral density. Moreover, the positive relationship between testosterone and bone mineral density was independent of estrogen and bone mass, suggesting a role for both hormones and the maintenance of bone with ageing in men. The authors suggested that perhaps testosterone is aromatized to estrogen and that estrogen is responsible for the maintenance of bone mass with advancing age. It is recognized that estrogen and testosterone use different cellular pathways to inhibit osteoclastic activity and bone resorption. Perhaps hormone balance and pathway activation shift as hormone levels are altered with age (Sullivan et al. 2005).

More recently, data from the Framingham study were analyzed for 793 men who had had serum estrogen and testosterone measures taken in the early 80s. These men were followed until 1999, and the incidence of hip fracture was calculated for those with low estrogen and testosterone. The findings indicated there were no significant increased risks for hip fracture among men with low testosterone. Men with the lowest levels of estrogen had the highest incidence rates of hip fracture. In subsequent analyses, men with low estrogen and testosterone combined had the most significant risk for hip fracture (Amin et al. 2006). Bone health in men has been minimally examined and provides an ample opportunity for future inquiry (Brown 2008). In summary, falling testosterone levels with age are associated with the loss of lean muscle and bone mass. Testosterone supplementation is probably not warranted for older men due to a high incidence of detrimental effects. Inactivity is likely a major factor contributing to lower testosterone values at all ages. Exercise increases testosterone levels in young men, but it is not clear if exercise has a similar effect in older men.

Although less common than in women, osteoporosis in men still constitutes a major burden for public health. Despite the higher competing risk of mortality from other causes in older men, the remaining lifetime risk of osteoporotic fractures after 50 years may be as high as 20–25% (vs. 45–55% in women) in high-risk Caucasian populations. For hip fractures, a systematic review found that the male-female incidence ratio was also about 1:2 and was remarkably constant globally, despite greater than ten-fold variation between geographic regions. Androgens and estrogens are respectively C19 and C18 metabolites of cholesterol. The predominant gonadal androgen in men is testosterone, 95% of which is secreted by the testes. The adrenals produce the remaining 5% after conversion of the precursor DHEA. In peripheral tissues, testosterone can be converted by 5α-reductase enzymes into the more potent androgen DHT. T can also be converted into 17β-estradiol (E2) by the aromatase (CYP19A1) enzyme. The testes synthesize approximately 20% of circulating E2 in men; the remaining 80% is derived from DHEA in peripheral tissues (Kaufman and Vermeulen 2005). The circulating levels of total testosterone and E2 decrease only marginally with age in men. However, the age-related increase in SHBG is more pronounced, resulting in a more significant decrease of bioavailable or free sex steroid levels (Naessen et al. 2010). Importantly, older men generally have higher circulating E2 levels than postmenopausal women, making it plausible that E2 contributes to the conservation of the male skeleton and/or other tissues during ageing.

The effects of androgens and estrogens on male bone health can be divided into two phases: (1) peak bone mass acquisition; and (2) subsequent maintenance. The male advantage in bone strength is mainly established during the first phase by placing cortical bone further from its central axis due to greater periosteal bone formation. Young adult women achieve similar cortical thickness by limiting endosteal expansion, but this does not provide the same biomechanical advantages. Men also have greater peak trabecular bone volume due to thicker, more plate-like trabeculae. However, these gender differences are probably site-specific and require further confirmation in more prospective studies (Vanderschueren et al. 2014).

Regardless of their importance in pathophysiology, guidelines in male osteoporosis rightly point out that the role of testosterone replacement in men with late-onset hypogonadism remains controversial. Evidence supporting the clinical utility of serum sex steroid measurements for fracture prediction beyond clinical risk factors is insufficient. Further studies on sex steroid signalling in the musculoskeletal system are a high research priority because they may help in the design of additional, preferentially gender-neutral, therapeutic strategies to reach the ultimate goal of not merely preventing bone loss but also reinforcing the musculoskeletal system as a whole to prevent osteoporotic fractures in both genders (Vanderschueren et al. 2014).

With one in seven men affected over their lifetime, prostate cancer is the most prevalent solid-organ malignancy in men worldwide. Prostate cancer and treatment with androgen deprivation therapy (ADT) affects a significant number of the male population. Endocrine effects of ADT are a critical consideration in balancing the benefits and risks of treatment on long-term survival and quality of life. Muscle

mass declines with ADT; however, the evidence that this correlates with a decrease in muscle strength or decreased physical performance is discordant. Cortical bone decay also occurs in association with an increase in fracture risk; hence, musculoskeletal health optimization in men undergoing ADT is crucial. The increase in fat and loss of muscle mass are associated with a decrease in predominantly upper body strength, including maximum chest press and handgrip strength. Men undergoing ADT also report a subjective decrease in the quality of life and increased fatigue compared with controls. Objective measures of physical performance are, however, much more variable, with many studies demonstrating no significant changes in the measures of endurance, dexterity, walking speed, measures of frailty, and lower limb performance (Cheung et al. 2014).

The role of exercise and current and emerging anabolic therapies for muscle and various new strategies to prevent loss of bone mass in men undergoing ADT are discussed. Future well-designed, prospective, controlled studies are required to elucidate the effects of ADT on physical performance, which are currently lacking, and larger randomized controlled trials are required to test the efficacy of medical therapies and exercise interventions to target proven deficits and to ensure safety in men with prostate cancer (Cheung et al. 2014).

2.12 Conclusions

Understanding male hormonal physiology and the functions of testosterone, in the sexual aspect and in other systems, will allow us to understand the clinical consequences of any alteration in the hormone levels. For a correct clinical and analytical evaluation of testosterone deficiency, prior knowledge of the male hormonal pathophysiology is needed. These notions will also help to make a correct replacement treatment in patients who require it.

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