Male Hypogonadism

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Pathophysiology

The male reproductive tract is in constant interaction with the hypothalamic–pituitary–testes, to produce and secrete androgenic hormones (HAs) and produce, maintain, and transport sperm and seminal fluid, thus enabling male fecundity. The HAs are critical for embryonic differentiation of internal and external male genitalia, development and maintenance of secondary sexual characteristics, and androgenic extra-gonadal effects [1].

During embryonic development, primordial gonads during the first weeks of pregnancy suffer a cascade of events that culminate in sexual differentiation. The undifferentiated germ cells of the gonads subsequently differentiate into Sertoli cells and interstitial cells differentiate into Leydig cells constituting the endocrine testicular tissue. In the presence of sex chromosomes XY, from the seventh week of pregnancy, the activity of the gene SRY (sex-determining region on the Y chromosome) starts, located on the short arm of the Y chromosome, which encodes a protein that, together with other factors encoded by other chromosomes (autosomal or X chromosome), act in embryonic differentiation from the primordial gonad. Sertoli cells secrete the anti-Mullerian hormone that promotes regression of Mullerian ducts. After about 8 weeks of gestation, the Leydig cells already have the capacity to produce steroids and, together with the stimulation of human chorionic gonadotropin (hCG) produced by the placenta, secrete testosterone, beginning the process of stabilizing Wolff ducts and with that the differentiation of the internal sexual organs. The differentiation of testosterone into dihydrotestosterone (DHT) by the enzyme 5α-reductase causes DHT to stimulates the differentiation of the external genitalia [2, 3].

The synthesis of testosterone occurs in Leydig cells (interstitial compartment) in response to the stimulation of luteinizing hormone (LH). The spermatogenesis in the somniferous tubules is dependent on the action of follicle-stimulating hormone (FSH) in Sertoli cells (germ cells) and by the action of testosterone. Approximately 95% of the testes match compartment germ cells, which explains the enormous daily production of sperm. The gonadotropins (LH and FSH) are produced in the pituitary in its anterior portion (gonadotrophs) through stimulation of GnRH produced in the hypothalamus, which is transported through the pituitary portal system [4]. Testosterone is the principal androgen plasma in men, is synthesized predominantly in the testes, and small quantities in the adrenal glands. The circulating testosterone (total testosterone) represents the set of existing forms, being the absolute value of testosterone, 2% in its free form, coupled with 44% of androgen binding protein (steroid hormone binding globulin [SHBG]) and 54% bound to albumin [3].

Testosterone is the most important testicular androgen in men. Low serum testosterone levels are associated with cardiovascular morbidity, metabolic syndrome, type 2 diabetes mellitus, atherosclerosis, osteoporosis, sarcopenia, and mortality. There is increasing evidence that serum testosterone is a major biomarker status of men's health in general. Studies in twins indicate that in an individual there is a strong heritability of serum testosterone. Research based on genomes has sought to evaluate the effects of genetic variants on serum concentrations of testosterone. Analysis of 14,429 men showed that genetic variants in SHBG and on their locus on the X chromosome are associated with a wide variation in serum testosterone concentrations and an increased risk of low levels. A genetic variant that affects the affinity of testosterone to SHBG, interfering directly in its free fraction, could influence the mathematical calculations that estimate their serum. Thus, in the future it may be necessary to evaluate the affinity of testosterone to SHBG and this is taken into account in the measurement of serum levels, as well as analysis of genetic polymorphisms closely related to these variables [5].

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The testicular disorders can be classified into disorders of production and/or action of sex steroids, disorders of spermatogenesis, and testicular neoplasms. Male hypogonadism and gynecomastia are the most prevalent disorders in the production of sex steroids in men. Defects in androgen action include mutations in different receptors (androgen, estrogen-alpha) and enzymes (5-α reductase, aromatase). The defects of spermatogenesis characterize infertility or sub-fertility [1].

Male hypogonadism is a syndrome associated with disturbances of the production or action of testosterone and/or disorders in spermatogenesis. Testosterone deficiency can result from abnormalities in testicular function, such as disorders in testosterone production and/or spermatogenesis disorders (primary hypogonadism), the regulation of the hypothalamic pituitary or testicular function (secondary hypogonadism), or disorder of hormone action due to a reduced or absent function of the androgen receptor (androgen insensitivity). Testosterone deficiency may occur as a result of Leydig cell dysfunction in primary hypogonadism by insufficient secretion of GnRH and/or LH at secondary hypogonadism (pituitary and hypothalamic) [6].

Primary gonadal failure may be due to congenital and acquired disorders. Already, a secondary gonadal failure may be due to functional or organic abnormalities (congenital and acquired; Table 14.1). Primary testicular failure is

Table 14.1 Causes of hypogonadism

Primary hypogonadism
Congenital
1. Chromosomal disorders
(a) *Klinefelter syndrome and related syndromes (such as Male 46 XX)*
(b) *Enzyme defects in the biosynthesis of testosterone*
(c) *Myotonic dystrophy*
2. Developmental disorders
(a) *Exposure to prenatal endocrine disruptors*
(b) *Cryptorchidism*
(c) *Anorchia due to bilateral torsion testes syndrome*
(d) *Noonan syndrome*
Acquired
1. Orchitis
2. Mumps and other viruses
3. Infiltrative diseases (such as amyloidosis, hemochromatosis)
4. Acquired immunodeficiency syndrome (AIDS)
5. Granulomatous diseases (such as leprosy and tuberculosis)
6. Irradiation
7. Surgical lesions
8. Trauma and testicular torsion of the testicle
9. Varicocele
10. Autoimmune testicular failure
(a) *Isolated*
(b) *Associated (as Hashimoto's thyroiditis, type 1 diabetes mellitus)*
11. Drugs
(a) *Anti-androgenic steroids (as flutamide, cimetidine, cyproterone, spironolactone, ketoconazole)*
(b) *Cytotoxic*
12. Endocrine disruptors (such as insecticides, heavy metals, gossypol, environmental estrogens)
Androgen resistance syndrome
1. Testicular feminization syndrome (Morris syndrome)
2. Reifenstein syndrome
Secondary hypogonadism
Congenital
1. Multiple pituitary hormone deficiency
2. Pituitary aplasia or hypoplasia
3. Defects in the secretion or action of GnRH
(a) *Mutation Kalig-1*
(b) *Mutation in GnRH receptor*
4. Defects in the action or secretion of gonadotropins
(a) *Inactivating mutations of the LH-β gene*
(b) *Inactivating mutations of the LH receptor gene*
(c) *Inactivating mutations of the FSH-β gene*
(d) *Mutation in DAX-1 and SF*
5. GnRH deficiency
(a) *Isolated (idiopathic hypogonadotropic or isolated hypogonadism)*
(b) *With anosmia (Kallmann syndrome)*
(c) *Associated with other abnormalities (Prader–Willi syndrome, Laurence–Moon, and Bardet–Biedl syndrome, CHARGE syndrome, Rud syndrome, multiple lentigines, basal encephalocele, cerebellar ataxia)*
(d) *Partial deficiency of GnRH (fertile eunuch syndrome)*
Acquired
1. Traumatic brain injury
2. Post-radiation central nervous system, post-surgery, pituitary infarction, carotid aneurysm
3. Neoplasms
(a) *Pituitary adenomas: prolactinomas, nonfunctioning adenomas, other adenomas*
(b) *Craniopharyngiomas, germinomas, gliomas, lymphomas*
4. Autoimmune hypophysitis
5. Functional disorders: anorexia nervosa, dysfunction secondary to stress or other systemic diseases
6. Infiltrative disease: sarcoidosis, Langerhans cell histiocytosis, hemochromatosis
7. Infectious diseases: tuberculosis, histoplasmosis, abscesses
8. Drugs
9. Endocrine disruptors
Combined hypogonadism
1. Aging
2. Alcoholism
3. Hemochromatosis
4. Sickle cell anemia
5. Congenital adrenal hypoplasia (mutation of DAX-1)
6. Endocrine disruptors

characterized by low levels of testosterone and/or disorders of spermatogenesis associated with high concentrations of LH and FSH (hypergonadotropic hypogonadism). Secondary testicular failure is associated with low testosterone levels and inappropriately normal or low concentrations of LH and FSH (hypogonadotropic hypogonadism).

Secondary hypogonadism is usually associated with similar decreases in sperm and testosterone production. This occurs because the reduction in LH secretion promotes a reduction of testosterone production in the testes and, consequently, of intratesticular testosterone (primary hormonal stimulus for the production of sperm). In primary hypogonadism there may be a decrease in spermatogenesis in major damage in the cells of the seminiferous tubules (Sertoli cells) compared with Leydig cells. When this occurs, the subjects may present normal LH and testosterone levels, even with a number of ejaculated sperm very low or near zero. In these cases, FSH levels will be high.

In cases of secondary hypogonadism there is also less susceptibility to the occurrence of gynecomastia, probably due to normal or low levels of FSH and LH, which do not stimulate testicular aromatase, not increasing the conversion of testosterone to estradiol.

Causes of Hypogonadism

Primary Hypogonadism (Hypergonadotropic)

Congenital Causes

Klinefelter Syndrome

The Klinefelter syndrome (KS) is the most common sex chromosomal disorder in men, affecting one in every 660 children born alive [7]. It was first described in 1942. KS has a genetic background, with characteristics involving various specialties as embryology, pediatrics, endocrinology, cardiology, psychology, psychiatry, urology, and epidemiology.

Genetic inheritance is the extra X chromosome, which can be inherited from either parent. Most genes undergo additional X inactivation, but some may escape and serve as a genetic cause of the syndrome. Of these genes, the one that has been clearly shown to influence the phenotype of KS was short-stature home box-containing gene on chromosome X (SHOX) located pseudoautosomal region 1 in Xp. The haploinsufficiency of SHOX gene has been implicated in growth retardation and bone abnormalities in Turner syndrome and Leri–Weill dyschondrosteosis, and is also implicated in the slightly accelerated growth in KS [8]. The more frequent karyotype in men with KS is 47, XXY (93%) but karyotypes 46, XY/47, XXY; 48, XXXY; 48, XXYY; and 49, XXXXY have been reported [7].

Klinefelter syndrome is commonly under-diagnosed or is diagnosed late. Most men with KS live without a diagnosis. Boys with KS are likely to receive a diagnosis during evaluation for developmental delay and behavioral issues. Men with KS usually come to attention during evaluation for infertility or hypogonadism. Only 25% of cases are diagnosed and the average age of diagnosis is 30 years. A recent Australian study found a prevalence of 223 cases per 100,000 live births in boys [9], proposing an increase in the prevalence observed in several previous studies [10] and suggesting that it might differ between populations.

Klinefelter syndrome is associated with increased morbidity resulting in loss of life, and an increase in mortality owing to various diseases. Large epidemiological studies in KS were performed in two main cohorts: a British [11] and a Danish [12]. Together these studies show that the expected lifetime was reduced by 1.5–2 years, with increased mortality from various diseases, including diabetes, pulmonary disease, epilepsy, cerebrovascular disease, and vascular insufficiency of the intestine. In both studies, mortality among men with KS was significantly greater (hazard ratio: 1.9) and remained so after adjustment for social cohesion and education level (hazard ratio: 1.5), indicating that socioeconomic parameters can explain some but not all excess mortality in KS.

The main findings of KS are small testes, hypergonadotropic hypogonadism, and cognitive impairment. Other abnormalities are associated with KS and its frequency is varied (Table 14.2) [7].

Azoospermia is found in the vast majority of men with KS who have the karyotype 47, XXY. The mechanism by which an extra X chromosome causes infertile patients is not well known. Men with germ cell mosaics can present in their testicles, especially at a younger age. The testicular histology in men with KS shows hyalinization of seminiferous tubules and an absence of spermatogenesis. Patients with mosaics may show normal-sized testes and spermatogenesis in puberty. However, the progressive degeneration and hyalinization of seminiferous tubules occur soon after puberty. Therapeutic advances with the use of intracytoplasmic sperm injection allow 47, XXY men with azoospermia to achieve biological fatherhood [13].

The behavioral phenotype of KS is characterized by language, executive, and socioemotional dysfunction and psychomotor impairment. Boys with KS often need speech therapy, and many suffer from learning difficulties and may benefit from special education. The prevalence of schizophrenia, attention deficit hyperactivity disorder, autism spectrum disorders, and problems with mood regulation is increased. Neuroimaging studies of children and adults with KS show increases in the volume of gray matter sensorimotor and parieto-occipital regions, as well as significant reductions in the amygdala, hippocampus, insular, temporal, and inferior frontal volumes of gray matter [14].

Table 14.2 Abnormalities associated with Klinefelter syndrome

Feature	Frequency (%)
Infertility (adults)	91–99
Small testes (both testes <6 ml)	>95
Increased gonadotropin	>95
Azoospermia (adults)	>95
Commitment to learning (children)	>75
Decreased testosterone	63–85
Decreased facial hair (adults)	60–80
Decreased pubic hair (adults)	30–60
Gynecomastia (teens/adults)	38–75
Delayed speech development (children)	40
Increased height (prepubertal/adults)	30
Adiposity (adults)	50
Metabolic syndrome (adults)	46
Osteopenia (adults)	5–40
Type 2 diabetes mellitus	10–39
Cryptorchidism	27–37
Reduced penis size (children)	10–25
Psychiatric disorders (children)	25
Congenital malformations, ogival palate, inguinal hernia	18
Osteoporosis (adults)	10
Mitral valve prolapse (adults)	0–55
Breast cancer (adults)	Increased risk (50 times)
Mediastinum cancer (children)	Increased risk (500 times)
Fractures	Increased risk (2–40 times)

Hypogonadism in KS may lead to changes in body composition and a risk of developing metabolic syndrome and diabetes type 2. Medical treatment is mainly testosterone replacement therapy to relieve acute and long-term hypogonadism, as well as treatment or prevention of comorbidities.

Other Chromosomal Abnormalities

Other chromosomal abnormalities that result in testicular hypo function were reported, including rare diseases 46, XY/XO and 47, XYY. The karyotype 46, XY/XO leads to a syndrome characterized by short stature and other typical features of Turner syndrome. The gonad digenesis varies from the normal testes. The risk for gonadoblastoma is about 20% of digenesis. Gonadectomy should therefore be conducted in these patients [15, 16]. The karyotype 47, XXY was initially associated with hypogonadism, but other reports have not confirmed this relationship further. Micro deletion-specific regions of the long arm of chromosome Y can be detected in approximately 20% of men with severe oligospermia or azoospermia. Some of these men have no other testicular lesions, but others have cryptorchidism [17].

Myotonic dystrophy, an autosomal-dominant disease, leads to muscle atrophy and is accompanied by hypogonadism that is usually not recognized until adulthood. Small testes and decreased production of sperm are more common than reduction of serum testosterone levels [18, 19].

Disorders of Androgen Synthesis

Mutations in genes encoding the enzymes necessary for the biosynthesis of testosterone may result in a decrease in their serum. The rare mutations found are enzyme cleavage of the side chain of cholesterol, 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase (present in the adrenals and testes), and 17β-hydroxysteroid dehydrogenase (present only in the testes). Depending on the degree of mutation differing degrees of fetal virilization are met [20].

Mutation in FSH and LH Genes

Changes in LH and FSH receptors are rare causes of primary hypogonadism. The mutation in the FSH receptor induces a variable sperm count, which tends to be generally low and concentrations of inhibin B and FSH levels. Mutations in LH receptor results in hypoplasia and Leydig cell testosterone deficiency in the first trimester in utero, resulting in different degrees of disorder of sexual development DDS [21–23].

Cryptorchidism

Cryptorchidism is a condition in which one or both of the testes fail to descend from the abdomen into the scrotum. The main sites are the inguinal canal and abdominal cavity. It is necessary to differentiate between the possible cryptorchid testes and shrunken testicles, that on manipulation, return to the scrotum normally. Cryptorchidism can affect one or both testes. If only one testes is affected, the sperm count is subnormal in 30% of cases (and the concentration of FSH is slightly raised), suggesting that even in the presence of one normolocated testicle, this may present different degrees of testicular dysfunction. If both testes are cryptorchid, the sperm count is usually severely impaired and serum testosterone may also be reduced. The risk of gonadoblastoma also increases if the testicle is not in its normal position [24, 25].

Congenital Anorchia

Congenital anorchia occurs in disorders (after 20 weeks of gestation) that lead to testes regression. The male sex differentiation at birth is normal, but the testes are absent and hypogonadism in general is important [26]. The diagnosis is confirmed after anorchia with a full search of imaging studies (both in the scrotum and in the abdominal cavity) and, if necessary, laparotomy. There are case reports that testosterone treatment in adult men with congenital anorchia and micropenis can lead to penis enlargement.

Acquired Causes

Varicocele

Damage to the seminiferous tubules due to varicosity of the venous plexus within the scrotum has been considered a pos-

sible cause of male infertility. Current data are conflicting about the real benefit of varicocele correction in relation to fertility [27].

Orchitis

Several infections may be associated with testicular damage. The most common cause is mumps and orchitis is a frequent manifestation when occurring in adulthood. The incidence has decreased owing to the vaccination of the population. The involvement of testicular mumps causes increased painful testicles, followed by atrophy. The seminiferous tubules are often severely affected, often resulting in infertility, especially when both testicles are involved. The Leydig cells can also be damaged, resulting in decreased production of testosterone.

Chronic Diseases

Gonadal dysfunction is a common finding in men with chronic kidney disease (CKD) and end-stage kidney disease. Testosterone deficiency, generally accompanied by elevated serum gonadotropin, is present in 26–66% of men with varying degrees of renal impairment. Uremia-associated hypogonadism is multifactorial in origin, and rarely improves with the onset of dialysis, although usually it normalizes after renal transplantation. Although there are encouraging data suggesting benefits of testosterone replacement therapy for CKD patients, more studies are needed regarding the safety and efficacy [28].

The gonadal function requires a normal liver function. It is well known that the clinical symptoms of hypogonadism are common in patients with liver cirrhosis. The pathogenesis of hypogonadism in cirrhotic patients is complex and not well explained. It involves both a gonadal dysfunction and a central disturbance [29]. Hypogonadism is a potential complication of hemochromatosis, usually seen in patients with severe iron overload and liver cirrhosis [30].

Other infiltrative or granulomatous disease may promote primary gonadal failure, varying clinical demonstrations, and testicular dysfunction according to the degree of involvement of the underlying disease. Examples are tuberculosis and leprosy.

HIV Infection

Men who have HIV may have hypogonadism to varying degrees. The premature decline of serum testosterone is common (16%) among young and middle-aged HIV-infected men and is associated with inappropriately low or normal LH and accumulation of visceral adipose tissue. Testosterone deficiency may be regarded as a process of accelerated or premature aging. The role of HIV and/or treatment of HIV infection have yet to be elucidated [31]. The frequency of hypogonadism and its severity appear to have decreased since the introduction of antiretroviral therapy.

Irradiation

Direct radiation to the testes, as the treatment for leukemia, can damage them. Even when radiation is indirect, damage may occur in the seminiferous tubules. The degree of damage is proportional to the amount of radiation exposure. Radioactive iodine may cause a decrease in sperm count when the doses administered are high for the treatment of differentiated thyroid carcinoma.

Gonadal Toxicity of Cancer Chemotherapy

The number of surviving young men with cancer has increased dramatically over the past 20 years as a result of early detection and better treatment protocols for cancer. Over 75% of cancer patients diagnosed in youth are long-term survivors.

The gonadal dysfunction has emerged as an important long-term complication of cancer chemotherapy, especially in young patients with hematological and testicular malignancies. Infertility can be a significant issue for many cancer survivors. The male hypogonadism after chemotherapy may contribute to fatigue, sexual dysfunction, irritability, loss of lean mass, and osteopenia. Quality of life and recovery from cancer treatment is worsened by this clinical symptom.

Cytotoxic chemotherapy may cause gonadal injury, and the nature and extent of the damage depends on the drug, the dose received, and the age of the patient. Many drugs are toxic (Table 14.3), including procarbazine, cisplatin, and alkylating drugs such as cyclophosphamide, melphalan, and chlorambucil. However, all chemotherapeutic drugs can cause damage to gonadal function [32]. The relative contribution of each individual drug can be difficult to determine because most treatments are conducted with multiple drug regimens [33].

Trauma and Torsion of Testes

Any trauma in the testes may be sufficient to damage both the seminiferous tubules and the Leydig cells. Testicular torsion is one of the most common reasons for the loss of a testicle before puberty. The torsion of a testes is a twist in the spermatic cord, which results in severe loss of blood to the

Table 14.3 Estimated risk of gonadal dysfunction with cytotoxic agents

High risk	Medium risk	Low risk
Cyclophosphamide	Cisplatin	Vincristine
Ifosfamide	Carboplatin	Methotrexate
Chlormethine	Doxorubicin	Dactinomycin
Busulfan	BEP	Bleomycin
Melphalan	ABVD	Mercaptopurine
Procarbazine		Vinblastine
Chlorambucil		
MOPP		

ABVD adriamycin, bleomycin, vinblastine, and dacarbazine, *BEP* bleomycin, etoposide, and cisplatin, *MOPP* nitrogen mustard, oncovin (vincristine), procarbazine, and prednisone

testes. The loss of the testes can occur owing to a lack of blood if the twist is not reverted spontaneously or surgically corrected within a few hours. The degree of damage depends on the length of the twist. A twist that lasts more than 8 h can promote enough damage to decrease the sperm count. Even when the twist involves only one testicle, both testicles may be damaged; however, it is not clear how this can occur [34–36].

Medications

Ketoconazole directly inhibits the biosynthesis of testosterone, thereby causing a deficiency in production [37]. Chronic use of glucocorticoids can also decrease testosterone levels in about one third of individuals. The mechanism is not clear, but the inhibition can occur in both testes and in the pituitary gland [38, 39].

Autoimmune Testicular Failure

It may occur in isolation or as a manifestation of polyglandular autoimmune syndrome and should be considered in all patients with other concomitant autoimmune diseases [40].

Secondary Hypogonadism (Hypogonadotropic)

Congenital Causes

The etiology of congenital gonadotropin dysfunction is rare. Clinical findings vary among individuals mainly because of the time of onset of dysfunction of gonadotropins. Sexual differentiation is normal because testosterone secretion by Leydig cells in the fetal first trimester of pregnancy is dependent on the stimulation of placental hCG. Penile development occurs primarily during the third trimester of pregnancy, and is often subnormal because testicular testosterone secretion at this stage is dependent on fetal LH secretion, which is also subnormal. This results in many cases in micropenis. The linear growth in childhood is normal, deficits occurring only when associated with deficiency in the production of growth hormone or thyroid hormone. Most diagnoses are made during puberty. Pubertal development can start and progress slowly, becoming it incomplete in many cases. In some patients, depending on the degree of gonadotropin deficiency, delayed puberty may present or absent [41].

Isolated Hypogonadotropic Hypogonadism

It is characterized by isolated deficiency of gonadotropins, without changes in smell and due to deficient secretion of GnRH, GnRH receptor mutation, or mutations of β fractions of LH or FSH. Several genetic mutations may be involved in the production process, hormonal secretion, or action (Table 14.4). Many cases remain of unknown etiology [42, 45].

Kallmann Syndrome

Kallmann syndrome is characterized by hypogonadotropic hypogonadism and another congenital abnormality that is not gonadal, including anosmia or hyposmia, red–green daltonism, midline facial defects, abnormalities of the urogeni-

Table 14.4 Genes involved in the etiology of hypogonadotropic hypogonadism [22, 23, 42–44]

Gene	Product	Function	Clinical
CHD7	Protein linker of chromodomain-type DNA helicase-7	Development of the neural crest, protein bound to DNA	CHARGE syndrome — semicircular canal aplasia, hypoplasia of the olfactory bulb, GH deficiency, hypothyroidism, congenital malformations that include hypogonadotropic hypogonadism (with micropenis and/or cryptorchidism)
DAX1/ NR0B1A	Gene 1 of sex reversal	Development of adrenal secretion of gonadotropin control	Adrenal hypoplasia congenital X-linked (primary adrenal insufficiency that is expressed in the early stages of life)
FGF8	Fibroblast growth factor type 8	FGFR1 Binder/migration of GnRH neurons	Kallmann syndrome
FGFR1	Receptor type 1 fibroblast growth factor (FGF receptor 1)	Migration of GnRH neurons	Kallmann syndrome
FSHβ	B subunit of FSH	Binder receptor FSH	Isolated FSH deficiency (azoospermia, small testes in soft and undetectable serum FSH)
GnRH1	Pre-hormone GnRH	GnRH synthesis and cell signaling	Isolated hypogonadotropic hypogonadism
GnRHR	GnRH receptor	Synthesis of LH and FSH	Isolated hypogonadotropic hypogonadism, LH-isolated deficiency (partial mutations)
GPR54/ Kiss1R	Receptor 1 of Kisspeptin	Stimulation of secretion of GnRH	Isolated hypogonadotropic hypogonadism with attenuated LH response to exogenous GnRH stimulation
HESX-1	Homeobox protein ANS	Marking the previous visceral endoderm embryo	Syndrome of septo-optic dysplasia (optic nerve hypoplasia, radiological changes of online medical and hypoplastic anterior pituitary (hypopituitarism with neuro-ectopic posterior pituitary) and Pickhardt–Fahlbusch syndrome
HS6ST1	6-*O*-sulfotransferase heparin sulfate	Catalyzes transfer of the sulfate at position-6 in the biogenesis of heparin sulfate	Hypogonadotropic hypogonadism

Table 14.4 (continued)

Gene	Product	Function	Clinical
KAL1	Anosmin-1	Cell adhesion glycoprotein (expressed in embryonic development in olfactory bulb, cerebellum, spinal cord, kidney, and retina), migration of GnRH neurons	Kallmann syndrome
LEP	Leptin	Hormone regulating food intake, energy expenditure, and hypothalamic reproductive function	Homozygous mutation in the leptin exhibits morbid obesity and hypogonadism (apparently of hypothalamic origin)
LEPR	Leptin receptor	Membrane receptor	Morbid obesity and hypogonadism (apparently of hypothalamic origin)
LHX3		Transcription factor required for the development of pituitary	Hypopituitarism (corticotropic-preserving function) associated with limitation of neck rotation (rigid cervical spine), elevated and anteverted shoulders
LHβ	B subunit of LH	Binder receptor LH	Isolated FSH deficiency (fertile eunuch syndrome — deficient production of testosterone associated with varying degrees of spermatogenesis)
NELF	Factor nasal embryonic LHRH	Neuronal migration	Hypogonadotropic hypogonadism
PROK2	Type 2 prokineticin	Migration of GnRH neurons	Kallmann syndrome
PROKR2	Receptor type 2 prokineticin	Migration of GnRH neurons	Kallmann syndrome
TAC3	Neurokinin B	Binder TACR3, stimulates GnRH secretion	Hypogonadotropic hypogonadism
TAC3R	Neurokinin B receptor	Stimulates the secretion of GnRH	Hypogonadotropic hypogonadism
WDR11	Protein WD	Interaction with transcription factor EMX1/GnRH neuronal migration	Hypogonadotropic hypogonadism

tal tract, synkinesis (mirror movements), and sensorineural hearing loss. Hypogonadism is due to deficient secretion of GnRH owing to defects in the migration of GnRH-secreting neurons that have the same embryological origin as those olfactory neurons. Most cases are sporadic, but there may be a familial transmission (X-linked inheritance is autosomal dominant or recessive). Studies have shown mutations in genes encoding several adhesion molecules on the cell surface, receptors or necessary for the migration of neurons, such as fibroblast growth factor receptor 1 (also called KAL1) procineticina-2 (PROK2) and its receptor (PROKR-2). These mutations together represent less than half of the cases described [22, 23, 43, 45].

Laurence–Moon and Bardet–Biedl Syndrome

These are etiologies of hypogonadism associated with retinitis pigmentosa and developmental delay. Laurence–Moon syndrome is associated with spastic paraplegia and Bardet–Biedl is associated with post-axial polydactyly, renal dysplasia, and early-onset obesity [46, 47].

Deficiencies of Transcription Factors

Some individuals have involvement of other hormonal axes in association with gonadotropin deficiency. Mutations in *PROP-1* mutations represent the most common known genetic cause of hypopituitarism both in sporadic and familial cases [22, 23].

Acquired Causes

Hypogonadotropic hypogonadism can be caused by any disease that interferes with the hypothalamic–pituitary axis. The mechanisms that may be involved (one or more) are hypothalamic disorders (that impair the GnRH secretion), disorders of the pituitary stalk (that interfere with the passage of GnRH into the pituitary gland), and pituitary disorders (that directly decrease the secretion of LH and FSH).

Disorders of Gonadotropin Secretion

Hyperprolactinemia

Hyperprolactinemia of any cause can suppress gonadotropin secretion and thus testicular function [48]. Hypogonadism is reversible with normalization of prolactin.

Drugs

– *Sexual steroids*:

The use of androgen, estrogen, or progesterone may alter the secretion of gonadotropins. The recreational use of male sex hormones can interfere with the aim of anabolism in the secretion of gonadotropins during the period they are being used and, after several months of drug withdrawal when high doses are used. Recent data show that abuse of androgens can lead, in addition, to hypogonadism, increased cardiovas-

cular morbidity, and mortality [49]. Estrogens and progestins used as appetite stimulants can promote secondary hypogonadism in some individuals.

– *Glucocorticoids*:

Chronic treatment with glucocorticoids can lead to hypogonadism. Prolonged use in various diseases in current medical settings, and the indiscriminate use of steroids, showed the effect of medication on the pulsatility of gonadotropins and consequently on gonadal function [38].

– *Opiates*:

When administered chronically, especially when continuing to control chronic pain, opiates often cause pronounced hypogonadism [50, 51]. Opioids, endogenous and exogenous, modulate gonadal function, acting mainly on opioid receptors in the hypothalamus, decreasing the secretion or causing loss of pulsatility of normal gonadotropin-releasing hormone (GnRH). Opioids may also have direct effects on the pituitary gland and testes [52].

– *GnRH Analogs*:

The prolonged administration of GnRH analogs leads to a decrease in the secretion of LH and hence in the secretion of testosterone. Currently, drugs as triptorelin and histrelin are much used in the adjuvant treatment of prostate cancer [53].

Chronic Diseases

Several systemic and chronic diseases, including cirrhosis, chronic kidney failure, chronic lung disease, and AIDS, cause hypogonadism by a combination of primary and secondary effects [54].

Critical Conditions

Any serious illness, surgery, myocardial infarction can cause hypogonadism. Decreased levels of LH are found in critically ill patients, suggesting an involvement in the pituitary gonadal function [55, 56].

Anorexia Nervosa

Although less common in adolescent males, anorexia may also be associated with secondary hypogonadism, characterized by functional hypothalamic changes, and interfering with the proper secretion of GnRH [57].

Diabetes Mellitus

Male patients with type 2 diabetes mellitus (T2DM) have a higher prevalence of low serum concentrations of testosterone than men without diabetes. The pathogenesis of this disorder is still uncertain, but it is known that there is a decrease in both total testosterones as its free fraction. Patients with T2DM have other signs and symptoms of metabolic syndrome, which may contribute to further enhancing the hormonal deficit [58–62].

Obesity

The European Male Aging Study demonstrated that men who are overweight (BMI 25–29 kg/m^2) and those who are obese (BMI $\geq$ 30 kg/m^2) tend to have lower serum concentrations of the hormone binding globulin (SHBG) and, therefore, lower serum total testosterone, inasmuch as the concentration of total serum testosterone to SHBG is due to a low concentration of free testosterone is normal. However, men who are obese may also have low levels of free testosterone. At all ages, total testosterone and SHBG concentrations were lower in overweight men than in men of normal weight and even lower in obese men. Free testosterone was similar in men with normal weight and overweight, but lower in obese men. Serum concentrations of LH did not increase in patients with BMI above the normal range, demonstrating a disorder in the central gonadal axis [61–63].

Disorders of Direct Gonadotroph

Benign Tumors and Cysts

Pituitary adenomas and sellar cysts can cause decreased cell function by a gonadotropic local mass effect, decreasing the release of LH and FSH.

Neoplasms

Malignant tumors of the central nervous system (CNS), metastases, or other malignancies can affect the functioning of the gonadal axis by interfering with the production of gonadotropins. Meningiomas are among the most common primary tumors and metastatic lesions of lung cancer and prostate cancer.

Infiltrative Diseases

Sarcoidosis and Langerhans cell histiocytosis (eosinophilic granuloma) can cause hypothalamic hypogonadism. The iron deposition in patients with hemochromatosis directly on the pituitary can induce secondary hypogonadism.

Infections

Tuberculosis meningitis and other causes of CNS infections may promote central hypogonadism. In most cases there is a concomitant impairment of another hypothalamic-pituitary axis (somatotropic or adrenocorticotropic axis).

Traumatic Brain Injury

The external carotid artery has been described in recent years as an important cause of hypopituitarism, including GH deficiency and male hypogonadism. Whiplash injury leading to concussions, brain trauma and the skull base can pull the pituitary stalk and sectional portal circulation. However, most of the dysfunctions of the hypothalamic–pituitary axis are still poorly understood, demonstrating a high rate of hypogonadism during acute trauma with subsequent recovery of gonadal function in a group of patients remaining in permanent hypogonadism (10–15% of individuals 1 year after the event). The time of recovery of gonadal function and the reason for the fall in gonadotropins at an acute moment are still matters of discussion and research [64].

Endocrine Disruptors and the Gonadotropic Axis

Endocrine disruptor compounds (EDCs) are exogenous compounds that have the potential to interfere in regulating the endocrine system and therefore may predispose to disease in man and animals [65]. The EDCs can be naturally derived from plants (phytoestrogens) in animals and man. Currently, artificial chemical compounds are of major concern worldwide. EDCs can interfere with the production, secretion, metabolism, transport, or in the peripheral action of endogenous hormones through its binding to hormone receptors.

Evidence for changes in the human male reproductive tract associated with EDCs is still limited. Humans are exposed to hundreds or thousands of environmental chemicals and a major limitation of epidemiological studies is that they generally measure human exposure to a single EDC [65, 66].

The male sex differentiation is androgen dependent. Thus, various diseases can be observed in males owing to exposure to EDCs. Postnatal exposures also have an impact on the development and maintenance of gonadal males (Table 14.5).

Quality of Semen

The decline in semen lifelong quality has been followed in several countries. Some studies suggest that semen quality decreases before 50 years of age, whereas others do not observe this decline [66].

Table 14.5 Association of endocrine disruptor compounds and possible diseases of the human male reproductive system

Stage of development	Disease/associated amendment
Fetal	Cryptorchidism, hypospadias, testes dysgenesis syndrome
Prepubertal	Precocious pubarche
Pubertal	Testes atrophy, precocious puberty, delayed puberty
Adult	Infertility, testes cancer, and enlarged prostate

Despite the importance and relevance of exposure to EDCs, especially polychlorinated biphenyls (PCBs), pesticides, and phthalates, the epidemiological evidence for the relationship with semen quality in adults is still limited, mainly because many of the data were obtained transversely.

Testes Dysgenesis Syndrome

Testes dysgenesis syndrome (TDS) is the association between cryptorchidism, hypospadias, and testicular cancer oligozoospermia resulting from altered testicular development. This association may mean that several elements acted at different times throughout the life of an individual, and may be due to exposure to a particular EDC or mixture. However, epidemiological data concerning EDCs with this syndrome in humans are still indirect [67].

The decreased anogenital distance, a marker of prenatal androgen activity, was observed in rats exposed to phthalates in the prenatal period and later identified in an epidemiological study with newborn human males [68].

Male Urogenital Tract Malformation

The association of the exposure of father and/or mother or a community to pesticides with the presence of hypospadias or cryptorchidism in newborns is suggestive of the involvement of EDCs. Epidemiological data supporting this link are those from individuals living in agricultural areas and/or that directly assessed the exposure of parents to organochlorine pesticides [69].

Testicular Germ Cell Cancer

The frequency of testicular germ cell tumors (TGCTs), which comprise more than 95% of all testicular cancers, has increased significantly during the past four decades, well beyond the expected population growth. To date, the evidence for the relationship between EDCs and risk of TGCTs has been limited. Interestingly, in a case–control study, no association was observed between serum concentrations of organochlorine compounds in patients with controls and TGCT, but an association was observed with serum levels of organochlorines in their mothers during antenatal care being a predictive factor for increased risk for TGCT in adulthood [70].

Gynecomastia

Di-(2-ethylhexyl) phthalate (DEHP) is one of the most commonly used phthalates in plastics manufacture. DEHP has been reported as an androgen receptor antagonist. Mono-(2-ethylhexyl) phthalate (MEHP) is known as the first and primary metabolite of DEHP. It was observed that plasma levels of DEHP and MEHP were significantly higher in patients with gynecomastia compared with pubertal controls [71].

Diagnosis

The diagnosis of androgen deficiency occurs in three stages. Initially, it should include a general health assessment to look for signs and symptoms of androgen deficiency and exclude systemic disease, eating disorders, and lifestyle problems, such as excessive exercise or drug abuse. The signs and symptoms of androgen deficiency are nonspecific and are modified by age of onset, severity, and duration of disability, comorbidities, use of androgen sensitivity, and prior therapies. If an androgen deficiency is initiated before the patient has completed pubertal development, it often appears as delayed or incomplete sexual development and eunuchoid proportions (arm span greater than height by more than 5 cm). In men in whom androgen deficiency develops after complete pubertal maturation, symptoms include reduced sexual desire and activity, reduced spontaneous erections, loss of body hair and reduced frequency of shaving, infertility, decreased muscle mass and strength, small or shrinking testicles, and breast enlargement. In older men, there may be a background of nonspecific symptoms associated with aging.

After the initial clinical investigation, serum total testosterone (TT) should be measured, preferably in the morning, using a reliable biochemical assay. An examination with a low value should be repeated at least once for confirmation. Measurement of testosterone should be avoided during the period of acute disease as there is suppression of the hypothalamic–pituitary–gonadal axis resulting in decreased serum levels of TT. Also, conditions that elevate the serum androgen-binding protein (SHBG) decrease the dosage of TT (Table 14.6). The TT measured represents the set of presentation forms of serum testosterone. The absolute value of TT is equal to 2% free testosterone, 44% bound to SHBG, and 54% bound to albumin. Therefore, it is recommended that free testosterone (FT) is determined in some individuals, particularly those that have altered levels of SHBG, as in the case of obese patients. The method of measuring TT considered more accurate is liquid chromatography–tandem mass spectrometry, but it is not available in the vast majority of laboratories. Thus, the measurement of total testosterone by direct and automated methods (such as electrochemiluminescent assay - ECLIA) fulfills its role in most diagnoses [72]. As most laboratories do not have this methodology and use radioimmunoassay for their evaluation, it is recommended to obtain the FT values from the construction proposed by Vermeulen, based on the values of TT, SHBG, and albumin (Table 14.7). Other causes of low testosterone levels should be discarded, such as hyperprolactinemia, thyroid disorders, chronic diseases, or other disorders. Estradiol should be measured in all adult patients with gynecomastia. DHT is measured in cases of abnormal differentiation of the genitalia and when this is suspected. Semen analysis is of great importance in assessing the fertility and gonadal function of the individual [73].

The cutoff points of normal TT for the diagnosis of hypogonadism in adult males is a subject of discussion between different researchers and medical companies. The Endocrine Society (ES) requires TT values below 280–300 ng/dL to be monitored and repeated measurement of SHBH for the calculation of FT [74]. The ES recognizes that there is variation in the normal values between laboratories and according to the dosage methodology used. As the cutoff for FT, Endocrine Society suggests 5–9 ng/dL. But the consensus established by various international medical societies (International Society of Andrology, International Society for the Study of the Aging Male, European Association of Urology, European Academy of Andrology, American Society of Andrology) presents a different proposition [75]. Symptomatic patients with a TT above 350 ng/dl do not require androgen replacement. If the TT value is below 230 ng/dl, the diagnosis of male hypogonadism is made. However, if the TT result is in the so-called "gray area" (between 230 and 350 ng/dl) dosage of SHBG and calculation of FT are indicated. Hypogonadal patients are considered to be those with a calculated FT below 6.5 ng/dL. Very low values of TT (below 150 ng/dL) should be investigated to rule out secondary hypogonadism or hyperprolactinemia associated with hyperprolactinemia. Recently, Anawalt and coworkers suggested a new "gray area" for TT between 150 and 400 ng/dl [76].

Table 14.6 Conditions associated with changes in serum steroid hormone binding globulin

Decreased concentrations	Obesity
	Nephrotic syndrome
	Hypothyroidism
	Glucocorticoids
	Progestins
	Androgenic steroids
	Acromegaly
	Diabetes mellitus
Increased concentrations	Aging
	Hepatitis and liver cirrhosis
	Hyperthyroidism
	Use of anticonvulsants
	Use of estrogen
	HIV/AIDS

Table 14.7 Vermeulen formula: Calculation of free testosterone

Vermeulen formula: FT = TT (nM/l)/SHBG (nM/l) × 100[a,b]

FT free testosterone, *TT* total testosterone, *SHBG* sex hormone binding globulin

[a]Assuming that the albumin concentration is normal

[b]The calculation of free testosterone, conducted by the formula of Vermeulen, can be obtained at the website: http://www.issam.ch/freetesto.htm

The third step is to measure the level of LH of those who allegedly have an androgen deficiency to determine whether the fault lies at or in the region of the hypothalamic–pituitary–testicular axis. Other laboratory tests and imaging should be evaluated according to each case. On suspicion of testicular diseases, testicular ultrasound can be requested for evaluation of characteristics, location, and associated abnormalities. MRI is performed in suspected cases of CNS diseases and for pituitary evaluation in selected cases. An olfactory test must be performed in order to detect the presence of anosmia, hyposmia, and as part of the evaluation for Kallmann syndrome. Karyotype is indicated in cases of suspected chromosomal abnormalities as part of hypogonadism. Genotyping for known monogenic causes monogenic is currently a research procedure and is not performed in routine clinical practice. It may be performed when there is a specific positive family history or when the patient has phenotypic signs suggestive of a specific mutation. When performed, genetic testing should always be accompanied by genetic counseling.

Treatment

The main goal of treatment of patients with hypogonadism is the re-establishment of sexual function and its subsequent maintenance, along with the secondary sexual characteristics and sexual extra effect of androgens (bone mineral density, muscle hypertrophy, wellness, among others) [77–79]. According to the etiology of hypogonadism, after assessment of the fertility of an individual, one can suggest the induction of spermatogenesis, if there is a desire for fertility.

If primary hypogonadism is diagnosed early, replacement with testosterone is the best option. For congenital secondary hypogonadism, some medical centers recommend starting with gonadotropins to allow the testicles to reach the size at puberty. After testicular growth, the testosterone replacement therapy may be administered until the moment that fertility is desired. Right now, the gonadotropins should be employed in order to To stimulate sperm production, the use of gonadotropins can be helpful [80]. Anti-estrogens may be an alternative therapy; however, their effectiveness has not been adequately tested. In the presence of symptoms of increased estrogen production (gynecomastia and breast tenderness), a short course with the non-aromatizable androgens (dihydrotestosterone, mesterolone, or oxandrolone) may be advisable. However, after a few months of therapy, switching to other aromatizable preparations is recommended to prevent bone loss. When there is concern about the safety of the prostate, the use of steroids or modulators of the nonselective androgen receptor (less susceptible 5α-reductase) may be advisable. One interesting possibility is combined use with inhibitors of testosterone 5α-reductase. Theoretically, Estrogen receptor-beta ligands could be used and studies are underway. however, the development of these compounds, although promising, is still at the preliminary research stage [80].

The major routes of androgen administration [78] are described in the following sections.

Oral Androgens

The use of prepared 17α-alkylated anabolic steroids (fluoxymesterone and methyltestosterone) should not be prescribed because of the high rate of hepatotoxicity. The ester testosterone undecanoate (40–80 mg, 2–3 times daily) is only effective via oral administration owing to its absorption via the lymphatic system, thus minimizing the side effects of its use. The disadvantages are multiple daily doses and variability in serum hormone. It has not been approved for use in the US.

Transdermal Androgens

Marketed since the 1990s, this form is widespread throughout the world and provides ease of use and a close to physiological replacement. Present in the form of gels and adhesives [81].

Testosterone Gel (1%)

Hydroalcoholic formulation, applied in doses of 50–100 mg per day, is applicable in body regions with little hair. It is practical and has good tolerability, allowing flexibility in dosage with few side effects, mostly limited to local irritation. The disadvantages are the potential transfer of the gel to the partner through direct contact with skin [81].

Testosterone Topical Solution (2%) Applied to the Axillae

The 2% formulation of testosterone topical solution, approved by the US Food and Drug Administration (FDA) in November 2010, is a non-occlusive topical formulation administered to the axillae with an applicator instead of the hands. About 5–10% of the testosterone applied to the axilla is absorbed and appears in serum [82].

Transdermal Patches

Both scrotal and nonscrotal, they can be applied once a day, at night. They are easy to apply and can be ready to interrupt if necessary. The gel is less well tolerated owing to the high

rate of local irritation. An area is needed that is clear for adhesion. The application can provide scrotal testicular atrophy light.

Injectable Androgens

The existing drugs on the market are oily formulations that allow an increased dosing interval and the prolongation of the action of the testosterone derivative [83, 84].

– *Testosterone cypionate (200 mg ampoules)*:

An oil formulation that can be safely administered intramuscularly. It elevates serum testosterone levels, reaching a peak serum rapidly around the first 2–5 days with a mean nadir around 15–20 days. Doses are administered at intervals ranging from 2 to 4 weeks, depending on the clinical response of the patient. The advantages are that fewer applications are needed, the low cost, and easy access. The disadvantage is that it does not mimic the physiological hormonal cycle, with supraphysiological levels achieved in the first days after application.

– *Testosterone esters (ampoules containing 250 mg of four esters: propionate, phenylpropionate, testosterone decanoate, and isocaproate)*:

Also an oily formulation that is administered intramuscularly. The mixture of four kinds of testosterone esters with different proportions and peaks of activity confers hormone peaks at different times. Try to avoid the peak supraphysiological initial cycle and get closer to normal hormonal levels. The advantages and disadvantages are similar to those of testosterone cypionate.

– *Undecylate (or undecanoate) testosterone (ampoules 1000* mg*)*:

Oil formulation and administration intramuscularly, using the castor oil vehicle. It shows no peak action and its action is longer, keeping close to physiological levels for a period of 10–14 weeks. At the time of the first application the range for the second dose should be 6 weeks and it settles down after a mean interval between doses of 12 weeks, individually adjusted according to the clinical response and the laboratory. The advantages are mimicry of the normal hormonal cycle, longer duration of action of application, and convenience in dosing. The disadvantage is the high cost.

Subcutaneous Implants

Subcutaneous implants come in the form of pellets. The dose and regimen vary with the formulation used, but generally have a duration of action of about 3–6 months and the dose varies between 150 and 450 mg. The disadvantages are local complications, discomfort, infection at the site of application, and the possibility of extrusion of the pellet. The advantage is dosage for long-term use.

Other forms of treatment

Adhesive oral 30 mg applicable gum twice a day [85]. Another option is the hCG. Although not an androgen, it stimulates the testes to produce testosterone and is especially useful when one wishes to stimulate the production of sperm and hence male fertility.

Male Hypogonadism Associated with T2DM and Obesity: To Treat or Not to Treat?

Only in the last decade, the main consensus on male hypogonadism started adding conditions between T2DM risk for decreased testosterone, drawing attention to the need for the treatment of these patients [74, 75]. The TIMES2 Study is an important work that evaluated hypogonadal patients with T2DM and metabolic syndrome. Their results show a significant decrease in homeostatic model assessment-insulin resistance among hypogonadal diabetic patients after 6 months of treatment with testosterone replacement gel and a better control of HbA1c after 9 months of treatment [86]. Heufelder et al. evaluated hypogonadal men with a newly diagnosed T2DM treated with testosterone and a change in lifestyle (CL) compared with placebo and CL. After 52 weeks, testosterone replacement resulted in better control of HbA1c and a significant reduction in waist measurement (14.6 cm versus a loss of 6.7 cm respectively) [87].

A number of studies demonstrated that treatment of hypogonadism improves weight loss in hypogonadal obesity. Svartberg et al. found in a case–control study an improvement in body shape of elderly hypogonadal men treated with testosterone for 1 year [88]. The study evaluated 184 hypogonadal men with metabolic syndrome from Moscow [89]. After 30 weeks of administration of parenteral testosterone undecanoate, a significant drop in weight, BMI, and waist circumference, as well as improvement of some components of metabolic syndrome and inflammatory markers [89].

Thus, treatment of hypogonadism in obese men can be effective in helping weight loss because it improves energy and mood, reduces fatigue, and may motivate men to adhere to diet and exercise, which is fundamental in combating obesity [90].

Testosterone and Cardiovascular Disease

Longitudinal cohort studies examining the association of sex hormones measured using immunoassays at baseline with the incidence of cardiovascular disease (CVD) events during

follow-up and the results have been controversial [91–93]. In a large population-based cohort of older men, TT or FT in the lowest quartile of values predicted an increased incidence of stroke or transient ischemic attacks [94] whereas higher LH was associated with the incidence of ischemic heart disease events [95]. Most of the studies evaluated older patients and other inclusion criteria were variable and questionable. A small study (also in older men) reported testosterone in the lowest and highest quintiles to be associated with CVD events, suggesting a U-shaped association [96].

In a recent large cohort sex steroids were evaluated using mass spectrometry. In the Osteoporotic Fractures in Men (MrOS) Study, the risk of experiencing a cardiovascular event was 30% lower in men with higher total testosterone [97]. In the Cardiovascular Study, testosterone was not associated with cardiovascular death, or nonfatal myocardial infarction or stroke [98]. In an updated analysis from the Western Australian Health In Men Study (HIMS), testosterone was not associated with incident myocardial infarction and, by contrast, higher testosterone was associated with a lower incidence of stroke [99]. The Atherosclerosis Risk in Communities Study showed that lower testosterone was associated with adverse cardiovascular risk factors, but not with incidence of coronary heart disease events [100]. The recent studies have demonstrated that low testosterone as an independent predictor for higher incidence of stroke in older men has been confirmed by the Copenhagen Study [101].

Cohort studies based on the use of immunoassays for sex steroids provide limited evidence but demonstrate an association of low TT or FT with incidence of stroke and transient ischemic attack [94, 101]. The two largest cohort studies, which measured testosterone using mass spectrometry, reported associations of low testosterone with CVD events in MrOS [97], and stroke in HIMS [99].

Based on current evidence, lower circulating testosterone seems to be a biomarker for CVD risk, particularly an increased incidence of stroke. An age differential should be highlighted. In younger and middle-aged men, lower testosterone levels are associated with adverse cardiovascular risk factors rather than incidence of CVD, whereas in older men, lower testosterone is associated with an increased incidence of CVD manifesting as stroke more prominently than myocardial infarction.

In the last few years, some randomized controlled trials (RCTs) have been published that have shown the effects of testosterone supplementation on protecting against myocardial ischemia. The Testosterone in Older Men with Mobility Limitations (TOM) trial promoted several discussions on the subject due to discontinuous of the trial by the excess of cardiovascular adverse events in the testosterone arm [102]. Others RCTs demonstrated different results than the TOM study [103–109]. In the absence of definitive RCT data, meta-analyses of testosterone RCTs have been undertaken to explore the association between testosterone supplementation and cardiovascular adverse events and, in general, have not found testosterone supplementation to be associated with excess cardiovascular adverse effects [110–115].

Monitoring and Follow-Up

In adolescent or young adult patients, the prostate is not a concern. However, in older men, especially after the age of 40, the prostate should be monitored. Currently, it is known that testosterone replacement does not cause the appearance of prostate cancer in patients who do not have a background for it. However, testosterone and mainly dihydrotestosterone can stimulate prostate tissue [116]. In the last decade, some case series described the use of testosterone therapy in hypogonadal men after treatment for prostate cancer and no clinical or biochemical progression of the tumor. This is not yet an established practice, but it can be a safe treatment in these cases [117–123]. Similarly, with increasing recognition that men with low-grade prostate cancer are at a low risk for morbidity and mortality, there is a growing practice of deferring treatment until there is evidence for more aggressive pathology (active surveillance) Some of these men have symptomatic testosterone deficiency and desire treatment, but the use of testosterone replacement therapy in these men is highly controversial, although small studies have shown some that it is somewhat safe to use [124–126].

Initiation of testosterone therapy is not recommended in men with breast cancer or prostate cancer, with a palpable nodule or indurations, with prostate-specific antigen (PSA) greater than 4 ng/ml or undiagnosed urological treatment, hematocrit above 50%, obstructive sleep apnea, severe, untreated urinary tract symptoms with an International Prostate Symptom Score over 19, heart failure, uncontrolled or poorly controlled (Table 14.8) [74].

Table 14.8 Conditions in which testosterone replacement is associated with a high risk for adverse events and should be contraindicated

High risk for adverse events (absolute contraindication)	Metastatic prostate cancer or activity
	Breast cancer
Moderate risk for adverse events (relative contraindication)	Palpable nodule or induration prostate
	Prostate-specific antigen greater than 4 ng/ml or undiagnosed urological treatment (or greater than 3 ng/ml in subjects at a high risk for prostate cancer, such as African Americans or men with first-degree relatives with a history of prostate cancer)
	Hematocrit above 50%
	Obstructive sleep apnea, severe, untreated
	Severe urinary tract symptoms (International Prostate Symptom Score above 19)
	Heart failure, uncontrolled or poorly controlled

Table 14.9 Monitoring testosterone therapy

1. Evaluate the patient 3–6 months after treatment initiation and then annually to assess whether symptoms have responded to treatment and whether the patient is suffering from any adverse effects
2. Monitor testosterone level 3–6 months after initiation of testosterone therapy
Therapy should be aimed at raising serum testosterone level to the mid-normal range
Injectable testosterone enanthate or cypionate: measure serum testosterone level midway between injections. If testosterone is >700 ng/dl (24.5 nmol/l) or <400 ng/dl (14.1 nmol/l), adjust dose or frequency
Transdermal patches: assess testosterone level 3–12 h after application of the patch; adjust dose to achieve testosterone level in the mid-normal range
Buccal testosterone bioadhesive tablet: assess level immediately before or after application of fresh system
Transdermal gels: assess testosterone level any time after the patient has been on treatment for at least 1 week; adjust dose to achieve serum testosterone level in the mid-normal range
Testosterone pellets: measure testosterone levels at the end of the dosing interval. Adjust the number of pellets and/or the dosing interval to achieve serum testosterone levels within the normal range
Oral testosterone undecanoate[a]: monitor serum testosterone level 3–5 h after ingestion
Injectable testosterone undecanoate: measure serum testosterone level just prior to each subsequent injection and adjust the dosing interval to maintain serum testosterone within the mid-normal range
3. Check hematocrit at baseline, at 3–6 months, and then annually. If hematocrit is >54%, stop therapy until hematocrit decreases to a safe level; evaluate the patient for hypoxia and sleep apnea; reinitiate therapy with a reduced dose
4. Measure bone mineral density of lumbar spine and/or femoral neck after 1–2 years of testosterone therapy in hypogonadal men with osteoporosis or low trauma fracture, consistent with regional standard of care
5. In men 40 years of age or older with baseline PSA greater than 0.6 ng/ml, perform digital rectal examination and check PSA level before initiating treatment, at 3–6 months, and then in accordance with guidelines for prostate cancer screening depending on the age and race of the patient
7. Obtain urological consultation if there is:
An increase in serum PSA concentration >1.4 ng/ml within any 12-month period of testosterone treatment
A PSA velocity of >0.4 ng/ml year using the PSA level after 6 months of testosterone administration as the reference (only applicable if PSA data are available for a period exceeding 2 years)
Detection of a prostatic abnormality on digital rectal examination
An AUA/IPSS of >19
8. Evaluate formulation-specific adverse effects at each visit
Buccal testosterone tablets: inquire about alterations in taste and examine the gums and oral mucosa for irritation
Injectable testosterone esters (enanthate, cypionate, and undecanoate): ask about fluctuations in mood or libido, and rarely coughing after injections
Testosterone patches: look for skin reaction at the application site
Testosterone gels: advise patients to cover the application sites with a shirt and to wash the skin with soap and water before having skin-to-skin contact, because testosterone gels leave a testosterone residue on the skin that can be transferred to a woman or child who might come in close contact. Serum testosterone levels are maintained when the application site is washed 4–6 h after application of the testosterone gel
Testosterone pellets: look for signs of infection, fibrosis, or pellet extrusion

[a]Not approved for clinical use in the USA
PSA prostate-specific antigen, *AUA/IPSS* American Urological Association/International Prostate Symptom Score

When testosterone therapy is instituted, one should achieve the average normal levels of testosterone during treatment with any of the formulations adopted. The choice of formulation of testosterone must take into account the patient's preference, the pharmacokinetics, and the cost. Men receiving testosterone therapy should be monitored continuously through a standardized plan that includes medical consultation with a physical examination and laboratory tests (PSA and hematocrit; Table 14.9) [74].

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