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Review/ Derleme

Diagnosis and Treatment of Primary, Secondary, and Functional Male Hypogonadism: A Narrative Review

Birincil, İkincil ve Fonksiyonel Erkek Hipogonadizminin Tanı ve Tedavisi: Anlatısal Derleme

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ABSTRACT

Male hypogonadism refers to a condition characterized by reduced testosterone production or impaired sperm production. Traditionally, it was classified into two categories: congenital and acquired hypogonadism. However, with the emergence of the concept of functional hypogonadism, which develops as a result of chronic diseases, medications, or aging, male hypogonadism is now considered under three subtypes.

The clinical manifestations and treatment strategies vary depending on the underlying cause of hypogonadism. Additionally, the desire for fertility significantly influences the treatment protocol.

This systematic review examines the diagnostic and therapeutic approaches to primary, secondary, and functional male hypogonadism.

Keywords: Testosterone, Functional Hypogonadism, Fertility, Androgen Deficiency, Aging, Late-Onset Hypogonadism

ÖZET

Erkek hipogonadizmi, testosteron üretiminin azalması veya spermatogenezde bozulma ile karakterize bir durumdur. Geleneksel olarak konjenital ve edinsel olmak üzere iki grupta sınıflandırılsa da, kronik hastalıklar, bazı ilaçlar veya yaşlanma sonucunda gelişen fonksiyonel hipogonadizm kavramının ortaya çıkmasıyla birlikte, günümüzde üç alt tipe ayrılmaktadır.

Hipogonadizmin altta yatan nedenine bağlı olarak klinik bulgular ve tedavi yaklaşımları değişkenlik göstermektedir. Ayrıca, hastanın fertilite isteği de tedavi protokolünü önemli ölçüde etkilemektedir.

Bu sistematik derlemede, primer, sekonder ve fonksiyonel erkek hipogonadizmine yönelik güncel tanı ve tedavi yaklaşımları ele alınmaktadır.

Anahtar Kelimeler: Testosteron, Fonksiyonel Hipogonadizm, Fertilite, Androjen Eksikliği, Yaşlanma, Geç Başlangıçlı Hipogonadizm

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Male Hypogonadism

Male hypogonadism is characterized by a reduction in one or both of the two primary functions of the testes: sperm production and testosterone production. This condition may result from testicular diseases (primary hypogonadism) or from disorders in the hypothalamic-pituitary axis (secondary hypogonadism)(1).

The diagnosis of androgen deficiency requires the presence of low testosterone levels together with specific and/or non-specific symptoms attributable to androgen deficiency. After establishing the diagnosis of hypogonadism, serum luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels are measured to determine whether the hypogonadism is primary or secondary(1).

In primary hypogonadism, testosterone and/or sperm count are low while LH and/or FSH are elevated; in secondary hypogonadism, testosterone and/or sperm count are low while LH and/or FSH are normal or low. Making this distinction is of critical importance for determining the underlying etiology and selecting the appropriate therapeutic approach(1).

Although comprehensive epidemiological data regarding the prevalence of male hypogonadism in Turkey are limited, the European Male Aging Study (EMAS) conducted in Europe provides important findings. In this large-scale study, the prevalence of late-onset hypogonadism (LOH) was found to be 2.1% among 2,966 men aged 40-79 years. A distinct increasing pattern is observed in prevalence distribution by age groups, with hypogonadism detected at rates of 0.1% in the 40-49 age group, 0.6% in the 50-59 age group, 3.2% in the 60-69 age group, and 5.1% in the 70-79 age group(2).

The overall prevalence of hypogonadism ranges between 6-12%, with this variability depending on the study population and the stringency of diagnostic criteria(3). Current epidemiological data demonstrate that hypogonadism is present in approximately 35% of men over 45 years of age and in 30-50% of men with obesity or type 2 diabetes mellitus(1).

Table 1: Congenital and acquired causes of primary (hypergonadotropic) and secondary (hypogonadotropic) hypogonadism

Primary (hypergonadotropic) hypogonadism	Secondary (hypogonadotropic) hypogonadism
Congenital causes • Chromosomal anomalies • Klinefelter syndrome • Mutations in FSH and LH receptor genes • Cryptorchidism, anorchia • Myotonic dystrophy • Disorders of androgen synthesis	**Congenital causes** • Isolated GnRH deficiency • Congenital hypogonadotropic hypogonadism (with anosmia - Kallmann syndrome - or without anosmia) • GnRH deficiency associated with intellectual disability and obesity 1. Laurence-Moon-Biedl syndrome 2. Prader-Willi syndrome • Idiopathic deficiencies of anterior pituitary hormones • Congenital malformations associated with craniofacial anomalies
Acquired causes • Infections (particularly mumps) • Radiation exposure • Medications (ketoconazole, alkylating agents) • Trauma • Testicular torsion • Autoimmune damage • Chronic diseases (cirrhosis, chronic kidney failure) • Environmental toxins • Idiopathic	**Acquired causes** • Tumors (benign tumors, cysts, germinomas, meningiomas, craniopharyngiomas, metastatic tumors) • Functional gonadotropin deficiency (chronic systemic diseases, acute illnesses, malnutrition, eating disorders, hypothyroidism, hyperprolactinemia, diabetes mellitus, Cushing's disease, medications) • Pituitary apoplexy • Head trauma

Classification of Male Hypogonadism

Due to the increasingly widespread use of genetic testing, the classification of male hypogonadism has become more complex and detailed. While classical approaches divided hypogonadism into congenital and acquired causes, recent updates have added functional hypogonadism as a third group to the list. Under the heading of functional hypogonadism, the effects of chronic diseases, medications, and aging on androgen and sperm production are examined. Table 1 examines the congenital and acquired causes of primary and secondary hypogonadism(4).

Primary Hypogonadism

The most common congenital cause of primary hypogonadism is Klinefelter syndrome with an incidence of 1:500-1000 live births . In addition to the classic 47,XXY karyotype, mosaic forms (46,XY/47,XXY) and rarely seen variants (48,XXXY, 49,XXXXY) exist(5). The clinical presentation is highly variable depending on mosaicism, polymorphisms in the androgen receptor gene, paternal X chromosome copy number, and which X chromosome is inactivated(6, 7). AMH and inhibin B, which are biomarkers of Sertoli cells, begin to decrease in the early pubertal period before testosterone starts to decline. Due to inhibin B deficiency, FSH is always higher than LH. Initially, while testosterone is normal, only elevated/normal LH may be observed; as testosterone decreases, LH continues to rise (8). Risk is increased for SLE, RA, Sjögren syndrome, Hashimoto thyroiditis, breast cancer, diabetes mellitus, osteoporosis, venous thromboembolism, essential tremor, Parkinson's disease, non-Hodgkin lymphoma, and certain lung cancers; however, prostate cancer risk is reduced compared to the general population (9). As the X copy number increases in individuals, the risk of anomalies and intellectual disability increases (10). Peripheral leukocyte karyotyping may be sufficient for diagnosing classic types; fibroblast cultures from areas close to external genital organs may be required in controversial cases(11).

In FSH receptor mutations, which are among gonadotropin receptor gene mutations, FSH cannot exert its effect due to inactivating mutations in FSH receptors on Sertoli cells, resulting in low sperm count and low inhibin B levels. In LH receptor mutations, mutations in LH receptors on Leydig cells result in low testosterone levels. These patients show a decreased/insufficient testosterone response to hCG stimulation test(12).

In cryptorchidism, another cause of primary hypogonadism, testicular descent cannot be achieved due to mutations in the insulin-like 3 and LGR8 (leucine-rich G-protein associated receptor 8) genes responsible for testicular descent into the scrotum. Even when corrective surgeries are performed in the prepubertal period, subnormal sperm count is observed in unilateral defects, and markedly low sperm count and low testosterone are observed in bilateral defects(13, 14).

Disorders of enzymes responsible for androgen synthesis are among the congenital causes of primary hypogonadism: 3β-hydroxysteroid dehydrogenase, 17α-hydroxylase, 17β-hydroxysteroid dehydrogenase type 3, and 17,20 lyase enzyme constitute these enzymes(15).

In androgen insensitivity syndrome, testosterone and DHT resistance is observed at the tissue level. Clinically, it may present with insufficient virilization or completely female external genitalia. Due to SRD5A2 gene mutation, 5α-reductase type 2 enzyme cannot perform the conversion from testosterone to DHT(16, 17).

In myotonic dystrophy, small testes and decreased sperm production are observed due to increased repetitive glutamine sequences in androgen receptors; low testosterone levels accompany supranormal FSH levels(18).

Acquired causes of primary hypogonadism include infections, radiation, chemotherapy (cyclophosphamide, chlorambucil, cisplatin, busulfan), radioactive iodine therapy, medications, and environmental toxins (dibromochloropropane, pesticides, ethinyl estradiol, octylphenol, nonylphenol, plastic-phthalate, combustible substances, industrial pollutants)(19-23).

Secondary Hypogonadism

Among congenital causes, there are different conditions with or without GnRH deficiency.

Conditions Associated with GnRH Deficiency

Kallmann Syndrome: Leads among conditions presenting with GnRH deficiency and accompanying anosmia. Its prevalence is 1:30,000 in males and 1:125,000 in females (24). From a genetic perspective, it has been associated with at least 25 different genes(25).

Anosmic Forms (frequently associated with anosmia):

- ANOS1(KAL1), SEMA3A, SOX10, IL17RD, FEZF1

Normosmic Forms (preserved sense of smell):

- GNRHR, GNRH1, KISS1R, KISS1, TAC3, TAC3R, LEPR, LEP, DMXL2, OTUD4, RNF216, STUB1, POLR3B, PNPLA6, NR0B1

Variable Sense of Smell (may be impaired or normal):

- FGFR1/FGF8, PROKR3/PROK2, CHD7, NSMF, HS6ST1, FGF17, SPRY4, DUSP6, FLRT3, WDR11, AXL

Pathophysiology: Anosmic gene mutations are responsible for the migration and organization of GnRH-producing neurons, while anosmic gene mutations are responsible for regulating the pulsatile release of GnRH and the regulation of GnRH's effects on LH-FSH(26).

Clinical Findings: Anosmic Kallmann syndrome patients tend to develop a more severe and complex phenotype compared to normosmic HH patients. Additional findings may include bimanual synkinesis, orofacial cleft, dental developmental anomalies, renal anomalies, and hearing loss(27).

Reversibility: In some KS/HH cases, it has been reported that the HPG axis regains normal function in adulthood and GnRH, LH, FSH levels return to normal (in 10-22% of cases)(28).

Hypogonadotropic Hypogonadism Without GnRH Deficiency

Genes responsible for this condition: HESX1, LHX3, PROP1, FSHβ, LHβ, SF1, PC1(29).

LHβ Subunit Gene Mutations: In some families, LH secretion is preserved but LH binding to the receptor is impaired; in another group, LH dimerization is disrupted due to mutation and cannot be secreted, resulting in low serum LH levels(30, 31).

FSHβ Subunit Gene Mutations: Delayed puberty, low testosterone and FSH but high LH are observed. It is concluded that normally functioning Sertoli cells are needed for normal Leydig cell function(32).

Causes leading to gonadotroph cell damage include malignant tumors, benign tumors, cysts, adenomas, metastasis, hemochromatosis, infection, apoplexy, trauma located in the pituitary and hypothalamus(29, 33).

Clinical Features and Physical Examination Findings

Physical examination findings of the patient provide important diagnostic clues in determining the etiology. Due to testosterone having different physiological roles in fetal, prepubertal, and postpubertal adult life, clinical signs and physical examination findings of androgen deficiency show marked differences depending on the stage of sexual development and age(1).

Fetal Period Hypogonadism

In cases of hypogonadism occurring during the fetal period, various degrees of genital anomalies are observed as a result of insufficient male sexual differentiation. This spectrum may include findings such as ambiguous genitalia, micropenis, hypospadias, bifid scrotum, and cryptorchidism, and in severe cases, may present with completely normal-appearing female genitalia(4).

Prepubertal Period Hypogonadism

When androgen deficiency develops during the prepubertal period, delayed puberty, loss of libido, decreased spontaneous erections, gynecomastia, decreased physical performance, ejaculatory dysfunction, infertility, aspermia, oligospermia, and azoospermia are observed. Alongside these findings, important changes in physical appearance occur: eunuchoidal habitus (lower body being longer than upper body due to delayed epiphyseal closure

secondary to testosterone deficiency), infantile genitalia, small testicular volume, lack of male-pattern hair development, absence of acne, poor muscle development, lack of voice deepening, decreased peak bone mass/osteoporosis/osteopenia, gynecomastia, small prostate size. Additionally, these physical findings are accompanied by decreased motivation, depressive mood, irritability, and psychosocial adjustment difficulties(4).

Postpubertal Period Hypogonadism

When hypogonadism develops in the postpubertal period, the majority of cases represent late-onset hypogonadism. In these patients, sexual symptoms may include decreased libido, reduced sexual activity, decreased morning erections, and infertility along with spermatogenesis disorders (aspermia, azoospermia, and oligospermia). Physical examination findings can vary depending on the onset and severity of hypogonadism. In late-onset hypogonadism, which constitutes the majority of postpubertal cases, findings such as eunuchoidal habitus, significantly small testicular volume (<6 ml), and markedly decreased prostate volume are typically not observed. These findings are more characteristic of prepubertal hypogonadism or may be seen in cases of severe, early postpubertal hypogonadism(4).

Late-onset hypogonadism patients may present with more subtle findings including mild to moderate testicular volume reduction, hair loss, decreased body hair, gynecomastia, decreased muscle strength, reduced physical strength and performance, osteopenia/osteoporosis, increased low-trauma fracture risk, and height loss. Anemia might also be detected. In severe cases, metabolic syndrome findings may be observed. Additionally, vasomotor symptoms such as decreased energy, depression, sleep disorders, sweating, and hot flashes can accompany the clinical picture(4).

Clinical Approach and Diagnostic Evaluation

In addition to complaints and clinical findings, the patient's comorbidities, previous illnesses, medications used, previous surgical interventions, and family history should be thoroughly questioned. In physical examination, anthropometric measurements, breast, testis, and scrotal examinations should be carefully performed.

Normal prepubertal testicular volume is less than approximately 4 ml. Testicular size greater than 4 ml indicates the onset of puberty. In adults, normal testicular volume ranges between 15-30 ml. In males with Klinefelter syndrome, testes are palpated as small (usually <3 ml) and firm in consistency. The use of the Tanner Sexual Maturity Rating (SMR) scale during adolescence is helpful both in making the diagnosis and evaluating the response to treatment. Olfactory testing should also be performed in patients suspected of congenital hypogonadotropic hypogonadism(34).

Although symptoms may be more subtle in adults, height measurements and direct radiography when necessary may be useful to detect bone fractures due to osteoporosis and reveal height loss. Standardized scoring systems such as the Aging Male Symptoms Score (AMS) and International Prostate Symptom Score (IPSS) can be used in clinical evaluation and treatment follow-up(35).

Testosterone Measurement: Technical Considerations and Standardization

Testosterone measurement should be performed between 8-11 AM while the patient is fasting. Since testosterone levels can be affected by daily circadian rhythm, ultradian fluctuations, seasonal changes, and various external factors, a standardized protocol is required. Therefore, results should be confirmed with two low testosterone values measured before 11:00 AM at least 1 week apart. Testosterone measurement should not be performed during acute illness periods; this may lead to falsely low results. Biotin use should definitely be questioned before testosterone measurement(1).

The definition of biochemical testosterone deficiency varies considerably among international guidelines, reflecting ongoing debate in the field. The American Urological Association (AUA) recommends using 300 ng/dL (10.4 nmol/L) as the threshold for diagnosing hypogonadism, while the Euro-

pean Association of Urology (EAU) adopts a higher cutoff of 12 nmol/L (approximately 350 ng/dL). The Endocrine Society does not specify a single definitive threshold, instead suggesting a range between 230-346 ng/dL as potentially indicative of deficiency. These threshold values are generally established for measurements using liquid chromatography-tandem mass spectrometry (LC-MS/MS), considered the gold standard for testosterone measurement. However, since this methodology is not universally available, inter-laboratory measurements may vary by approximately 20%, further complicating diagnostic standardization. Additionally, it has been suggested that these threshold values may need reconsideration for younger men (20-44 years), as current cutoff points were primarily derived from studies in older populations and may not adequately reflect age-specific variations in testosterone levels(26, 36)

Sex Hormone-Binding Globulin (SHBG) and Free Testosterone

Approximately 98% of testosterone circulates bound to plasma proteins; 60% is bound to SHBG with high affinity, and 38% is bound to albumin with low affinity. Only the 2% free fraction is biologically active. Since changes in SHBG levels can affect total testosterone levels, free testosterone measurement is recommended for accurate assessment of hypoandrogenemia when conditions that alter SHBG levels are detected(37, 38).

Table 2: Conditions Affecting SHBG Levels

Decreased SHBG	Increased SHBG
Obesity	Advanced age
Type 2 Diabetes Mellitus	Hepatitis, cirrhosis
Nephrotic syndrome	Estrogens
Glucocorticoids	Hyperthyroidism
Progestins, Androgens	Anticonvulsant medications
Untreated hypothyroidism	HIV infection
Acromegaly	Smoking
SHBG gen mutation/polymorpism	

3. Free Testosterone Measurement Methods

The gold standard method for measuring free testosterone levels is equilibrium dialysis or centrifugal ultrafiltration. However, since these methods are not always feasible, free testosterone can be calculated using the Vermeulen formula when albumin, SHBG, and total testosterone levels are known. It has been proven that free testosterone values calculated with the Vermeulen formula show very good correlation with equilibrium dialysis and represent a reliable and rapid method in clinical practice.

If the calculated free testosterone from the measurement is <6.5 ng/dL (<225 pmol/L), biochemical testosterone deficiency is demonstrated(39). However, it should be remembered that calculated free testosterone values may show discordance with equilibrium dialysis when SHBG concentration is high(1).

Table 3: Individuals Who Should Be Investigated for Hypogonadism with Total Testosterone Measurement

Presence of androgen deficiency symptoms and findings
Pituitary mass, pituitary radiotherapy, or other sellar diseases
Treatments with medications that affect testosterone (Glucocorticoids and Opioids)
HIV-related weight loss
End-stage renal failure and ongoing hemodialysis treatment
Moderate to severe chronic obstructive pulmonary disease
Osteoporosis or low-trauma fracture (especially in young men)
Type 2 diabetes mellitus and other metabolic diseases
Sexual dysfunction (1, 2)

Diagnostic Process and Criteria

The diagnosis of hypogonadism is made in men who have symptoms and findings consistent with androgen deficiency and have low testosterone levels on at least 2 occasions. In men with confirmed hypogonadism, serum LH and FSH measurements should be performed to distinguish primary hypogonadism from secondary hypogonadism. In primary

hypogonadism, elevated FSH and LH levels accompany low testosterone, while in secondary hypogonadism, low or inappropriately normal FSH-LH levels accompany low testosterone levels.

Aging, systemic diseases, and medications can combinedly cause primary and secondary hypogonadism. The hCG stimulation test, one of the diagnostic auxiliary tests, has an important place in secondary hypogonadism; it demonstrates whether the testes can function and whether treatment can be performed with gonadotropins(1, 3)

Screening and Risk Groups

General population screening for androgen deficiency is not recommended; however, high-risk groups are excluded from this recommendation(1, 29)

Additional Diagnostic Evaluations

In individuals with fertility desire who are found to have hypogonadism, semen analysis should be requested immediately to demonstrate the degree of impairment in sperm production. In men with hypogonadism who have experienced low-trauma or fragility fractures, DEXA scanning should be performed to evaluate bone mineral density to exclude osteopenia or osteoporosis(40).

In individuals with suspected secondary hypogonadism, it is recommended to measure serum prolactin levels to exclude prolactinoma, measure transferrin saturation and ferritin to exclude hemochromatosis, and add pituitary MRI and additional metabolic tests to the process in unexplained cases to avoid missing other endocrine diseases. In cases with suspected primary hypogonadism, karyotype analysis must be performed(5, 41).

Treatment

The goals of hypogonadism treatment are: achieving virilization and fertility, providing/improving sexual functions, improving general health status, preventing osteoporosis, and reducing cardiovascular disease risk(1).

The target testosterone level with treatment is in the range of 350-750 ng/dl (12-26 nmol/L), with the most ideal target stated as 450-600 ng/dl (15.6-20.8 nmol/L). It is recommended to apply more conservative targets (300-500 ng/dl) in elderly men(1, 42, 43).

Before starting treatment, the patient should be consulted to understand whether fertility is their primary desire. While only testosterone replacement therapy is recommended in men with primary hypogonadism since the damage cannot be reversed, gonadotropin treatments come into play if there is a desire for fertility in secondary hypogonadism(1, 42).

Testosterone Replacement Therapy (TRT)

The following testosterone preparations are available in Turkey:

- Testosterone undecanoate 1000 mg intramuscular form (every 10-14 weeks)
- Testosterone cypionate 250 mg intramuscular form (every 3 weeks)
- Testosterone gels (each sachet contains 50 mg testosterone)

Formulation Characteristics:
Oral Testosterone Forms

- Conventional oral testosterone: Metabolized very rapidly by the liver, difficult to maintain stable serum concentrations, and carries risk of hepatotoxicity.
- Oral testosterone undecanoate: Does not carry risk of hepatotoxicity, absorbed through the lymphatic system, bypasses first-pass metabolism in the liver, recommended to be taken with meals in a 2x1 regimen.

Injectable Ester Forms

- Testosterone propionate, testosterone phenylpropionate, testosterone isocaproate, testosterone decanoate : Contains 30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate in a 1 ml oil solution, available as 250 mg IM injection every 3-4 weeks in our country. This mixed ester formulation is designed to provide both rapid and sustained testosterone release. However, due to the different pharmacokinetic profiles of its components, testosterone levels initially rise to supraphysiological levels within days after injection, followed by gradual decline. These fluctuations may cause

side effects such as mood swings and variations in sexual desire in some patients.

• Testosterone undecanoate IM: Second dose is administered 4 weeks after the first dose, then every 10-14 weeks. Blood testosterone levels always remain at physiological doses, but there is a risk of pulmonary fat embolism due to high injection volume.

Topical Forms

• Gel preparations: Available in 1%, 1.6%, and 2% concentrations, applied once daily to hairless skin areas (shoulder, upper arm, or abdomen). The gel dries within 5 minutes after application, with serum testosterone levels rising after 30 minutes due to rapid absorption. Patients can shower 4-6 hours post-application.Due to alcohol content, the gel should not be applied to mucosal surfaces. Application to the genital area is contraindicated because of high 5-alpha reductase enzyme activity in this region, which increases the risk of androgenic side effects (acne, seborrhea, alopecia, and prostatic effects). Additionally, this helps minimize potential transfer to partners.Increasing the surface area of application can result in 20-30% variation in absorption levels. While gel formulations provide stable testosterone levels, potential drawbacks include risk of interpersonal transfer and local skin irritation(44).

Other Forms (Not Available in Turkey)

• Transdermal patches: 1 patch contains 4 mg testosterone, changed every 24 hours.

• Buccal testosterone: 2x30 mg, provides slow release.

• Intranasal testosterone: 3x1 to both nostrils, starting with a daily dose of 33 mg is recommended.

• Subcutaneous pellets: Not routinely recommended due to requiring surgical procedure and need for renewal every 3-6 months.

To evaluate TRT efficacy, measurement of total testosterone level 3 months after treatment initiation is recommended. The target is 450-600 ng/dl. Measurement timing varies according to preparation type:

• IM ester forms: Between 2 doses

• Gels and patches: 4-12 hours after application

• Oral undecanoate: 6 hours after intake(1).

If testosterone level is in the target range and stable, measurement every 6-12 months is sufficient(3, 42).

Table 4: Conditions where TRT is contraindicated(1)

Patients with fertility desire
History of invasive advanced-stage prostate cancer
Patients with severe lower urinary tract symptoms due to benign prostatic hyperplasia
PSA >4 ng/dL or >3 ng/dL in high-risk groups
Presence of breast cancer in males
Presence of severe sleep apnea syndrome
Initial hematocrit >50%
History of thrombophilia
History of stroke or myocardial infarction within the last 6 months
Presence of New York Heart Association Class IV heart failure

Dose Monitoring

Men started on TRT should be evaluated for polycythemia every 3-6 months. If hematocrit value is >54%, discontinuation/cessation of TRT is recommended, and when it returns to normal range, treatment should be continued at the same dose or lower dose(1).

Prostate gland follow-up, especially when TRT is started in men over 50 years:

• Should be performed at the 3rd month, 12th month of treatment, and annually thereafter.

• Physical examination, IPSS score, and PSA should screen for prostate cancer

• If PSA value increases by 1.4 ng/ml compared to the value from 1 year ago or PSA >4 ng/ml is detected, urology consultation is required(1, 45).

Regarding cardiovascular safety, the TRAVERSE study (2023) is the largest randomized controlled study conducted on 5,246 men with hypogonadism and high cardiovascular risk. According to study results, no increase in major cardiovascular events

was found in the TRT group compared to the placebo group. However, numerical increases in non-fatal arrhythmia, atrial fibrillation, and acute kidney failure events were observed in the TRT group(46, 47).

In patients receiving TRT, fasting blood glucose, glycolyzed hemoglobin, and lipid levels should also be evaluated every 3-6 months. Sleep apnea should be evaluated every 3-6 months, and polysomnography should be recommended if necessary when disease suspicion exists. Regarding changes in bone density, bone mineral densitometry measurement is recommended 2 years after starting TRT(45, 48).

Gonadotropin Therapies

Gonadotropin therapies are used in hypogonadotropic hypogonadism patients to achieve fertility and correct androgen deficiency. Spermatogenesis can be achieved in 64-80% of males with congenital hypogonadotropic hypogonadism after gonadotropin therapy, typically within 14 months .Among those achieving spermatogenesis, 92% prove fertile, with 71% of pregnancies occurring despite sperm counts <20×10^6/ml .While some couples (7-12%) achieve natural conception during treatment, many require assisted reproductive techniques, with IVF/ICSI success rates of approximately 63% Induction of spermatogenesis in men with hypogonadotropic hypogonadism .Overall, ART in CHH patients yields pregnancy rates of 46%, with outcomes comparable to other infertility causes(45, 49, 50).

Table 5: Novel androgen therapies

7α-methyl-19-nortestosterone Does not interact with 5α-reductase enzyme More limited effect on prostate tissue May provide advantage in patients with BPH(55, 56).
SARM (Selective Androgen Receptor Modulators) Phase 3 clinical trials are ongoing Shows agonist effects on bone and muscle while showing antagonist effects on prostate Appears promising in patients receiving androgen deprivation therapy(57)

Available Preparations

- hCG: 1500-2000-5000 IU, 2-3 times/week IM/SC
- rhCG/chorionic gonadotropin alfa: 250 mcg, 1-2 times/week SC
- pFSH: 75-150 IU, 2-3 times/week SC
- rFSH: 75-150-300-600-900 mcg, 75-150 IU 2-3 times/week SC
- hMG: 75-150-600-1200 IU, 2-3 times/week IM/SC

Treatment Protocol

- Initial: hCG 1000-2000 IU IM 2-3 times/week
- After 6-12 months with insufficient response: 75 IU FSH 3 times/week is added
- Insufficient sperm count: Can be increased to 150 IU
- Spermatogenesis induction may extend up to 18-24 months

Agents that Increase Gonadotropin Levels SERMs and Aromatase Inhibitors:

- Clomiphene citrate: 25-50 mg/day
- Anastrozole: 1 mg/day
- Letrozole: 2.5 mg/day
- Exemestane: 25 mg/day

These agents may be particularly beneficial in men with obesity and metabolic disorders but are off-label use, and SERMs may increase the risk of venous thromboembolism(1, 42).

Treatment in Functional Hypogonadism

Functional hypogonadism is defined as borderline low testosterone levels developing due to aging and/or comorbid conditions such as obesity, diabetes, and metabolic syndrome. In this condition, the first goal of treatment should be correcting the underlying causes. Achieving ideal body weight and correcting pathological fat distribution is the priority goal. It has been shown that 7-10% weight loss significantly increases testosterone levels (52). Particularly resistance exercises are effective in increasing testosterone levels. It has been shown that 160 minutes of exercise per week improves testosterone levels in obese men (51). Quality sleep for 7-9 hours daily is critical for testosterone secretion. Additionally, cessation of smoking and alcohol use, achieving glycemic control, blood pressure regulation, and normalizing lipid profile are important.

In the presence of obesity and diabetes, metformin can increase testosterone levels by reducing insulin resistance. In studies with liraglutide, a GLP-1 receptor agonist, significant increases in LH and FSH levels were found along with an average weight loss of 7.9 kg(52). If weight loss cannot be achieved despite all conservative treatments, bariatric surgery can be planned considering patient preference.

If hypogonadism persists despite lifestyle changes and treatment of comorbidities:

In Patients Without Fertility Expectations:

- TRT: Testosterone gel forms should be preferred (51)
- SERMs (Clomiphene citrate 25-50 mg/day): Requires intact HPG axis
- Aromatase inhibitors: Off-label use, caution due to venous thromboembolism risk

In Patients With Fertility Expectations:

- hCG therapy: 1000-2000 IU 2-3 times/week IM/SC
- If insufficient response after 6 months: hMG (75 IU 3 times/week) is added
- If fertility cannot be achieved with at least 2 years of combined treatment, assisted reproductive techniques are recommended (50)

Late-Onset Hypogonadism Treatment (Over 65 Years)

Future fertility expectations should be questioned in men over 65 years, and sperm cryopreservation should be recommended if fertility is desired. Treatment should be individualized considering the person's risk factors, and appropriate preparation and dose should be selected. The goal is to maintain target testosterone levels in the range of 350-600 ng/dl and achieve symptom regression(53).

In the comprehensive Testosterone Trials (TTrials) study conducted on hypogonadal men over 65 years (n=790), testosterone gel (target: 400-600 ng/dl) was compared with placebo for 1 year: (54)

Positive Effects:

- Sexual function: Increased sexual desire, but no improvement in ED was found
- Bone health: Increased bone mineral density, especially in lumbar spine and hip region
- Depression: Improvement in depressive mood scores
- Anemia: Significant improvement in favor of TRT (47).

Limited/Negative Effects:

- Physical function: No difference between groups was found in the 6-minute walk test
- Cognitive function: No improvement was observed in memory and cognitive functions
- Cardiovascular effects: Increase in non-calcified coronary plaque and total coronary plaque volume, but no difference was found in coronary calcification score (46).

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