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TESTOSTERONE REPLACEMENT THERAPY IN MEN WITH HYPOGONADISM – REVIEW OF LITERATURE

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ABSTRACT

Testosterone replacement therapy (TRT) is the fundamental intervention in the treatment of male hypogonadism. Despite many years of clinical experience, in recent years the benefits and risks of TRT have been intensely discussed. The aim of this review article is to summarize the current state of knowledge on the pathophysiology of hypogonadism, diagnostic criteria, indications and effects of therapy, taking into account different patient groups. An analysis of available scientific publications was conducted, including clinical trials, meta-analyses, and official expert guidelines. The results of the review indicate that testosterone therapy significantly improves sexual function in men (including libido and erection) and has a beneficial effect on well-being. An increase in muscle mass, improvement in body composition (increase in lean mass and reduction of visceral fat), and also an increase in bone mineral density were observed. At the same time, attention is drawn to possible adverse effects of TRT, such as the development of polycythemia (elevated hematocrit), inhibition of sperm production, and potential exacerbation of obstructive sleep apnea symptoms in some patients. Testosterone therapy can bring significant benefits in the treatment of hypogonadism, especially in terms of improving sexual function and overall quality of life. However, the choice of treatment should be tailored to the patient in each case, taking into account possible risks, such as cardiovascular risk or impact on fertility. Due to remaining uncertainties, further prospective studies are necessary to more precisely assess the long-term safety of testosterone therapy.

KEYWORDS

Hypogonadism, Testosterone, Testosterone Replacement Therapy, Metabolic Syndrome, Diabetes, Fertility, Controversies

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Introduction

Hypogonadism in men is described as a disorder of testicular function in testosterone production, which causes a deficiency of this hormone due to abnormalities at one or multiple levels of the hypothalamic-pituitary-testicular (HPG) axis. Depending on the location of the defect, we distinguish primary or secondary hypogonadism. Abnormalities within the testes correspond to primary hypogonadism, whereas pituitary or hypothalamic disorders correspond to secondary hypogonadism (1). Excluding older individuals, hypogonadism occurs in approximately 2% of adult men. If we include men of older age, this number increases to around 38% (4). Classifying a patient as hypogonadal can occur only in the presence of clinical symptoms of testosterone deficiency combined with persistently low total testosterone levels in fasting serum, obtained at two different time points (3). Testosterone plays a key role in the mental and physical well-being of men. In the case of men who did not fully develop secondary sexual characteristics during puberty, externally administered testosterone therapy reduces the negative consequences of past deficiency. Testosterone therapy improves sexual function, enhancing libido and erection in individuals who previously experienced a deficiency of this hormone. Testosterone administered as TRT positively influences mood and sense of well-being. Moreover, studies have noted an increase in bone mineral density (in the vertebrae and femoral bone) in men receiving testosterone supplementation. TRT leads to an increase in lean body mass, muscle strength, and a reduction in visceral and subcutaneous fat in individuals with testosterone deficiency (1). Currently, worldwide, due to greater access to information, an increasing number of clinical studies, growing self-awareness, aging populations, and the desire to care for one's health, there is a growing interest in the topic of TRT. The aim of this article is to provide a comprehensive review of current evidence on TRT in men with hypogonadism, including indications for treatment, forms of therapy, benefits of treatment, and risks associated with exogenous testosterone supplementation.

Methodology

For the purposes of this article, an analysis of current scientific publications concerning testosterone therapy and hypogonadism was conducted. The literature review was carried out using databases such as PubMed and Google Scholar, employing keywords such as “testosterone”, “hypogonadism”, and other related terms. Special emphasis was placed on documents produced by international scientific societies (including ISSM, BSSM, EAU), as well as on meta-analyses and systematic reviews of the literature. The analysis included both randomized clinical trials (RCTs) assessing the efficacy of TRT and publications concerning the safety of this therapy. The selection of sources covered works published up to 2025, with particular emphasis on those describing clinical treatment effects (such as improvement of sexual function, exercise capacity, or metabolic parameters) and possible adverse events, including the impact of TRT on the cardiovascular system and fertility.

Mechanism of Testosterone Action and Regulation of the HPG Axis

The hypothalamic-pituitary-gonadal (HPG) axis is responsible for regulating hormones in the blood. It consists of the hypothalamus, which produces the gonadotropin GnRH; the pituitary gland, which releases luteinizing hormone (LH) and follicle-stimulating hormone (FSH); and the gonads - in men, the testes. GnRH from the hypothalamus stimulates the pituitary to secrete LH and FSH. LH acts on Leydig cells in the testes, leading to the production of testosterone. Testosterone itself reduces the production of GnRH, LH, and FSH through negative feedback. Additionally, testosterone is converted by CYP19A1 aromatase into 17β-estradiol, which in turn inhibits gonadotropin secretion by the hypothalamus (2). In men with primary hypogonadism, sex steroid levels are low, while gonadotropin levels are high. In secondary hypogonadism, hypothalamic-pituitary dysfunction leads to low levels of LH and FSH despite androgen deficiency (5).

Testosterone and its metabolite 5α-dihydrotestosterone (DHT), which is produced by the conversion of testosterone via the 5α-reductase enzyme, are the main steroid androgens. Androgens, by crossing the cell membrane and interacting with the androgen receptor, elicit genomic and non-genomic effects. Androgen receptors are present in many tissues throughout the male body. Androgens play a key role in male developmental and physiological processes, especially in reproductive tissues. They are responsible for sexual development, the synthesis of muscle proteins, erythropoiesis, regulation of cardiovascular function, and other functions (6). Testosterone is the main hormone that influences bone metabolism. Meanwhile, DHT is necessary for maintaining prostate health and the development of male secondary sexual characteristics (7). Understanding these mechanisms is crucial for evaluating the potential therapeutic effects and adverse events of testosterone replacement therapy.

Methods of Measuring Testosterone Concentration

Testosterone in plasma is bound to sex hormone-binding globulin (about 44% in men), albumin (about 33-54%), cortisol-binding globulin, and alpha-1-acid glycoprotein, and the rest remains in a free (biologically active) form. Immunoassays, despite their availability and approval by the U.S. Food and Drug Administration (FDA), do not allow precise quantitative determination of steroid hormone concentrations (8). They can be subject to errors in men with atypical SHBG levels. Liquid chromatography with tandem mass spectrometry (LC-MS/MS) tests are a more accurate alternative for measuring total testosterone concentration in blood, but their availability may be limited (8,9).

Classification and Pathophysiology of Hypogonadism

Primary Hypogonadism

Primary hypogonadism results from testicular dysfunction. It is caused by deficiency or lack of Leydig cell function (11). It is characterized by low serum testosterone concentration with high levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) in the blood. For this reason, it is also called hypergonadotropic hypogonadism (10). The causes of primary hypogonadism include Klinefelter syndrome, undescended testes, orchitis, anorchia, hemochromatosis, chemotherapy or radiotherapy associated with malignancies, and also physiological aging of men (10,11).

Klinefelter syndrome (47,XXY) is the most common chromosomal cause of primary hypogonadism. It affects spermatogenesis and hormone production. It occurs in about 3% of unselected infertile men and more than 10% of men with azoospermia. It is estimated that at least half of cases are never diagnosed and remain untreated throughout life. When serum testosterone decreases, testosterone replacement therapy is necessary. It has been shown that early testosterone replacement not only alleviates biological symptoms such as anemia, osteoporosis, muscle weakness, and erectile dysfunction, but also results in better social adaptation and integration (11).

Secondary Hypogonadism

Secondary hypogonadism is caused by defects in the hypothalamus or pituitary gland, resulting in low testosterone levels due to insufficient stimulation of Leydig cells in the testes. Additionally, low or inappropriately normal levels of FSH and LH are present. In patients with secondary hypogonadism, fertility can be restored through hormonal stimulation. The causes of secondary hypogonadism include Kallmann syndrome, pituitary disorders (including pituitary adenoma), head trauma, HIV infection, obesity, alcohol abuse, corticosteroid therapy, stress-induced hypogonadism, uremia, as well as liver failure, type 2 diabetes, metabolic syndrome, or chronic opioid use (10,12). It is worth mentioning that a low serum testosterone level may also be caused by a condition known as mixed hypogonadism, in which both primary and secondary hypogonadism are present (10).

Recently, another classification of hypogonadotropic hypogonadism has been recognized, based on the concept of organic versus functional hypogonadism. Functional hypogonadism refers to a state without any recognizable structural pathology of the HPG axis and without significant pathological conditions that could suppress the axis. Testosterone level remains near the lower limit of normal, occasionally very low, while gonadotropins are generally within normal range. This abnormality is more often associated with diseases such as obesity, metabolic syndrome, type 2 diabetes, or aging. It is considered that the mild reduction of testosterone occurring with age is mainly caused by the accumulation of diseases (12). Organic forms result from damage to the structures of the hypothalamic-pituitary-gonadal axis. They have a straightforward, established diagnostic and therapeutic path. These may include congenital GnRH defects (Kallmann syndrome, KISS1R mutations), pituitary tumors (prolactinoma), skull injuries, pituitary adenomas or inflammatory infiltrates in autoimmune diseases and sarcoidosis (10,13).

Diagnosis of Hypogonadism

Clinical Symptoms

The diagnosis of hypogonadism in men is based on the presence of clinical symptoms such as decreased libido, erectile dysfunction, depressed mood, fatigue, loss of muscle mass, increased fat tissue, decreased bone density (osteopenia, osteoporosis), decreased fertility, small testicular size, and confirmation of low testosterone level (10). In men suspected of hypogonadism, a physical examination is recommended. However, it should be remembered that in some men the physical examination may be normal (14).

Laboratory Tests

Due to diurnal variation in testosterone secretion, blood tests for testosterone measurement should be performed in the morning - between 7:00 and 11:00. This is especially important in men under 40 years of age. In patients who work at night or shifts, testosterone should be measured within 3 hours after waking. It is recommended to measure testosterone on an empty stomach. Hypogonadism evaluation should not be performed during acute illness. If the testosterone level is borderline or low on the first measurement, it is recommended to repeat the test at least twice. The optimal time for repeat testing is 4 weeks after the first measurement. Additionally, serum SHBG and albumin levels should be verified (10,15). Measurement of SHBG can be useful, because some conditions cause significant changes in its level, which further affects total testosterone level and its interpretation. These conditions include obesity, aging, diabetes, thyroid disorders, nephrotic syndrome, liver cirrhosis, excess or deficiency of GH, HIV infection and medications (16,17). Guidelines suggest that total testosterone levels < 8 nmol/L (231 ng/dL) indicate the need for treatment. If total testosterone level is between 8-12 nmol/L (231-346 ng/dL), it is recommended to measure serum LH and FSH levels. This will allow differentiation of primary versus secondary hypogonadism (10). Although reference values for testosterone may differ depending on the method used and population studied, typically the lower limit of normal is 250-300 ng/dL (8.7-10.4 nmol/L), and the upper limit 950–1000 ng/dL (33.0-34.7 nmol/L). In most patients with hypogonadism undergoing testosterone therapy, optimal mean concentrations fall in the mid-normal range, around 400-800 ng/dL (13.9-27.8 nmol/L) (22).

Differential Diagnosis

In the diagnostic process, it is necessary to exclude coexisting diseases and environmental factors leading to lowered testosterone, such as alcoholism, untreated obstructive lung disease (COPD), liver failure, kidney failure, hypothyroidism, stress, intense physical exertion, and acute illnesses. Additionally, the lipid profile, glucose level, liver enzymes, hemoglobin, and hematocrit should be assessed (16).

Forms of Testosterone Replacement Therapy

The choice of preparation depends on patient preference, cost, convenience of use, availability, and potential impact on fertility. Preparations should provide physiological androgen levels without peak fluctuations and minimize side effects. Advanced age or disability should not be a contraindication to initiating testosterone replacement therapy (18). Below are described the currently available testosterone preparations on the market, their advantages and disadvantages, dosing, and routes of administration.

Topical Preparations

The use of gel preparations allows achieving stable testosterone levels throughout the week, ensuring minimal fluctuations if applied daily (19). Treatment is painless, and the dose is easy to adjust - it is determined based on a blood test performed 2 to 6 hours after gel application (18). We aim for target values of 20-30 nmol/L (19). After stopping therapy, testosterone levels quickly return to baseline. When using gel preparations, attention should be paid to safety issues related to transfer to other persons - for example, wearing clothing that covers application sites and washing hands after applying the product. It is recommended to wait 5-6 hours before bathing or showering to optimize testosterone bioavailability (19). Topical preparations can cause skin irritation in some patients, and application is time-consuming. Examples of preparations include: Testogel 1% (50-100 mg), Tostran 2% (40-70 mg), Testavan 2% (23-46 mg). Preparations should be applied to dry, clean skin of the shoulders, abdomen, and thighs. They should not be applied to the genital area (18).

Intramuscular Injections

Short-acting intramuscular injections: Short-acting intramuscular injections result in achieving average physiological testosterone levels. However, shortly after each injection they are characterized by raising testosterone to supraphysiological values, and before the next dose, levels fall below the normal range. They are administered intramuscularly two or three times a week by a healthcare professional. The dose is adjusted based on pre-injection testosterone concentration. We aim for 10-15 nmol/L (19). Injections are given into the gluteal muscle or the upper thigh. Advantages include easy dose adjustment and relatively inexpensive preparations. Disadvantages include the possibility of experiencing unpleasant "peaks and troughs" due to fluctuations between injections. Additionally, there is an increased risk of polycythemia due to supraphysiological testosterone levels. Pain or discomfort may occur at the injection site (18). Examples of products include Testoviron® Depot 50 (20 mg testosterone propionate and 55 mg testosterone enanthate) and Testoviron® Depot 100 (25 mg testosterone propionate and 100 mg testosterone enanthate), as well as Sustanon® 250 (30 mg testosterone propionate, 60 mg testosterone phenylpropionate, 60 mg testosterone isocaproate, and 100 mg testosterone decanoate) (19).

Long-acting intramuscular injections: Intramuscular injections can also be administered using long-acting forms of testosterone. They are given deeply into the gluteal muscle. After the first injection, the second is given after 6 weeks, and the third after 12 weeks from the first dose. The interval between successive injections is determined based on the lowest testosterone concentration measured just before the third administration, in order to achieve values close to the lower limit of the reference range (18). We aim for values of 20-30 nmol/L (19). It is recommended to monitor the minimum testosterone concentration and blood morphology once a year or after 3-5 injections. The main advantage of long esters is a more stable profile of testosterone levels compared to short-acting injections, limiting fluctuations between peak and trough concentrations. It offers convenient three-month dosing without the side effects typical of testosterone implants. The downsides of long-acting preparations are that they require administration into a large muscle, which may be a limitation. The drug is not suitable for self-administration, affecting patient convenience. It is not recommended as first-line therapy, because if side effects occur there is no way to immediately stop its action. Rarely, adverse events may occur, such as pulmonary microembolism, manifesting as a sudden bout of coughing (18).

Oral Preparations

Oral administration of testosterone was not initially possible due to its extensive metabolism in the digestive tract and high first-pass effect in the liver, which led to obtaining too low plasma concentrations. The discovery that modifying the molecule by 17α-methylation protects testosterone from hepatic degradation led to the development and FDA approval of 17-methyltestosterone preparations with increased oral bioavailability. However, the use of 17-methyltestosterone and other 17α-alkylated derivatives has been limited due to significant hepatotoxic side effects observed in early clinical reports. The most commonly described adverse effects included cholestasis, vascular lesions (peliosis hepatis), transient hepatitis, and the development of liver tumors (20). Another approach was 17-beta esterification. Testosterone undecanoate (TU) taken orally is primarily absorbed into the lymphatic system, then hydrolyzed in the body to natural

testosterone. Its efficacy is limited due to low and unstable bioavailability, significant fluctuations in serum concentration, and short half-life. As a result, to achieve a full TRT effect, it is necessary to take 3-4 capsules of 40 mg daily, preferably with meals to enhance absorption. Another option is the DHT derivative mesterolone, but the use of this preparation results only in partial androgenic effects, and therefore it is not suitable for testosterone replacement therapy (21).

Buccal Testosterone

Mucoadhesive tablets placed on the gums enable constant release of testosterone directly into the bloodstream, bypassing liver metabolism, which leads to increased bioavailability. Tablets containing 30 mg testosterone are administered twice daily at equal intervals of 12 hours. This allows reaching a maximum concentration after 10-12 hours from the first dose, and a steady state is achieved within 24 hours. After removing the tablet, the testosterone level returns to baseline within 4-6 hours. In clinical trials lasting up to 12 months, buccal testosterone showed good tolerance (21). About 16% of men using the preparation reported adverse effects related to the gums. Tablets may detach, especially if food is consumed soon after application. Additionally, patients often need some time to get used to their use (18).

Subcutaneous Implants

Testosterone in the form of subcutaneous implants is used as pellets in doses of 100 or 200 mg, in such an amount that the total dose is 600-1200 mg (18). Testosterone level reaches its peak about one month after insertion and remains within the normal range for 4 to 6 months depending on the dose (21). The most common adverse effect is the risk of pellet extrusion. The procedure can be painful and is associated with the risk of infection at the implantation site and formation of a scar (18,21).

Special Patient Groups

Older Men

The period of transition from adulthood to old age represents a significant time of changes covering the physical, psychological, and social spheres for men. One of the key, often overlooked processes is the gradual decline in testosterone levels, which can significantly decrease with age. It is estimated that in about 25-30% of men over 60 years of age, reduced serum testosterone levels are observed, defined as total testosterone below 350 ng/dL and free testosterone below 225 pmol/L. In older men, testosterone production and testicular function gradually decline, usually at a rate of about 1-2% per year after the age of fifty. Reduced testosterone levels are associated with the occurrence of sexual dysfunctions in men. As a result, a mild form of hypogonadism resulting from relative testosterone deficiency can occur in aging men. The symptoms of this condition are similar to hypogonadism observed in younger men and include, among others: erectile dysfunction, decreased muscle strength, excessive body weight, osteoporosis, hot flashes, fatigue, depressed mood, and difficulty concentrating. This condition is called late-onset hypogonadism (LOH) (23). It has been shown that in older men, TRT improves sexual function, increases bone density and hemoglobin, but does not significantly affect vitality, cognitive function, or the formation of atherosclerotic plaque. Due to the limited number of long-term safety studies on testosterone therapy, replacement therapy in older men should be conducted with great caution (24).

Men with Obesity

In men with overweight or obesity, a mild to moderate reduction in serum testosterone level is often observed, with concomitant normal LH and FSH values. These individuals may report nonspecific complaints resembling symptoms of androgen deficiency or symptoms of other comorbid conditions typical of older age. This phenomenon results from a decrease in circulating SHBG levels, which is a consequence of metabolic disorders accompanying obesity, such as hyperinsulinemia, elevated triglyceride levels, and fatty liver. Testosterone therapy is not recommended in men with overweight or obesity solely due to a reduced testosterone level, unless confirmed pathological hypogonadism exists, which should be ruled out based on history, physical examination, and appropriate laboratory tests. In the case of simple obesity, weight reduction is key to health improvement - meta-analyses have shown that diet, physical activity, and bariatric procedures lead to a significant increase in serum testosterone level, proportional to the degree of weight loss (25).

Type 2 Diabetes

Hypogonadism often coexists with type 2 diabetes (T2DM), and testosterone replacement therapy (TRT) is an important element of therapeutic management. Sodium-glucose cotransporter 2 (SGLT2) inhibitors play an important role in T2DM treatment. Therapy with these agents is associated with an increased risk of developing secondary erythrocytosis in patients with type 2 diabetes. Up to 40% of men with type 2 diabetes have a confirmed testosterone deficiency, although the exact causal relationship between these two disorders

has not yet been clearly established (26). Randomized controlled trials have shown that TRT leads to a significant absolute increase in hematocrit by 2-4%, regardless of therapy duration or form of testosterone administration (27). Studies show that TRT can significantly improve glycemic control, positively affecting parameters such as HOMA-IR, fasting serum glucose (FSG), fasting serum insulin (FSI), and glycated hemoglobin (HbA1c). In newer analyses, it was found that baseline HOMA-IR strongly correlates with BMI, waist circumference, and C-peptide levels. Moreover, testosterone supplementation had a beneficial effect on metabolic syndrome markers - a decrease in HOMA-IR was observed, an increase in HOMA% (indicating better β-cell function), and a decrease in C-peptide and proinsulin levels. In men with concomitant hypogonadism and diabetes treated with TRT, a reduction in body weight and improvement in glycemic indices were observed. In one study, patients receiving testosterone experienced decreases in waist circumference, body weight, fasting glucose, HbA1c, improvement in lipid profile, blood pressure, and liver enzyme activity (28). Conversely, a meta-analysis conducted in 2021 showed no significant changes in HOMA-IR and glucose and cholesterol levels during testosterone treatment (39). Further interventional studies are needed to precisely clarify the relationship between circulating sex hormone levels and glucose metabolism (28).

Cardiovascular Diseases

The effect of TRT on cardiovascular risk has been controversial. Some observational studies suggested an increased risk of myocardial infarction and stroke, but meta-analyses and recent randomized trials have not confirmed these concerns. In men aged 40 and over with low or low-normal testosterone, TRT was not associated with an increased risk of all-cause mortality, cardiovascular mortality, stroke or myocardial infarction (29,30). However, TRT significantly raised the incidence of arrhythmias, caused a decrease in HDL cholesterol levels, and led to a slight increase in systolic blood pressure in the treated group (29).

Chronic Kidney Disease (CKD)

One of the hormonal disorders seen in chronic kidney disease (CKD) is hypogonadism. It is detected in about 27-66% of CKD patients (32). Testosterone replacement therapy in CKD patients can bring significant benefits - it may increase muscle mass and strength, support anemia treatment through stimulation of erythropoiesis, improve bone mineral density, and positively affect the cardiovascular system by improving body composition and increasing insulin sensitivity. Testosterone therapy may lead to fluid retention, increased blood pressure, and worsening of existing heart failure, especially in patients with CKD and coexisting cardiovascular conditions. Additionally, there are concerns that testosterone may accelerate the progression of kidney disease through mechanisms related, among others, to kidney tubular function, which indicates the need for careful patient selection and close monitoring of therapy (33).

Patients with HIV

Hypogonadism is one of the more common comorbid conditions in men infected with HIV. Its prevalence is estimated at around 26%, and considering free testosterone (fT) levels, it may reach about 40%. Evidence indicates that generally poor health is a key risk factor for the development of hypogonadism in HIV-infected individuals. Moreover, an inverse relationship has been shown between CD4+ cell count and the prevalence of this disorder, suggesting that weaker control of HIV infection increases the likelihood of hypogonadism. Long-term androgen supplementation has a beneficial effect on body composition, increasing lean body mass. However, due to the general fragility and weakness of patients with HIV, the decision to initiate testosterone therapy should be made individually (34).

Opioid-Induced Hypogonadism

The use of opioid analgesics often leads to the development of androgen deficiency in men - a condition that remains largely unrecognized and inadequately treated. Opioids disrupt the functioning of the hypothalamic-pituitary-gonadal axis, primarily by inhibiting the secretion of GnRH. The frequency of opioid-induced androgen deficiency ranges from 20% to 80%, depending on the type of drug used, duration of use, patient age, and the criteria adopted for diagnosing low testosterone. Men over 50 years of age are most at risk, especially those with comorbid conditions. Available, although limited, clinical studies suggest that testosterone therapy may improve libido, body composition, and some aspects of quality of life (35).

Benefits of TRT

Sexual Function and Quality of Life

Many studies confirm that testosterone therapy (TRT) tends to improve libido, erectile function, and overall well-being in men with reduced testosterone levels. Systematic reviews and meta-analyses on the efficacy of TRT in treating sexual disorders indicate increased satisfaction with intimate life and improvements in mood and energy levels (36). However, it should be emphasized that some high-quality studies, including a shortened Cochrane meta-analysis, have not shown significant differences in erectile function or sexual quality of life between men receiving TRT and those receiving placebo (37). In summary, in well-selected hypogonadal men, TRT often improves sexual function and well-being, although the results are not unequivocal in all studies (36,37).

Metabolism and Body Composition

Testosterone therapy exhibits anabolic properties - it promotes an increase in muscle mass and intensifies the metabolic rate. In studies comparing the effect of TRT and physical activity, it has been observed that testosterone administration significantly increases lean body mass in middle-aged and older men (38).

Bone Density

Testosterone plays a fundamental role in regulating bone metabolism. Studies suggest that testosterone therapy may limit the loss of bone mineral density and support its regeneration in men with testosterone deficiency. Its influence on the activity of osteoblasts and osteoclasts contributes to the maintenance of normal bone tissue structure and strength (36). However, it should be noted that meta-analyses do not always confirm a significant increase in bone mineral density or a reduction in fracture risk during testosterone therapy. Nevertheless, many specialists believe that TRT may play a beneficial role in the prevention of osteoporosis in men with low testosterone levels, although further studies are needed to definitively determine its long-term impact on bone health (40).

Cardiovascular System and Inflammatory Processes

Scientific data indicate that testosterone therapy does not negatively affect cardiovascular function in the short- and medium-term. Meta-analyses and the recent multicenter TRAVERSE trial confirmed that the incidence of major cardiovascular events (MACE) in patients receiving TRT does not differ significantly from that observed in the placebo group (41). It is worth emphasizing that TRT may positively affect endothelial function and does not increase markers of inflammation. A 2024 analysis found no significant changes in C-reactive protein (CRP) or HDL and LDL cholesterol fractions in men undergoing testosterone therapy (42). Overall, current scientific evidence does not indicate an increased risk of worsening cardiovascular disease under appropriately controlled TRT (41,42).

Cognitive and Psychological Functions

Testosterone therapy may contribute to improvements in mood and alleviation of depressive symptoms in men with reduced testosterone levels. Reviews of clinical studies show that in hypogonadal patients, TRT often results in increased energy levels, better mood, and reduction of depressive symptoms (36). Some studies suggest that TRT may have beneficial effects on certain cognitive functions, such as memory and concentration, although further research is needed to definitively confirm these effects (43). In summary, testosterone therapy supports the improvement of well-being and mood in men, while available evidence regarding its impact on specific cognitive functions remains limited.

Risks and Side Effects

Polycythemia and Hematologic Disorders

One of the most frequently observed side effects of TRT is increased erythrocyte production, polycythemia. Testosterone strongly stimulates erythropoiesis, which can lead to a significant increase in hematocrit level. According to a 2024 analysis, the use of testosterone therapy is associated with a several-fold higher risk of developing erythrocytosis compared to untreated individuals, which may promote thrombosis. In the first stage of management, it is recommended to reduce the testosterone dose and identify and modify factors that contribute to the development of erythrocytosis, such as smoking or severe obstructive sleep apnea. Only afterwards - after joint analysis with the patient and considering uncertainties regarding efficacy and safety - can therapeutic phlebotomy be considered (44).

Fertility and Spermatogenesis

Exogenous testosterone administration inhibits the secretion of gonadotropins in the hypothalamic-pituitary-gonadal axis (HPG), resulting in lowered testosterone levels in the testes, which is necessary for normal spermatogenesis. As a result, many men develop oligozoospermia or azoospermia (45). The use of

long-acting testosterone injections is associated with a significantly higher risk of infertility in men undergoing testosterone replacement therapy (31). After stopping testosterone therapy, fertility generally recovers gradually; however, about 10% of patients may experience permanent impairment of spermatogenesis (45). For this reason, testosterone therapy is not recommended in men planning to preserve fertility in the future. In such situations, alternative treatment methods are preferred, such as therapy with gonadotropins or drugs that modulate estrogen action (49).

Prostate and Prostate Cancer

It has traditionally been feared that testosterone therapy might promote prostate enlargement and increase the risk of prostate cancer. However, recent studies show that in men with hypogonadism, TRT is not associated with a significant increase in prostate cancer risk nor with worsening of benign prostatic hyperplasia symptoms (40). Current clinical guidelines nevertheless recommend caution and regular monitoring of PSA levels in patients undergoing treatment, especially if there are previous prostate conditions. Active prostate cancer or unclear symptoms suggesting its presence constitute a contraindication to starting TRT (48). Available scientific evidence indicates that appropriately monitored therapy does not lead to significant changes in digital rectal examination or PSA levels (40).

Although results of clinical trials do not indicate that TRT exacerbates cardiovascular diseases, the literature has described isolated cases of coronary disease exacerbations or strokes related to improper testosterone use (47). A key piece of evidence confirming the safety of therapy in this area is the TRAVERSE (2024) study, which demonstrated that testosterone treatment does not increase the risk of major cardiovascular events (MACE) in men with existing CVD risk factors (41). Nevertheless, due to limited long-term data, a thorough evaluation of the patient's cardiovascular status is necessary before starting therapy, and regular monitoring of heart function and lipid parameters during treatment (50).

Obstructive Sleep Apnea (OSA)

Changes in ventilatory response to hypoxia and hypercapnia after testosterone administration may suggest a potential influence of testosterone on respiratory regulation; however, due to inconclusive results of available studies, further research is needed to precisely define this effect. In clinical practice, caution should be exercised in patients with OSA (51). Some studies suggest that men undergoing testosterone therapy may have a slightly higher prevalence of OSA than the general population, although the evidence is not definitive. Patients should be monitored for the worsening of symptoms such as snoring or daytime fatigue. In the case of men already diagnosed with OSA, before starting TRT, doctors should warn that therapy may worsen existing symptoms (46).

Gynecomastia, Acne and Other Side Effects

In some patients, excess testosterone may be converted to estrogens, which leads to the development of gynecomastia and breast tenderness - this phenomenon is observed even in 10-25% of individuals undergoing therapy (46). The increase in testosterone level in the blood is associated with a simultaneous increase in sebum secretion, which can lead to acne, although this is usually mild. Cases have also been documented in which testosterone supplementation caused changes in hair growth, but there is a lack of randomized placebo-controlled trials confirming these observations. Various forms of testosterone, both topical and intramuscular, can cause skin reactions such as erythema or itching in up to 60% of patients (46).

Controversial Aspects of TRT

Threshold Levels and Diagnosis

The literature emphasizes that the diagnosis of testosterone deficiency is based on the coexistence of characteristic clinical symptoms and laboratory confirmation of a reduced hormone level. At the same time, there are significant differences between the guidelines of different scientific societies regarding threshold values. According to ISSM, BSSM and EAU recommendations, testosterone therapy can be considered when total testosterone is below 231 ng/dL (≈8 nmol/L), whereas the American Urological Association (AUA) uses a higher threshold - about 300 ng/dL (≈10.4 nmol/L). The Endocrine Society (ES) sets the lower limit of normal at 264 ng/dL (9.2 nmol/L), while Canadian recommendations (CMAJ) do not define a specific threshold value and do not require repeating the confirming result of low testosterone. These differences indicate that diagnostic standards remain inconsistent and interpret biochemical thresholds of testosterone deficiency differently (52).

Functional vs Organic Hypogonadism

The Endocrine Society and the Australasian Endocrine Society clearly differentiate organic from functional hypogonadism, indicating that in the latter form, treatment of comorbid conditions and lifestyle

modification are key, often allowing for restoration of normal testosterone levels. In contrast, the ISSM, BSSM, and CMAJ guidelines do not introduce such a clear division, treating hypogonadism as a single clinical entity and allowing therapy even in patients with mild, physiological reduction of the hormone level. Such discrepancies highlight the ongoing scientific debate regarding the need for a more precise distinction between organic testosterone deficiency and transient functional disturbances secondary to other chronic diseases (52).

Fertility and Reversibility of Effects

Exogenous administration of testosterone leads to suppression of gonadotropin secretion, resulting in cessation of spermatogenesis. Consequently, long-term TRT is often associated with infertility, manifesting as a significant reduction in sperm count, or even azoospermia. For this reason, men planning fatherhood are advised to avoid TRT or to consider alternative treatments that stimulate the hypothalamic-pituitary-gonadal axis, such as using clomiphene or gonadotropins. After discontinuation of therapy, most patients experience gradual restoration of spermatogenesis - about two-thirds within six months, and others up to a year later. The time to fertility recovery mainly depends on the dose and duration of testosterone use. In general, the effect of TRT on reproductive capacity is reversible as long as therapy has not been conducted for an excessively long period or at very high doses; however, patients should be informed about this potential risk (5).

Monitoring and Practical Aspects of Treatment

Before initiating testosterone therapy, it is recommended to perform a complete blood count with hemoglobin (Hgb) and hematocrit (Hct), assess PSA level, and conduct a digital rectal exam (DRE). It is also necessary to have two separate morning measurements of testosterone concentration, as well as measurement of pituitary hormones – prolactin, FSH and LH. During treatment, periodic monitoring of biochemical parameters is indicated: every 3-6 months testosterone level, lipid profile, liver enzymes, PSA, Hgb and Hct should be re-evaluated. In the later course of therapy, testosterone level should be checked at intervals of 6-12 months. The goal of treatment is to maintain testosterone level at the upper limit of the physiological range, while avoiding excessive spikes after administration of the preparation. Regular assessment of both hormone levels and clinical symptoms is key to ensure the effectiveness and safety of therapy (5).

Discussion

The results of the conducted analysis indicate that testosterone replacement therapy (TRT) can provide significant clinical benefits in men with hypogonadism, although the effectiveness of treatment depends on the specifics of the population and the design of the analyzed studies. Numerous meta-analyses and systematic reviews confirm that TRT significantly improves intimate life, increases libido, and raises vitality in patients with testosterone deficiency (4,27). At the same time, it should be noted that not all randomized trials show clear benefits-for example, a shortened Cochrane meta-analysis did not find significant differences between the treated and placebo groups in terms of erectile quality and sexual satisfaction (37). These differences suggest that the positive effects of TRT on sexual function are most pronounced in appropriately selected, symptomatic patients (27,37).

It has been found that testosterone therapy can favorably affect metabolic parameters - in patients with hypogonadism and type 2 diabetes, improvement in insulin sensitivity and beneficial changes in lipid profile are observed.(28) However, some meta-analyses and randomized studies indicate that differences in glycemia levels after TRT do not reach statistical significance (39). The obtained results reflect this ambiguity - in some cases a decrease in HOMA-IR and HbA1c indices was observed, while other analyses did not confirm significant changes (39). Therefore, although TRT appears to have a beneficial metabolic effect, manifested among others by reduction of visceral fat and increase in insulin sensitivity, further interventional studies are needed to more precisely determine and understand the mechanisms responsible for these relationships.

The issue of cardiovascular safety of TRT remains one of the key topics discussed in the literature. Meta-analyses of randomized studies and the results of the large-scale TRAVERSE trial indicate that the incidence of major cardiovascular events (MACE), such as myocardial infarction or stroke, does not differ significantly between patients receiving testosterone and those receiving placebo (29,30,41). With appropriate patient selection and adequate treatment monitoring, testosterone therapy does not negatively affect the short-term course of cardiovascular disease (29). It should be emphasized, however, that isolated cases of cardiac events related to improper testosterone use continue to be reported in the literature (47). Therefore, before initiating treatment, a thorough assessment of the patient's cardiovascular status is recommended, and regular monitoring during therapy should be performed, in accordance with current guidelines (52).

The literature also confirms a beneficial effect of TRT on psychological well-being and certain aspects of cognitive function. Administration of appropriate doses of testosterone contributes to improvement of mood, general well-being, and reduction of depressive symptoms in men with hypogonadism (27).

Among the adverse effects of TRT, polycythemia is the most unequivocally documented side effect. Data indicate that testosterone therapy strongly stimulates erythropoiesis, often resulting in hematocrit rising above reference values (26,44). Due to the potential risk of thrombotic complications, regular monitoring of hematologic parameters and, if necessary, modification of treatment (e.g., dose reduction) is required. In cases of significant hematocrit elevation, therapeutic phlebotomy is also recommended (44).

Another important issue associated with TRT is its effect on spermatogenesis. Exogenous testosterone leads to strong suppression of the hypothalamic-pituitary-gonadal axis, which consequently often results in oligozoospermia or azoospermia (45). Contemporary data do not confirm earlier concerns regarding a negative impact of TRT on the prostate gland. Current literature reviews indicate that properly conducted and monitored testosterone therapy is not associated with an increased risk of developing or recurrence of prostate cancer or exacerbating benign prostatic hyperplasia (46,48). Nevertheless, given existing contraindications, it is recommended to regularly measure PSA and perform digital rectal exams during treatment (52).

In summary, this review showed high concordance with available literature. On one hand, it was confirmed that TRT can significantly improve sexual function, body composition, and overall well-being, confirming its clinical value in appropriately selected patients. On the other hand, differences in study designs, population heterogeneity, and a limited number of long-term analyses mean that some outcomes remain inconclusive. The data obtained are consistent with expert recommendations, which emphasize the necessity of individualizing therapy by considering both potential benefits and risks. It should also be noted that the efficacy and safety of TRT may differ among patient groups, which requires therapeutic decisions to be made in a personalized manner. Overall, the studies suggest that properly conducted testosterone therapy, with adherence to monitoring principles, provides more benefits than potential risks.

Conclusions

Testosterone therapy can bring significant health benefits for men diagnosed with hypogonadism - particularly in the areas of sexual function, muscle strength, and overall quality of life. At the same time, its use requires caution, because the therapy is associated with potential risks such as fertility suppression, development of polycythemia, or possible interactions with comorbid conditions. For this reason, the decision to begin treatment should always be made individually. Treatment requires regular medical supervision - including monitoring of hormonal, blood, and metabolic parameters - as well as proper patient preparation and education. Due to remaining uncertainties in the literature regarding the long-term safety of TRT, further prospective studies are necessary to determine its full profile of risks and efficacy over a longer term.

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