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Testosterone Replacement Therapies

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Related Policies (if applicable)
SUR717.001 Gender Assignment Surgery and Gender Reassignment Surgery and Related Services
RX501.007 Hormone Replacement Therapies (HRT) Using Implanted Pellets for Women and Delayed Puberty

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy does NOT address Gender Reassignment Services (Transgender Services). This medical policy IS NOT TO BE USED for Gender Reassignment Services. Refer to SUR717.001, Gender Assignment Surgery and Gender Reassignment Surgery with Related Services.

The following coverage addresses testosterone replacement treatment for males only:
Testosterone replacement therapy with a single testosterone product **may be considered medically necessary** when the patient does not have any contraindications noted on the FDA-(U.S. Food and Drug Administration) approved label **AND** has ONE of the following conditions:

- An established diagnosis of primary or secondary hypogonadism with androgen deficiency that includes:
  - Persistently low pre-treatment testosterone levels (refer to **NOTE 1** below); **and**
  - More than 2 pre-treatment symptoms of hypogonadism including at least 1 "more specific" symptom (refer to **NOTE 2** below); **OR**
- Human immunodeficiency virus-infected men with low testosterone levels and hypogonadal symptoms or significant weight loss (e.g., > 5% lean body mass); **OR**
- Men on chronic corticosteroid treatment with low testosterone levels (refer to **NOTE 1** below) and hypogonadal symptoms; **OR**
- Men requiring testosterone replacement therapy following post bilateral orchiectomy.

NOTE 1: Persistently low pre-treatment testosterone levels refer to serum levels that are below the lower limit of normal for the lab performing the test on at least 2 occasions when measured in the early morning (7-11 AM).

NOTE 2: "More specific" symptoms of hypogonadism, as classified by the Endocrine Society, include the following (1):

- Incomplete or delayed sexual development, or
- Decreased libido, or
- Decreased spontaneous erections, or
- Breast discomfort, gynecomastia, or
- Loss of axillar and/or pubic body hair, or
- Very small (<5 mL) or shrinking testes, or
- Infertility due to low sperm count, or
- Height loss due to vertebral fractures, low trauma fractures, low bone density, or
- Hot flushes, sweats.

EXCEPTION: Individual consideration may be given for men continuously on therapy for at least one year and a morning total serum level or free testosterone level tested within the last year remains below or within the testing laboratory's normal range.

Testosterone replacement therapy **is considered experimental, investigational and/or unproven** in all other situations in which the above criteria are not met, including but not limited to older men with type 2 diabetes mellitus and androgen deficiency or low testosterone levels in the absence of clinical signs and symptoms of hypogonadism.

The following coverage addresses testosterone therapy for women only:
Testosterone therapy for women **is considered experimental, investigational and/or unproven** for **ALL** conditions, with the exception of treatment for metastatic breast cancer.

For the associated policy related to hormone replacement therapies using implanted pellets for women and treatment of puberty, please see RX501.007 Hormone Replacement Therapies (HRT) Using Implanted Pellets for Women and Delayed Puberty.

Policy Guidelines

None.

Description

Testosterone replacement therapy is the primary treatment for androgen deficiency in men. Testosterone replacement is intended to counter the adverse effects of low testosterone levels with clinical signs and symptoms of hypogonadism. A variety of testosterone preparations are available for clinical use.

Testosterone and Testosterone Levels

Testosterone is produced in males, primarily by the testes, in response to stimuli from the hypothalamic and pituitary glands. Low testosterone is caused by deficient production of the hormone and is also known as androgen deficiency. Primary androgen deficiency results from failure of testosterone production at the testicular level in the presence of normal hypothalamic and pituitary function. Secondary androgen deficiency results from failure of the pituitary gland to produce androgen-stimulating hormones (luteinizing hormone, follicle-stimulating hormone). It can be caused by dysfunction at the hypothalamic or pituitary level.

Hypogonadism

Diagnosis

Hypogonadism is the clinical syndrome associated with androgen deficiency. The signs and symptoms of hypogonadism depend on the age of onset. In prepubertal males, the hallmark of androgen deficiency is the failure to develop secondary male sex characteristics. In adults, the signs and symptoms are nonspecific, with the most specific symptoms related to sexual

functioning such as decreased libido and erectile dysfunction. Symptoms are dependent on age, the severity of androgen deficiency, duration of androgen deficiency, sensitivity to androgen, and comorbid illness. (2) Symptoms and signs other than sexual dysfunction include loss of body hair, hot flashes or sweats, decreased energy, depression, sleep disturbance, reduced muscle mass and strength, and/or increased body fat. All can occur in the absence of androgen deficiency and, therefore, the diagnosis of hypogonadism can be challenging. A systematic review by Zarotsky et al. (2014) reported on risk factors, comorbidities, and consequences of male hypogonadism identified multiple comorbid conditions that are consistently risk factors for hypogonadism, including advanced age, obesity, metabolic syndrome, and poor general health status. (3) Multiple other conditions, including diabetes, coronary heart disease, hypertension, stroke, and peripheral artery disease, correlated with the presence of hypogonadism, although these were not identified as risk factors.

Testosterone levels decrease with age, beginning in the fourth or fifth decade of a person's life, and this decrease is sometimes referred to as male "andropause." In the European Male Aging Study of 3220 men, there was a decline in serum testosterone levels of 0.4% per year between the ages of 40 and 70. (4) Because this decline is gradual and modest, the clinical impact is uncertain. While there are also parallel decreases in androgen-dependent factors with age, such as sexual function, lean body mass, and bone mineral density, the degree to which these changes are due to decreasing testosterone has not been determined with certainty.

Because of the decline in testosterone levels with age, more elderly males will have lower levels than younger men. Using a cutoff of 325 ng/dL as the lower limit of normal testosterone levels, Travison et al. (2007) estimated, based on a prospective cohort of 890 men, that the rate of low testosterone is 20% for men in their 60s; 30% for men in their 70s; and 50% for men in their 80s. (5) In this study, other factors were associated with decreased testosterone, such as obesity and severe emotional stress. A much lower percentage of men have a combination of low testosterone levels and definite symptoms of hypogonadism. In the European Male Aging Study, this was estimated to be present in 2.3% of men when using a cutoff of at least 3 symptoms potentially related to androgen deficiency.

Another factor that makes the diagnosis of hypogonadism challenging is the measurement of testosterone levels. Testosterone levels fluctuate substantially due to various factors. There is a diurnal variation, which is more pronounced in younger men, with peak levels occurring in the early morning. This makes the timing of measurement important and requires repeated measurement before making a determination that testosterone is consistently low. Also, there is a wide range of levels seen in healthy men and assigning the proper age-appropriate cutoff is controversial. Some men exhibit clear symptoms of hypogonadism with testosterone levels that are in the low to normal range, while other men with low levels do not experience any symptoms.

Diagnosis of Androgen Deficiency

An established diagnosis of hypogonadism with androgen deficiency includes appropriate evaluation and diagnostic workup of a man who presents with symptoms of hypogonadism.

Clinical practice guidelines recommend measuring serum testosterone only in men with consistent clinical manifestations of hypogonadism. Screening in asymptomatic populations is not recommended. Measurement of serum total testosterone is initially used; serum-free testosterone levels can be measured when total testosterone is in the low to normal range, and alterations of serum hormone-binding globulin are suspected. (1)

The U.S. Food and Drug Administration's (FDA's) Advisory Committee Industry Briefing Document Testosterone Replacement Therapy, dated September 17, 2014 (55), noted that male hypogonadism may be classified as:

- Primary (due to testicular failure resulting in low serum testosterone concentrations and gonadotropins [follicle-stimulating hormone – FSH], with above normal range of luteinizing hormone – LH);
- Secondary (due to insufficient testicular stimulation by the pituitary gonadotropins resulting in low testosterone serum concentrations, but have gonadotropins in the normal or low range); or
- Combined primary and secondary hypogonadism.

Once a persistently low testosterone level has been established, diagnostic testing of the hypothalamic-pituitary axis should be performed to distinguish primary hypogonadism from secondary hypogonadism. When secondary hypogonadism is identified, the underlying etiology should be identified, and any reversible causes treated appropriately before consideration of testosterone replacement.

Men on chronic steroid treatment would be receiving ongoing treatment for a chronic condition as opposed to episodic treatment for an acute condition or acute flare of a chronic condition. The length of acute episodic steroid treatment may vary from several days to several months, but in most cases, will be less than 4 to 6 weeks.

Persistently low testosterone levels refer to serum levels below the lower limit of normal on at least 2 occasions when measured in the early morning. The threshold lower limit for serum testosterone levels is not standardized. The Endocrine Society has recommended a lower limit for normal levels of 300 ng/dL for total testosterone and 9.0 ng/dL for free testosterone. (1) Joint guidelines from several European and American specialty societies have recommended that replacement therapy be considered at serum total testosterone levels less than 350 ng/dL.

Treatment

There are numerous U.S. Food and Drug Administration (FDA)–approved testosterone formulations available for replacement therapy. For most delivery preparations, approval was based on the ability to increase levels to the normal range, not to demonstrate beneficial clinical outcomes. (6)

In 1981, the FDA issued the Androgen Class Labeling Guidelines, which is still in use as follows as reported in the September 17, 2014, Advisory Committee Industry Briefing Document Testosterone Replacement Therapy by the FDA (55).

"Androgens are indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

a. Primary hypogonadism (congenital or acquired): testicular failure due to cryptorchidism, bilateral torsion, orchitis, vanishing testis syndrome, orchidectomy.
b. Hypogonadotrophic hypogonadism (congenital or acquired)-idiopathic gonadotropin or LHRH [luteinizing-hormone-releasing hormone] deficiency, or pituitary-hypothalamic injury from tumors, trauma, or radiation."

The following are the different preparations and routes of administration:

- Oral Testosterone: The only commercially available oral testosterone products include testosterone undecanoate. There are currently 3 branded products which are not substitutable with one another. Oral testosterone is readily absorbed from the intestine and is rapidly metabolized by the liver. The rapid metabolism in the liver limits its clinical utility because it is difficult to maintain steady serum levels. In addition, the first pass through the liver may increase the probability of liver toxicity.
- Nasal Gel: Testosterone may be administered as a nasal gel, but this dosage form is limited by frequent administration (3 times daily).
- Intramuscular Testosterone: Testosterone undecanoate is an intramuscular (IM) depot preparation that is slowly absorbed into the circulation. It is administered by deep IM injection every 10 to 14 weeks and thus has the advantage of infrequent dosing. Disadvantages of this preparation include the IM injection route, which can be painful, and also inconsistent rates of absorption. Inconsistent absorption can lead to fluctuating testosterone levels and related clinical symptoms. Other intramuscular testosterone products include testosterone enanthate and testosterone cypionate.
- Topical Patch: Topical testosterone patches can be applied to non-genital skin areas. Patches are generally dosed once per day and result in stable testosterone levels over time. A limiting factor of patch use is the development of skin irritation at the patch site in a high percentage of users.
- Topical Gels: A number of topical testosterone gel preparations are commercially available. They range in strength from 1% to 2% and provide stable serum levels. The gel is applied daily on non-genital skin areas. Precautions need to be taken to avoid transmission of the drug to others by direct contact. Therefore, it is recommended that the gel is placed on covered skin and that hand washing is performed after application.
- Subcutaneous Pellets: Another depot formulation is a subcutaneous testosterone pellet. The pellets are placed subcutaneously in the buttocks, abdominal wall, or thigh under local anesthesia. They are replaced every 3 to 6 months. Limitations include the need for minor surgical procedures, and local reactions at the implantation site (e.g., infections, fibrosis).
- Subcutaneous Solution: Testosterone enanthate and testosterone cypionate can be administered subcutaneously once weekly.

Monitoring Strategies for Individuals on Testosterone Therapy

Monitoring of testosterone replacement should be performed beginning 3 to 6 months after replacement is initiated to ascertain whether serum levels are restored to the normal range, to

determine whether clinical symptoms have improved, and to monitor for adverse events. The goal of testosterone replacement is to raise levels into the mid-normal range. Higher replacement levels are unlikely to improve symptoms further and may increase the incidence and/or severity of adverse events.

Recommendations for monitoring for testosterone-related adverse events have been provided by the Endocrine Society guidelines on testosterone therapy in men with androgen deficiency. (1) These recommendations include:

- Determine hematocrit levels at baseline, at 3 to 6 months, and then annually. If the hematocrit level is above 54%, stop therapy until the hematocrit level decreases to a safe level, evaluate the patient for hypoxia and sleep apnea, and reinitiate therapy at a reduced dose.
- Repeating bone mineral density of the lumbar spine, femoral neck, and hip after 1 to 2 years of testosterone therapy in hypogonadal men with osteoporosis.
- For men 55 to 69 years of age, and for men 40 to 69 years of age who are at increased risk for prostate cancer, conduct a digital examination of the prostate and prostate-specific antigen (PSA) measurement before initiating treatment, at 3 to 12 months after initiating treatment, and then in accordance with evidence-based guidelines for prostate cancer screening, depending on the age and race of the individual.
- Obtain urological consultation if there is:
    - An increase in serum or plasma PSA concentration greater than 1.4 ng/mL within 12-months of initiating testosterone treatment.
    - A confirmed PSA of more than 4 ng/mL at any time.
    - Detection of a prostatic abnormality on digital rectal examination.
    - Substantial worsening of lower urinary tract symptoms.

Regulatory Status

Numerous preparations of testosterone have been approved by the FDA for use in testosterone replacement therapy. They include IM, oral, topical, subcutaneous, nasal, and buccal (no longer available in the U.S.) preparations.

In March 2015, the FDA issued a drug safety communication for prescription testosterone products. (7) The communication stated: “We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.”

The communication also stated: “FDA has concluded that there is a possible increased cardiovascular risk associated with testosterone use. These studies included aging men treated with testosterone. Some studies reported an increased risk of heart attack, stroke, or death associated with testosterone treatment, while others did not.”

Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function-including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

There is a large body of literature that evaluates the efficacy of testosterone replacement therapy. This body of evidence is primarily characterized by small- to medium-sized trials of short duration. There is a high degree of variability in the patient populations, dosing and delivery methods for testosterone replacement, and outcomes measured. There are also numerous systematic reviews of the available evidence. This policy focuses on the impact of testosterone on specific symptoms for adults with androgen deficiency and clinical symptoms of hypogonadism, and on the benefit for specific subpopulations. The discussion emphasizes the available systematic reviews and larger individual RCTs.

Androgen Deficiency and Clinical Symptoms of Hypogonadism
Testosterone replacement therapy is the primary treatment for androgen deficiency in men. Testosterone replacement is intended to counter the adverse effects of low testosterone levels.

There are numerous U.S. Food and Drug Administration approved testosterone formulations available for replacement therapy.

Systematic Reviews
A large number of systematic reviews that assess only RCTs or RCTs and non-RCTs have been published over the last 2 decades and reported on outcomes such as sexual function, (8-10) body composition, (11, 12) and bone mineral density (BMD) (13, 14) while individual RCTs have evaluated the impact of testosterone on depression (15-17) and cognition. (18) These are not

detailed here because they are outdated and/or include results of non-RCTs. A more recent systematic review that only included data from RCTs with low bias is discussed next.

The Endocrine Society commissioned a systematic review and meta-analysis, conducted by Ponce et al. (2018), to determine whether testosterone replacement therapy 1) improves sexual function, physical function, fatigue, mood, cognition, anemia, and BMD in men with hypogonadism and 2) is associated with an increased risk of lower urinary tract symptoms and erythrocytosis in men with hypogonadism. (19) The systematic review evaluated only placebo-controlled randomized trials (4 RCTs; n=1779) that assigned men with symptomatic hypogonadism with total testosterone level less than 300 ng/dL at the screening. The systematic review of characteristics and results are summarized in Tables 1 and 2. Results reported that testosterone replacement therapy was associated with a small but statistically significant improvement in libido, erectile function, sexual activity, and sexual satisfaction compared with placebo but no differences in energy levels or mood. Compared with placebo, testosterone treatment was associated with a significantly higher frequency of erythrocytosis but there was no significant difference in the change in lower urinary tract symptoms. Strengths of this review were the inclusion of only RCTs that were low-risk of bias, participants who met criteria for the diagnosis of hypogonadism (testosterone level ≤300 ng/dL, and presence of ≥1 symptoms or signs of hypogonadism), and reported outcomes were deemed clinically relevant and important to patients and ascertained using validated instruments. Limitations included the heterogeneity of instruments used to ascertain outcomes across trials, hypogonadism of multiple etiologies and lack of individual patient data meta-analysis to ascertain the relation between symptoms improvement and testosterone levels. Further, none of the trials selected in the systematic review were long enough or large enough to have sufficient statistical power to ascertain safety outcomes (prostate cancer, cardiovascular events, bone fractures).

Table 1. Systematic Review of Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration, week
Ponce et al. (2018) (19)	To 2017	4	Symptomatic hypogonadism with total testosterone level <300 ng/dL at screening	1779 (NR)	RCT	12-52

NR: not reported; RCT: randomized controlled trial.

Table 2. Systematic Review Results

Study	Libido	Erectile Function	Sexual Activity	Sexual Satisfaction	Energy	Mood	Erythrocytosis	LUTS
Ponce et al. (2018) (19)								
n	1383	1344	1486	676	1503	1179	1579	866
SMD, RR, or MD (95% CI)	0.17[a] (0.01 to 0.34)	0.16[a] (0.06 to 0.27)	0.23[a] (0.13 to 0.33)	0.16[a] (0.01 to 0.31)	0.08[a] (-0.02 to 0.18)	0.08[a] (-0.03 to 0.20)	8.14[b] (1.87 to 35.40)	0.38[c] (20.67 to 1.43)

CI: confidence interval; LUTS: lower urinary tract symptoms; MD: mean difference; RR: relative risk; SMD: standardized mean difference.
[a] SMD.
[b] RR.
[c] MD.

Randomized Controlled Trials

The National Institutes of Health sponsored 7 double-blind, placebo-controlled randomized trials that evaluated whether testosterone treatment of elderly men with low serum testosterone concentrations and symptoms and objective evidence of impaired mobility and/or diminished libido and/or reduced vitality would be efficacious in improving mobility (Physical Function Trial), sexual function (Sexual Function Trial), fatigue (Vitality Trial), cognitive function (Cognitive Function Trial), hemoglobin (Anemia Trial), bone density (Bone Trial), and coronary artery plaque volume (Cardiovascular Trial). (20) The major consideration in participant selection in these trials was a requirement of serum testosterone low enough to ensure that the men were unequivocally testosterone deficient, but not so low as to preclude sufficient enrollment or eventual generalizability of the results. Men were randomized to 12 months of testosterone gel (1%) or to placebo gel. General eligibility criteria for all trials age 65 years or older with serum testosterone levels averaging less than 275 ng/dL. Exclusion criteria were a history of prostate cancer, at high-risk of prostate cancer, International Prostate Symptom Score (IPSS) greater than 19, a condition known to cause hypogonadism, or at high cardiovascular risk. There were also trial-specific eligibility criteria. The Sexual Function Trial required decreased libido and a partner willing to have intercourse twice a month. The Physical Function Trial required difficulty walking or climbing stairs and gait speed of less than 1.2 m/s on the 6-minute walk test. The Vitality Trial required low vitality (self-report and indicated by the score on a validated test). Results are summarized in Table 3. Briefly, testosterone treatment resulted in substantial benefit for sexual function, anemia, and bone density outcomes but had a small impact on physical function and vitality and no effect on cognition. Although testosterone treatment was associated with an increase in coronary artery noncalcified plaque volume, the number of cardiovascular or prostate adverse events were comparable with the placebo arm. The major limitation of these trials is that the results apply only to men ages 65 years and older with confirmed testosterone concentrations less than 275 ng/dL and durability of treatment effect beyond a year has not been demonstrated. (21)

Table 3. Results From the Primary Outcomes of the 7 NIH-Sponsored Testosterone Trials

Trial and Outcomes	N	Mean Difference or OR (95% CI)[a]	Effect Size (95% CI)[b]	p
Sexual Function Trial				
PDQ-Q4 score[c]	459	0.58 (0.38 to 0.78)	0.45 (0.30 to 0.60)	<0.001
Sexual desire, DISF-M-II score	470	2.93 (2.13 to 3.74)	0.44 (0.32 to 0.56)	<0.001
Erectile function, IIEF score	470	2.64 (1.68 to 3.61)	0.32 (0.20 to 0.44)	<0.001
Physical Function Trial				
Men with ≥50 m increase in 6MWD test, %[c]	387	1.42 (0.83 to 2.45)	Not reported	0.20

6MWD, m	387	4.09 (-3.00 to 11.8)	0.06 (0.004 to 0.16)	0.28
Men whose PF-10 score increased ≥8, %	365	1.34 (0.90 to 2.00)	Not reported	0.15
PF-10 score	365	2.75 (0.20 to 5.29)	0.13 (0.01 to 0.26)	0.03
Vitality Trial				
Energy, increase ≥4 in FACIT-Fatigue score, %[c]	474	1.23 (0.83 to 1.84)	Not reported	0.30
Energy, FACIT-Fatigue score	471	1.21 (-0.04 to 2.46)	0.19 (-0.01 to 0.38)	0.03
SF-36 vitality score	404	2.41 (0.31 to 4.50)	0.18 (0.02 to 0.34)	0.03
Positive affect, PANAS score	463	0.47 (0.02 to 0.92)	0.14 (0.01 to 0.27)	0.04
Negative affect, PANAS score	463	-0.49 (-0.79 to -0.19)	-0.18 (-0.29 to -0.06)	<0.001
Depression, PHQ-9 score	464	-0.72 (-1.20 to -0.23)	-0.18 (-0.30 to -0.06)	0.004
Cognitive Function Trial				
Verbal memory; delayed paragraph recall[c]	493	-0.07 (-0.92 to 0.79)	-0.01 (-0.14 to 0.12)	0.88
Visual memory; Benton Visual Retention Test	492	-0.28 (-0.76 to 0.19)	-0.09 (-0.24 to 0.06)	0.24
Spatial ability; card rotation test	488	-0.12 (-1.89 to 1.65)	-0.01 (-0.13 to 0.11)	0.89
Executive function; Trail Making Test B-A, s[d]	490	-5.51 (-12.91 to 1.88)	-0.09 (-0.22 to 0.03)	0.14
Anemia Trial				
Hemoglobin increase from baseline ≥1.0 g/dL, %[c,e]	62	31.5 (3.7 to 277.8)	Not reported	0.002
Hemoglobin, g/dL[e]	62	0.83 (0.48 to 1.39)	1.30 (0.75 to 2.18)	0.001
Hemoglobin increase from baseline ≥1.0 g/dL, %[f]	64	8.2 (2.1 to 31.9)	Not reported	0.003
Hemoglobin, g/dL[f]	64	0.64 (0.12 to 1.17)	0.90 (0.17 to 1.65)	0.018
Bone Trial				
Spine trabecular BMD, % change from baseline[c]	207	6.8 (4.8 to 8.7)	0.23 (0.17 to 0.29)	0.001
Spine whole bone BMD, % change from baseline[d]	207	4.2 (3.2 to 5.3)	0.12 (0.09 to 0.15)	0.001
Hip trabecular BMD, % change from baseline	191	1.5 (0.9 to 2.0)	0.04 (0.03 to 0.06)	0.001
Hip whole bone BMD, % change from baseline	191	1.3 (0.8 to 1.7)	0.03 (0.02 to 0.04)	0.001
Cardiovascular Trial				
Noncalcified coronary artery plaque volume,[c] mm^3	138	41 (14 to 67)	0.11 (0.04 to 0.19)	0.003
Total coronary artery plaque volume, mm^3	138	47 (13 to 80)	0.09 (0.02 to 0.15)	0.006

Coronary artery calcium score, Agatston units	138	-27 (-80 to 26)	-0.03 (-0.07 to 0.02)	0.31

Adapted from Snyder et al. (2018). (21)
BMD: bone mineral density; CI: confidence interval; DISF-M-II: Derogatis Inventory of Sexual Function-Men-II, sexual desire domain (range, 0-33); FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue (range, 0-52, higher scores indicate less fatigue); IIEF: International Index of Erectile Function, erectile function domain (range, 0-30); NIH: National Institutes of Health; OR: odds ratio; PANAS: Positive and Negative Affect Scale (range, 5-50); PDQ-Q4: Psychosexual Daily Questionnaire (range, 0-12, higher scores indicate a greater number of activities); PF-10, physical function scale of the Medical Outcomes Short Form Health Survey (range, 0-100); PHQ-9: Patient Health Questionnaire 9 (range, 0-27; higher scores indicate a greater degree of depressive symptoms); SF-36, 36-item Short-Form Survey (range, 0-100); 6MWD: 6-minute walk distance.
[a] Treatment effect: for continuous outcomes, the treatment effect was the mean change in men allocated to testosterone minus the mean change in men allocated to placebo, adjusted for balancing factors: baseline total testosterone level (≤200 or >200 ng/dL), age (≤75 or >75 years), trial site, participation in the main trials, use or nonuse of antidepressants, use or nonuse of phosphodiesterase type 5 inhibitors, and baseline value of the outcome variable; for binary outcomes, the adjusted OR was the ratio of the outcome in men allocated to testosterone to the outcome in men allocated to placebo, adjusted for the same balancing factors.
[b] The effect size for continuous outcomes was calculated from the mean difference divided by the baseline standard deviation pooled across treatment arms; an effect size of 0.2 is considered a small effect, 0.5 a medium effect, and 0.8 a large effect.
[c] Primary outcome measure.
[d] Lower scores reflect better function.
[e] Among men with unexplained anemia.
[f] Among men with anemia of known cause.

Section Summary: Androgen Deficiency and Clinical Symptoms of Hypogonadism

For men with low testosterone levels and sexual dysfunction, evidence from RCTs and meta-analyses has demonstrated a beneficial effect on increased libido. Other sexual symptoms (e.g., erectile dysfunction) are also likely to be improved, but the evidence is less strong. For non-sexual symptoms, there is evidence that lean body mass increased, body fat decreased, and BMD increased with testosterone therapy. However, the impact of these changes on functional status and fractures is less clear. For outcomes such as decreased energy, depression, quality of life, and cognition, the evidence is limited and inconsistent in reporting the benefits of replacement therapy.

Androgen Deficiency and Human Immunodeficiency Virus (HIV) Infection

There is a high prevalence of androgen deficiency in individuals with HIV infection who are on antiretroviral treatment, with up to 25% of this population having low testosterone levels. Men with low levels of testosterone have worse outcomes of HIV disease, including faster disease progression, greater loss of muscle mass, and larger declines in physical functioning. (2)

Systematic Reviews

A systematic review of testosterone replacement in HIV-infected men with weight loss was performed by Bhasin et al. (2006). (22) They identified 8 trials of testosterone replacement in

HIV-infected patients with weight loss. The trials were of variable quality and heterogeneous in their methodologies. Combined analysis of changes in body weight, fat-free mass, and lean body mass was performed. There was an estimated increase of 1.1 kg in body weight (95% CI, 0.2 to 2.0 kg), 1.4 kg in fat-free mass (95% CI, 0.7 to 2.1 kg), and 1.3 kg in lean body mass (95% CI, 0.4 to 2.2 kg) associated with testosterone replacement. Reviewers also assessed the outcomes of muscle strength and depression. Three trials reported on changes in muscle strength, with 2 of 3 reporting significant improvements with testosterone therapy. Four trials reported on changes in depression, with combined analysis showing a modest improvement in depression scores for testosterone-treated patients. There were no significant changes in parameters of HIV infection (e.g., T lymphocyte or viral load for patients treated with testosterone).

Another systematic review and meta-analysis was performed by Santi et al. (2021) to determine the effectiveness of androgen administration on body composition in HIV-infected men. (23) They identified 17 trials (N=1267) investigating testosterone replacement therapy in HIV-infected individuals with weight loss. The studies were highly heterogeneous in their methodologies. Body weight changes were reported in 12 studies (n=734). There was an estimated mean difference (MD) increase in weight of 0.99 kg (95% CI, 0.25 to 1.72; p=.008), favoring testosterone. In a similar trend, the lean body mass and fat free mass changes were higher in the testosterone group compared to the control group (lean body mass MD, 2.67; 95% CI, 1.46 to 3.87; p<.0001; fat free mass MD, 2.99; 95% CI, 2.38 to 3.60; p<.00001). These results are limited by the high heterogeneity in methods amongst included trials.

Section Summary: Androgen Deficiency and HIV Infection

RCTs of patients with HIV infection and weight loss, included in 2 systematic reviews, found that testosterone replacement was associated with an increase in body weight and lean body mass and a decrease in body fat. Findings from these trials would suggest that testosterone replacement is likely to ameliorate the weight loss associated with HIV infection.

Androgen Deficiency and Chronic Steroid Treatment

Individuals treated with chronic steroid therapy have lower levels of testosterone compared with age-matched patients without chronic steroid use. This effect of steroids is thought to suppress the hypothalamic-pituitary axis as well as testosterone production in the testes. This hormonal suppression contributes to the increase in abdominal fat and decrease in BMD seen in patients treated chronically with steroids.

Systematic Reviews

The systematic review by Bhasin et al. (2006; discussed previously) identified 2 placebo-controlled randomized trials of testosterone replacement in patients on chronic steroid treatment for asthma or chronic obstructive pulmonary disease. (22) The trials were limited by small sample size and short duration of follow-ups. Pooled analysis of the 2 trials showed a significant increase in lean body mass of 2.3 kg (95% CI, 2.0 to 3.6 kg) and a significant decrease in fat mass of 3.1 kg (95% CI, -2.8 to -3.5 kg). There was also a significant improvement in

lumbar bone density of 4% (95% CI, 2% to 7%), although there was no significant improvement in BMD of the femoral neck.

Section Summary: Androgen Deficiency and Chronic Steroid Treatment

A meta-analysis of 2 RCTs in men receiving chronic steroid treatment found a significant increase in lean body mass and a significant decrease in fat mass in individuals receiving testosterone therapy vs placebo. Thus, the evidence would suggest that testosterone is likely to ameliorate adverse events related to chronic steroid use on these parameters.

Androgen Deficiency and Type 2 Diabetes

Systematic Reviews

Several systematic reviews have evaluated the use of testosterone supplementation in men with type 2 diabetes and hypogonadism. Selected systematic reviews are summarized in Tables 4 to 6. Kumar et al. (2022) published a systematic review and meta-analysis evaluating testosterone supplementation with men with hypogonadism and type 2 diabetes. (24) Twelve RCTs and 1 observational study (N=1596) were included. Improved glycemic control and lipid profiles were found in men treated with testosterone.

Zhang et al. (2018) published a systematic review and meta-analysis evaluating the effects of testosterone supplement treatment in hypogonadal men with type 2 diabetes. (25) Eight RCTs with a total of 596 participants were included (all but 3 of which are also included in Cai et al. [2014] below, and all of which are included in Kumar et al. [2022] above). Meta-analysis showed that testosterone supplement treatment can significantly improve glycemic control by reducing homeostatic model assessment of insulin resistance (MD, -0.79; 95% CI, -1.23 to -0.34), fasting glucose (MD, -0.98; 95% CI, -1.13 to -0.54), fasting insulin (MD, -2.47; 95% CI, -3.99 to -0.95), and HbA_{1c} % (MD, -0.45; 95% CI, -0.73 to -0.16). Also, results showed a decline in cholesterol (MD, -0.29; 95% CI, -0.38 to -0.19) and triglyceride (MD, -0.37; 95% CI, -0.59 to -0.15). Study limitations include lack of generalizability due to the racial and ethnic homogeneity of study populations, adjusted estimates were not performed due to insufficient data, and the variation in testosterone regimens between studies.

Cai et al. (2014) reported on the results of a systematic review and meta-analysis of RCTs that evaluated the effect of testosterone therapy on metabolic parameters in patients with type 2 diabetes and hypogonadism. (26) Five RCTs (N=351 subjects) identified met eligibility criteria, 3 of which were double-blind, placebo-controlled trials and 2 of which were open-label and single-blind, no-treatment controlled trials. In pooled analysis, testosterone was associated with reduced fasting plasma glucose levels (mean difference [MD], -1.10; 95% CI, -1.88 to -0.31), fasting insulin levels (MD, -2.73; 95% CI, -3.63 to -1.84), hemoglobin A_{1c} (HbA_{1c}) level (MD, -0.87; 95% CI, -1.32 to -0.42), and triglyceride levels (MD, -0.35; 95% CI, -0.62 to -0.07).

Table 4. Comparison of Studies Included in Systematic Reviews and Meta-Analyses

Study	Kumar et al. (2022) (24)	Zhang et al. (2018) (25)	Cai et al. (2014) (26)
Boyanov (2003) (27)	X	X	X

Dhindsa (2015) (28)	X	X	
Gianatti (2014) (29)	X	X	
Gopal (2010) (30)	X	X	X
Groti (2018) (31)	X		
Groti (2020) (32)	X		
Hackett (2014) (33)	X	X	
Hackett (2019) (34)	X		
Heufelder (2009) (35)	X	X	X
Jones (2011) (36)	X	X	X
Kapoor (2006) (37)	X	X	X
Khripun (2018) (38)	X		
Yassin (2029) (39)	X		

Table 5. Systematic Reviews and Meta-Analysis Characteristics

Study	Dates	Trials	Participants	N (Range)	Design	Duration
Kumar et al. (2022) (24)	Through May 5, 2022	13	Men with hypogonadism and type 2 diabetes	1596 (22-537)	12 RCT; 1 Observational	NR
Zhang et al. (2018) (25)	Up to Jan 2018	8	Men with hypogonadism and type 2 diabetes	596 (22-186)	RCT	12-52 weeks
Cai et al. (2014) (26)	Through July 2013	5	Men with hypogonadism and type 2 diabetes	351 (22-137)	RCT	NR

NR: not reported; RCT: randomized controlled trial.

Table 6. Systematic Review and Meta-Analysis Results

Study	Fasting Glucose	HbA1c	HDL	TG	BMI
Kumar et al. (2022) (24)					
Total N	1102	1454	1639	1639	1291
WMD (95% CI)	-0.35 (-0.79 to 0.10)	-0.35 (-0.64 to -.006)	0.07 (0.00 to 0.13)	-0.23 (-0.43 to -0.03)	-0.16 (-0.45 to 0.14)
I^2 (p)	*69.7%* (.07)	*47.5%* (.17)	*0%* (.8)	*79.2%* (.03)	*0%* (.58)
Zhang et al. (2018) (25)					
WMD (95% CI)	-0.98 (-1.43 to -0.54)	-0.45 (-0.76 to -0.16)	0.01 (-0.08 to 0.09)	-0.37 (-0.59 to -0.15)	0.29 (-0.84 to 1.41)
I^2 (p)	*82.7%* (.00)	*86.9%* (.00)	*88.0%* (.00)	*60.1%* (.014)	*59.9%* (.021)
Cai et al. (2014) (26)					
Total N	300	124		269	

WMD (95% CI)	-1.10 (-1.88 to -0.31)	-0.87 (-1.32 to -0.42)		-0.35 (-0.62 to -0.07)	
I^2 (p)	*78.7%* (.009)	*36%* (.0001)		*0%* (.01)	

BMI: body mass index; CI: confidence interval; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; TG: triglycerides; WMD: weighted mean difference.

Section Summary: Androgen Deficiency and Type 2 Diabetes

Several systematic reviews of RCTs have assessed testosterone replacement in individuals with hypogonadism and type 2 diabetes. Beneficial effects of testosterone replacement were seen on blood glucose and lipid parameters; however, authors of the most recent systematic review noted several limitations including the short follow-up period in many studies, the variability in testosterone dose and dosage from, and lack of clinical outcomes including cardiovascular events. In addition, the majority of studies were noted to have selective reporting bias. The benefits may be outweighed by the increased risk of adverse events of treatment in the diabetic population.

Older Men with Low Testosterone Levels Without Definite Hypogonadism

Randomized Controlled Trials

A few RCTs have evaluated the impact of testosterone replacement in elderly males with low testosterone levels, without definite evidence of hypogonadism. Most trials have been small and included only a limited range of outcomes. The largest RCTs are discussed next.

Mok et al. (2020) published the results of a randomized, double-blind, placebo-controlled study that enrolled 45 men aged at least 40 years without pathologic hypogonadism but with androgen deficiency-like energy and/or sexual symptoms to either daily testosterone or placebo gel treatment for 6 weeks. (40) The trial included 3 phases including a cross-over study design for the first 2 phases followed by a third mandatory extension phase in which participants chose which previous treatment they preferred to repeat while remaining masked to their original treatment. Primary endpoints were energy and sexual symptoms as assessed by a visual analog scale called lead symptom score. Results showed that 6 weeks of treatment with testosterone did not improve energy or sexual symptoms more than placebo in symptomatic men without pathologic hypogonadism.

Traustadottir et al. (2018) performed a double-blind, randomized, placebo-controlled, parallel-group trial to determine the effects of testosterone supplementation on oxygen consumption (VO2) peak during incremental cycle ergometry for older men with low testosterone. (41) Patients were randomized to either the testosterone group (n=69) or placebo group (n=60). Men in the testosterone group maintained the same VO2 peak from baseline (24.2 ± 5.2 mL/kg/min); however, the VO2 peak fell significantly from baseline (23.6 ± 5.6 mL/kg/min) for the placebo group (average 3-year decrease, 0.88 mL/kg/min; 95% CI, -1.39 to 0.38 mL/kg/min; p=0.035). There was significant change in the difference in VO2 peak between groups (average 3-year difference, 0.91 mL/kg/min; 95% CI, 0.010 to 0.122 mL/kg/min; p=0.008). A limitation of the study was the participants who completed measures of aerobic capacity across the time points were limited to one site.

A larger multicenter RCT reported by Legros et al. (2009) from Europe, enrolled 322 patients who were 50 years or older, with mild-to-moderate symptoms of hypogonadism and a low testosterone level. (42) Patients were randomized to daily testosterone 80, 160, or 240 mg or to placebo, and the primary outcome was the change in the Aging Males Symptom (AMS) scale at 6 months. There were no statistically significant differences in the total AMS score between groups at 6 months, although the scores in the testosterone group showed a greater numeric improvement. There was a statistically significant difference in the AMS sexual domain subscore for the testosterone 160-mg testosterone group, but not for the 80- and the 240-mg groups. There were no statistically significant differences in adverse events between groups, including the change in prostate-specific antigen (PSA) level.

A trial by Emmelot-Vonk et al. (2008) enrolled 237 men between the ages of 60 to 80 years who had low testosterone levels but were otherwise healthy. (43) Patients were randomized to oral testosterone 80 mg or to placebo and followed for 6 months. A range of outcome measures were reported, including functional mobility, body composition, muscle strength, cognitive function, BMD, metabolic parameters, and quality of life. Safety outcomes were also included: PSA, prostate volume, renal function, liver function, and hematocrit levels. For most outcome measures, there was no improvement in the testosterone group compared with placebo therapy. There was an increase in lean body mass and a decrease in the percent body fat. However, these changes were not accompanied by improvements in functional capacity or muscle strength. There were no significant changes in cognitive function, BMD, or quality of life. There was worsening metabolic profile, though not statistically significant (p=0.07), with 47.8% of men in the testosterone group meeting the definition for metabolic syndrome at the end of the study compared with 35.5% of men in the placebo group. There was a significant, but small, increase in hematocrit concentration for men in the testosterone group, and an increase in creatinine levels that was of borderline significance. Otherwise, there were no group differences in safety outcomes.

Several smaller RCTs have been published, ranging in size from 13 to 131 patients. (44-48) The most consistent finding reported in these trials was an increase in lean body mass (4 studies) and a decrease in body fat (3 studies). The impact on strength was mixed, with 2 studies reporting an improvement in the testosterone group and 2 studies reporting no difference between groups. An increase in hemoglobin and/or hematocrit concentration was reported in 1 study, and an increase in BMD was reported in another. None of these RCTs reported on functional status, quality of life, or sexual performance.

Section Summary: Older Men with Low Testosterone Levels Without Definite Hypogonadism
Several RCTs have been published, and most have been small and reported on a limited range of clinical outcomes. For most outcomes reported, there was no significant benefit reported for testosterone replacement. Some studies have reported improvements in lean body mass and decreased body fat, and 1 RCT reported improvement in sexual function. However, these trials did not report improvements in functional status or muscle strength. The adverse event profile of testosterone therapy is not well-defined, and there have been concerns about increased

adverse prostate-related outcomes and cardiovascular outcomes. This uncertainty in the adverse event profile creates challenges in determining the risk-benefit profile of treatment in otherwise healthy men.

Adverse Events of Testosterone Therapy

There is a long list of potential adverse events with testosterone replacement, as follows (6):

- Prostate-related events, including development or worsening of prostate cancer, prostatic hypertrophy, increases in PSA levels, and symptoms of prostatism;
- Cardiovascular events;
- Adverse changes in lipid profile;
- Erythrocytosis and increases in hematocrit;
- Precipitation or worsening of sleep apnea;
- Liver toxicity;
- Suppression of spermatogenesis;
- Acne;
- Worsening of male pattern baldness; and
- Gynecomastia.

The clinical significance of many of these potential adverse events is unclear. Several meta-analyses have studied adverse events expected to be more common. This review of adverse events will include both randomized and nonrandomized studies, with emphasis on systematic reviews and meta-analyses of the available studies.

Cardiovascular Events

Systematic Reviews

Corona et al. (2024) conducted a systematic review and meta-analysis evaluating the cardiovascular safety of testosterone replacement therapy in men and included 106 placebo controlled RCTs. (49) The analysis found no difference between testosterone therapy and placebo when analyzing overall major adverse cardiovascular events (MACE). The single trial that looked at cardiovascular safety as the primary endpoint showed an increase in the incidence of non-fatal arrhythmias and atrial fibrillation; however, when all other trials were taken into account, this finding was not supported.

Hudson et al. (2022) evaluated the cardiovascular risk associated with testosterone use in 35 studies (N=5601) published between 1992 and August 27, 2018. (50) Risk of cardiovascular events was similar during testosterone and placebo treatment in men with hypogonadism (7.5% vs. 7.2%; odds ratio [OR], 1.07; 95% CI, 0.81 to 1.42; p=.62). The authors concluded that short- to medium-term studies do not indicate increased risk of cardiovascular events with testosterone replacement in men with hypogonadism.

Albert and Morley (2016) reported the findings of a systematic review that included 45 trials with 5328 subjects with mean age 63.3 years and a mean follow-up of 10.6 months. (51) Over the duration of available follow-up, testosterone treatment was not associated with increased

risk of cardiovascular events (RR=1.10; 95% CI, 0.86 to 1.41; p=0.45). However, there was an increase event rate during the first 12 months (RR=1.79; 95% CI, 1.13 to 2.83; p=0.012), predominantly among those 65 years or older (RR=2.90; 95% CI, 1.35 to 6.21; p=0.006).

Corona et al. (2015) published an overview of previously published meta-analyses on the association between testosterone replacement therapy and cardiovascular risk. (52) Reviewers included the 3 meta-analyses described below, as well as two others, all of which focused on RCT evidence. Reviewers reported that only one of the 5 meta-analyses supported an association between testosterone therapy and an increased cardiovascular risk. They stated that, in the single positive meta-analysis, cases of peripheral edema and self-reported syncope were included in the category of cardiovascular events, which might have overstated the number of clinically significant events. The other 4 meta-analyses did not find significant differences between testosterone and placebo groups in the incidence of overall cardiovascular events or specific events including cardiovascular death, fatal and nonfatal myocardial infarctions (MI), and cerebrovascular events.

Fernandez-Balsells et al. (2010) published a systematic review of randomized and nonrandomized comparative studies. (53) They included 51 studies and examined the outcomes of mortality, cardiovascular events, cardiovascular risk factors, prostate events, and erythrocytosis. Patients treated with testosterone had increased hematocrit concentrations (weighted mean difference [WMD], 3.2%; 95% CI, 1.4% to 5.0%), and decreased high-density lipoprotein (HDL) levels (WMD, 0.5 mg/dL; 95% CI, 0.13 to 0.85 mg/dL). No significant differences were reported in mortality, cardiovascular events, or prostate-related events.

Calof et al. (2005) performed a meta-analysis of placebo-controlled randomized trials. (54) Nineteen studies were selected (N=1084 patients) and assessed the outcomes of mortality, prostate-related events, changes in hematocrit concentration, and sleep apnea. Patients treated with testosterone were more likely to have a hematocrit greater than 50% (OR=3.7; 95% CI, 1.8 to 7.5). There were no significant differences in mortality, cardiovascular events, or sleep apnea.

In another systematic review of placebo-controlled randomized trials, Haddad et al. (2007) examined the rates of adverse cardiovascular events and changes in cardiovascular risk factors. (55) This review included 30 trials (N=1642 men). Total adverse cardiovascular events were numerically more frequent in testosterone-treated patients, but the difference compared with placebo was not statistically significance (OR=1.8; 95% CI, 0.8 to 4.2). There were small changes in blood pressure, lipid levels, and glucose, but none of these changes were statistically significant.

Randomized Controlled Trials

Lincoff et al. (2023) evaluated the cardiovascular safety of testosterone replacement therapy in a multicenter noninferiority trial in middle-aged and older men with hypogonadism. (56) Patients (N=5,246) were randomized to receive daily transdermal testosterone gel or placebo gel. The noninferiority margin was an upper limit of <1.5 for the 95% CI of the hazard ratio

among patients who received at least 1 dose of testosterone or placebo. One hundred eighty-two patients (7.0%) in the testosterone group and 190 patients (7.3%) in the placebo group experienced a primary cardiovascular outcome incident (hazard ratio, 0.96; 95% CI, 0.78 to 1.17; p<0.001 for noninferiority). In both groups, the incidence of secondary end-point events (i.e., first occurrence of any component of the composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization in a time-to-event analysis) were comparable.

Cohort Studies

In addition to RCTs and meta-analyses of them, several large cohort studies have been published. Finkle et al. (2014) conducted a large retrospective cohort study using administrative claims data to assess the relation between testosterone therapy and nonfatal MI. (57) The authors generated a cohort of 55,593 men who filled their first prescription for one of several testosterone prescriptions between 2008 and 2010 from the Truven Health MarketScan® Commercial Claims and Encounters Database, which includes diagnoses, procedures, and prescriptions for all enrollees of contributing health plans. Testosterone recipients were compared with a population of men who filled their first prescription for a phosphodiesterase type 5 inhibitor (PDE5I; sildenafil or tadalafil; N=167,279) during the same time period. For testosterone recipients, the rate ratio (RR) of MI in the post- compared with the pre-testosterone period was 1.36 (95% CI, 1.03 to 1.81). Compared with subjects in the PDE5I group, the rate ratio for MI risk for testosterone recipients was 1.90 (95% CI, 1.04 to 3.49). After stratifying by age, for testosterone recipients younger than age 55 years, the RR for MI in the post-testosterone period was 0.95 (95% CI, 0.54 to 1.67); for testosterone recipients ages 75 and older, the RR for MI in the post-testosterone period was 3.43 (95% CI, 1.54 to 7.56; p=0.03 for trend). No similar trend was seen for PDE5I recipients. Although this study suggested an association between testosterone use and nonfatal MI, it was limited by its retrospective design and the potential for confounding by measured and unmeasured variables.

Another large retrospective cohort study conducted by Baillargeon et al. (2014) evaluated administrative claims data from Medicare to assess the relation between testosterone administered IM and the risk of MI. (58) The study included 6355 Medicare beneficiaries who received at least 1 testosterone injection between 1997 and 2005 and who were matched in a 1:3 ratio to 19,065 testosterone nonusers based on a composite MI prognostic score. After adjustment for demographic and clinical covariates, testosterone therapy was not associated with an increased risk of MI (adjusted hazard ratio [HR]=0.84; 95% CI, 0.69 to 1.01). Testosterone therapy was associated with a reduced risk of MI in men with a MI prognostic score in the highest quartile (HR=0.69; 95% CI, 0.53 to 0.92), while men in the lower three quartiles showed no difference in MI risk with testosterone therapy.

A large retrospective comparative cohort study by Vigen et al. (2013) evaluated the risk of cardiovascular events in patients treated with testosterone replacement therapy. (59) This study used data from the Veterans Administration Clinical Assessment Reporting and Tracking Program to identify all male patients who had both undergone coronary angiography and had a total testosterone level checked between 2005 and 2011. There were 8709 patients with a low

testosterone level, defined as less than 300 ng/dL. The population had high levels of comorbidity, with 80% of patients having coronary artery disease, 50% diabetes, and 20% prior to MI. There were 1223 patients treated with testosterone and 7486 who were not. After a mean follow-up of 27.5 months, the primary outcome of all-cause mortality, MI, or stroke was more frequent in the group treated with testosterone (HR, 1.29; 95% CI, 1.04 to 1.58; p=0.02).

A case-control study performed within a cohort of 934,283 men ages 45 to 80 years was published by Etminan et al. (2015). (60) It identified 30,066 cases of MI and matched each case with 4 controls. There was no evidence of increased current testosterone replacement therapy use in case patients (RR, 1.01; 95% CI, 0.89 to 1.16). There was also no association between past testosterone replacement therapy use and MI or evidence of different risk level by type of preparation. A small increase in risk was reported for first-time testosterone replacement therapy users (RR, 1.41; 95% CI, 1.06 to 1.87).

Effects on Prostate Gland

Several meta-analyses have specifically evaluated the relation between testosterone and prostate-related events. Cui et al. (2013) conducted systematic review of RCTs, which reported on the effect of testosterone replacement on prostate growth. (61) Sixteen RCTs comparing testosterone replacement with placebo (n=1030 patients) were included, 7 of which were short term (<12 months) and 9 long-term (12 to 36 months). Seven studies evaluated transdermally administered testosterone, while 6 evaluated injected testosterone and 3 evaluated orally administered testosterone. In the short-term, transdermal, but not orally administered or injected, testosterone administration was significantly associated with changes in PSA levels (standardized mean difference [SMD], 0.30; 95% CI, 0.07 to 0.54; p=0.002). However, there was no significant association between testosterone administration and PSA levels over the longer term. Testosterone administration by any method was not associated with significant differences in International Prostate Symptom Score (IPSS), prostate volume, or maximum urine flow rate.

In a separate publication, Cui et al. (2014) conducted a systematic review of RCTs that reported on the effect of testosterone replacement therapy on prostate cancer risk. (62) This analysis included 22 RCTs (total N=2351 patients), 11 of which reported short-term (<12 months) outcomes and 11 of which reported long-term (12 to 36 months) outcomes. Five studies evaluated injectable testosterone, 1 evaluated oral testosterone, and 5 studies evaluated transdermal testosterone over the short term; there was no significant association between any administration method and prostate cancer, prostate biopsy, or prostate nodules. However, for the studies evaluating transdermal testosterone, there was a significant association between testosterone treatment and change in PSA level (SMD=0.33; 95% CI, 0.21 to 0.45; p<0.000). There was no association between testosterone therapy and abnormal PSA levels. For long-term administration, 3 studies evaluated injectable testosterone, 2 studies evaluated oral testosterone, and 6 studies evaluated transdermal administered testosterone. There was no significant association between testosterone administration by any method and prostate cancer, prostate biopsy, or prostate nodules. No significant association was found between testosterone administration over the long-term and change in PSA level.

A systematic review by Kohn et al. (2016) identified 14 RCTs on testosterone therapy in aging men and assessed lower urinary tract symptoms with the IPSS. (63) In a pooled analysis, there was no statistically significant difference in change in IPSS among men treated with testosterone vs placebo (p=0.11). Similarly, another systematic review, Kathrins et al. (2016) identified 35 prospective studies and found that most trials did not demonstrate a correlation between testosterone therapy and enlarged prostate volume, de novo lower urinary tract symptoms, or worsening lower urinary tract symptoms. (64)

Venous Thromboembolism

A meta-analysis by Cannarella et al. (2023) evaluated the risk of testosterone replacement therapy and thromboembolic events in patients with pre-treatment total testosterone <12 nmol l-1. (65) Twenty-four studies (which included 14 RCTs) were analyzed. Based on data gathered from RCTs, testosterone replacement therapy did not influence the risk of stroke (OR, 1.34; 95% CI, 0.09 to 18.97; p=0.83), arterial thrombosis (OR, 1.27; 95% CI, 0.47 to 3.43; p=0.64), MI (OR, 0.51; 95% CI, 0.11 to 2.31; p=0.39), pulmonary embolism (OR, 1.38; 95% CI, 0.27 to 7.04; p=0.70), or mortality (OR, 0.70; 95% CI, 0.20 to 2.38; p=0.56). When only evaluating observational cohort study data, there was a significant decrease in the risk of MI, venous thromboembolism, mortality, and arterial thrombotic events.

Houghton et al. (2018) published a systematic review and meta-analysis to determine if there is an association between exogenous testosterone (any route) and venous thromboembolism. (66) Eleven studies (6 RCTs, 5 observational studies) with a total of 1,251,876 (RCT, n=2236; observational, n=1,249,640) patients were included. Meta-analysis of all studies found no significant association between venous thromboembolism and testosterone therapy (OR, 1.41, 95% CI, 0.96 to 2.07); there was also no significant association when stratified by study design: RCT (OR, 2.05, 95% CI, 0.78 to 5.39), cohort studies (OR, 1.06, 95% CI, 0.85 to 1.33), and case-control studies (OR, 1.34, 95% CI, 0.78 to 2.28). The analysis was limited by high heterogeneity among the included studies (I^2=84.4%).

A large case-control study by Baillargeon et al. (2015) evaluated the risk of venous thromboembolism associated with testosterone replacement therapy. (67) This study assessed 30,572 men ages 40 years and older. Subjects had a diagnosis of venous thromboembolism and were on an anticoagulant drug. Cases were matched with 3 controls on age, time of onset, location, diagnosis of hypogonadism, and the presence of a prothrombotic condition. There was no increased risk of testosterone replacement therapy in the venous thromboembolism group (OR=0.91; 95% CI, 0.38 to 2.16). The lack of an association persisted when different time frames of testosterone replacement therapy exposure were examined.

Summary of Evidence

For individuals who have androgen deficiency and clinical symptoms of hypogonadism who receive testosterone replacement therapy, the evidence includes randomized controlled trials (RCTs) and systematic reviews. Relevant outcomes are overall survival (OS), symptoms, morbid events, functional outcomes, and quality of life. For men with low testosterone levels and

sexual dysfunction, the evidence has been fairly consistent in demonstrating a beneficial effect on increased libido. Other sexual function symptoms (e.g., erectile dysfunction) are also likely to be improved, but the evidence is less strong. For other symptoms, there is evidence that lean body mass is increased, body fat is decreased, and bone mineral density is increased with testosterone therapy. However, the impact of these changes on functional status and fractures is less clear. For outcomes such as decreased energy, depression, quality of life, and cognition, the evidence is limited and inconsistent in reporting benefits of replacement therapy. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have androgen deficiency and human immunodeficiency virus (HIV) infection who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. A limited number of trials have included patients with HIV infection and weight loss. These trials have reported improvements in body weight, lean body mass, and a decrease in body fat, which indicates that testosterone replacement is likely to ameliorate weight loss associated with HIV infection. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have androgen deficiency on chronic steroid treatment who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. A limited number of trials have included patients with androgen deficiency in chronic steroid treatment. These trials have reported improvements in body weight, lean body mass, and a decrease in body fat, which are likely to ameliorate the effects of chronic steroids on these parameters. The evidence is sufficient to determine that the technology results in an improvement in the net health outcome.

For individuals who have androgen deficiency and type 2 diabetes who receive testosterone replacement therapy, the evidence includes systematic reviews of RCTs. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. The available systematic reviews have reported that testosterone replacement leads to modest improvements in glucose control (e.g., hemoglobin A_{1c} levels, insulin sensitivity) and lipid parameters. There is a lack of trials reporting on clinical outcomes, and the small benefits may be outweighed by the adverse events of treatment. Current professional guidelines reflect the controversy regarding the balance of risks and benefits. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

For individuals (older men) with low testosterone levels without definite hypogonadism who receive testosterone replacement therapy, the evidence includes RCTs and systematic reviews. Relevant outcomes are OS, symptoms, morbid events, functional outcomes, and quality of life. The available RCTs are mostly small and have reported on a limited range of clinical outcomes. For most outcomes, there was no benefit for testosterone replacement. Some studies have reported improvements in lean body mass and decreased body fat, and a recent RCT found

improved sexual function. However, these studies did not report improvements in functional status or muscle strength. Although the adverse event profile of testosterone therapy is not well-defined, there are concerns about increased adverse prostate-related outcomes and cardiovascular outcomes. This uncertainty in the adverse event profile creates challenges in determining the risk-benefit profile of treatment in otherwise healthy men. The evidence is insufficient to determine that the technology results in an improvement in the net health outcomes.

The U.S. Food and Drug Administration (FDA) has not approved the use of testosterone for the treatment of menopause or sexual dysfunction in women and is considered experimental, investigational and/or unproven. However, for use in women to treat metastatic breast cancer, the FDA has approved specific testosterone enanthate preparations. For this use alone, testosterone replacement therapy may be considered medically necessary.

Practice Guidelines and Position Statements

American Diabetes Association (ADA)

The ADA Comprehensive Medical Evaluation and Assessment of Comorbidities: *Standards of Medical Care in Diabetes-2022* recommends screening with a morning serum testosterone level for men with diabetes who have symptoms of low testosterone (hypogonadism), such as decreased sexual desire or activity, or erectile dysfunction. (68) Treatment in asymptomatic men is controversial. Testosterone replacement in men with symptomatic hypogonadism may have benefits including improved sexual function, well-being, muscle mass and strength, and bone density. In men with diabetes who have symptoms or signs of low testosterone (hypogonadism), a morning total testosterone level should be measured using an accurate and reliable assay. In men who have total testosterone levels close to the lower limit, it is reasonable to check sex hormone–binding globulin, as it is often low in diabetes and associated with lower testosterone levels. Further testing (such as luteinizing hormone and follicle-stimulating hormone levels) may be needed to determine if the patient has hypogonadism. Testosterone replacement in older men with hypogonadism has been associated with increased coronary artery plaque volume and, in some studies, an increase in cardiovascular events, which should be considered when assessing the risks and benefits of treatment. The 2023 ADA standards of care and the 2024 ADA standards echo the 2022 recommendations of screening with a morning serum testosterone level in men with diabetes who have symptoms or signs of hypogonadism. (69, 70)

American Urological Association

The 2018 guidelines for the evaluation and management of testosterone deficiency from the American Urological Association are summarized in Table 7. (71)

Table 7. Practice Guidelines for Evaluation and Management of Testosterone Deficiency

Recommendation	SOR	LOE
Clinicians should adjust testosterone therapy dosing to achieve a total testosterone level in the middle tertial of the normal reference range.	Conditional	Grade C

Exogenous testosterone therapy should not be prescribed to men who are currently trying to conceive.	Strong	Grade A
Clinicians should not prescribe alkylated oral testosterone.	Moderate	Grade B
Commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible.	Conditional	Grade C

SOR: strength of recommendation; LOE: level of evidence.

Endocrine Society

In 2018, the Endocrine Society published clinical practice guidelines on testosterone therapy in men with androgen deficiency (see Table 8). (1)

Table 8. Practice Guidelines on Testosterone Therapy in Men with Hypogonadism

Recommendations	SOR	QOE
“We recommend testosterone therapy in hypogonadal men to induce and maintain secondary sex characteristics and correct symptoms of testosterone deficiency.”	Recommend	Moderate
"We recommend against testosterone therapy in men planning fertility in the near term or in men with breast or prostate cancer, a palpable prostate nodule or induration, a prostate-specific antigen level > 4 ng/mL, a prostate-specific antigen level > 3 ng/mL combined with a high risk of prostate cancer (without further urological evaluation), elevated hematocrit, untreated severe obstructive sleep apnea, severe lower urinary tract symptoms, uncontrolled heart failure, myocardial infarction or stroke within the last 6 months, or thrombophilia."	Recommend	Low
"In hypogonadal men 55 to 69 years old, who are being considered for testosterone therapy and have a life expectancy >10 years, we suggest discussing the potential benefits and risks of evaluating prostate cancer risk and prostate monitoring and engaging the patient in shared decision-making regarding prostate cancer monitoring. For patients who choose monitoring, clinicians should assess prostate cancer risk before starting testosterone treatment and 3 to 12 months after starting testosterone."	Suggest	Very Low
"In hypogonadal men being considered for testosterone therapy who are 40 to 69 years old and at increased risk of prostate cancer (e.g., African Americans and men with a first-degree relative with diagnosed prostate cancer), we suggest discussing prostate cancer risk with the patient and offering monitoring options."	Suggest	Very Low
"In men with type 2 diabetes mellitus who have low testosterone concentrations, we recommend against testosterone therapy as a means of improving glycemic control."	Recommend	Low

Adapted from Bhasin et al. (2018). (1)
SOR: strength of recommendation; QOE: quality of evidence.

Ongoing and Unpublished Clinical Trials

Some currently ongoing and unpublished trials that might influence this policy are listed in Table 9.

Table 9. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT04731376	Perioperative Testosterone Replacement Therapy for the Improvement of Post-Operative Outcomes in Patients With Low Testosterone	100	Oct 2025
NCT04049331	Testosterone Replacement in Male Cancer Survivors With Fatigue and Low Testosterone	240	Jan 2026
NCT04301765	Improving Cancer-related Fatigue, Sexual Dysfunction and Quality of Life in Older Men With Cancer and Androgen Deficiency (TEMEC)	230	Jan 2026
Unpublished			
NCT03518034[a]	A Study to Evaluate the Effect of Testosterone Replacement Therapy (TRT) on the Incidence of Major Adverse Cardiovascular Events (MACE) and Efficacy Measures in Hypogonadal Men (TRAVERSE)	5246	Jan 2023
NCT04456296[a]	A Study of the Effect of Testosterone Replacement Therapy on Blood Pressure in Adult Male Participants With Hypogonadism	676	Jul 2023
NCT03339635	Short-term Testosterone Replacement in Testicular Cancer Survivors	32	July 2024

NCT: national clinical trial.
[a] Denotes sponsorship or cosponsorship by the manufacturer.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	11980, 11981, 11982, 11983
HCPCS Codes	G0516, G0517, G0518, J1071, J1072, J2320, J3121, J3145, S0189

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision

Date	Description of Change
02/01/2025	Document updated with literature change. Coverage unchanged. References 34, 49, 56, 65, and 69 added; others updated.
02/01/2024	Document updated with literature review. Coverage unchanged. References 13, 23, 24, 27-32, 34, 35, 37-40, 49, 65, 66 added; some removed; others revised.
01/01/2023	Reviewed. No changes.
05/01/2021	Document updated with literature review. The following change was made to Coverage: The experimental, investigational and/or unproven in all other situations statement was revised to include older men with type 2 diabetes mellitus and androgen deficiency. References 1, 8, 19-21, 23, 29, 50, 52 and 53 were added, others updated, and some removed.
03/15/2020	Reviewed. No changes.
08/01/2018	Document updated with literature review. The following change was made: NOTE 3 was replaced with EXCEPTION and the statement was revised to Individual consideration may be given for men continuously on therapy for at least one year and a morning total serum level or free testosterone level tested within the last year remains below or within the testing laboratory's

	normal range. References 10-11, 14, 22-24, 35-36, 40, 43-47, 57 added; some references removed.
04/15/2016	Reviewed. No changes.
12/15/2015	Document updated with literature review. The following was added in Coverage section: “NOTE 3: Individual consideration may be given for men currently on therapy when pretreatment levels are not available and the total serum level or free testosterone level remains below or within the testing laboratory’s normal range.” Otherwise, coverage unchanged.
02/12/2015	CPT/HCPCS code(s) updated. Testosterone therapy for women is considered experimental, investigational and/or unproven for ALL conditions, with the exception of treatment for metastatic breast cancer.
12/01/2014	Document updated with literature review. The following criteria was added to the medically necessary coverage statement: “Men requiring testosterone replacement therapy following post-bilateral-orchiectomy” Otherwise, coverage remains unchanged.
10/01/2014	New medical document. Testosterone replacement therapy of one testosterone product may be considered medically necessary when the patient does not have any contraindications noted on the U.S. Food and Drug Administration-approved label for men with an established diagnosis of (primary or secondary) hypogonadism with androgen deficiency, when criteria is met; or HIV-infected men with low testosterone levels and hypogonadal symptoms or significant weight loss (e.g., > 5% lean body mass); or men on chronic-corticosteroid treatment with low testosterone levels and hypogonadal symptoms. Testosterone replacement therapy is considered experimental, investigational and/or unproven in all other situations in which the above criteria are not met, including but not limited to older men with low testosterone levels in the absence of clinical signs and symptoms of hypogonadism. CPT/HCPCS code(s) updated. This topic was previously addressed on RX501.007, Subcutaneous Hormone Implants.