Chicago Metro SUNA
An Official Chapter of the Society of Urologic Nurses and Associates

Testosterone Therapy

Diagnosis and Treatment Options

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Testosterone deficiency: a historical perspective

2014 Mar-Apr; 16(2): 101–108.

- Aristotle knew the effects of castration in reproductive biology
- 1786 John Hunter in London transplanted testes into capons
- 1849 Arnold Adolph Berthold postulated internal secretion from his testicular transplantation experiments
- 1920s Sergio Voronoff transplanted testes from animals to men
- 1935 Enrest Lacquer isolated testosterone from bull testes
- 1950s longer-acting injectable testosterone enanthate

Questionnaire

1. Do you have a decrease in libido (sex drive)?
2. Do you have a lack of energy?
3. Do you have a decrease in strength and/or endurance?
4. Have you lost height?
5. Have you noticed a decreased "enjoyment of life"?
6. Are you sad and/or grumpy?
7. Are your erections less strong?
8. Have you noted a recent deterioration in your ability to play sports?
9. Are you falling asleep after dinner?
10. Has there been a recent deterioration in your work performance?

NOTE. A positive questionnaire result is defined as a "yes" answer to questions 1 or 7 or any 3 other questions.

What Happened?

- In 2013, a study encompassing insurance prescription data on more than 10 million men ages 40 and older from 2001 to 2011 was published in JAMA Internal Medicine. Over that decade, androgen replacement therapy – testosterone prescribed in the form of topical gels, skin patches, pills and injections – more than tripled.
- Testosterone prescriptions for U.S. men ages 30 and older decreased by 48 percent overall from 2013 to 2016, according to findings published July 10, 2018, in JAMA after researchers revisited the database.

Testosterone Trials (TTrials)

Endocrine Reviews, Volume 39, Issue 3, 1 June 2018, Pages 369–386

Seven placebo-controlled, double-blind trials in 788 men with a mean age of 72 years to determine the efficacy of increasing the testosterone levels of older men with low testosterone

- **Sexual Function Trial**, testosterone increased sexual activity, sexual desire, and erectile function.
- **Physical Function Trial**, testosterone **did not increase the distance** walked in 6 minutes in men whose walk speed was slow.
- **Vitality Trial**, testosterone **did not increase energy** but slightly improved mood and depressive symptoms.
- **Cognitive Function Trial**, testosterone **did not improve cognitive function**
- **Anemia Trial**, testosterone increased hemoglobin in both men who had anemia of a known cause and in men with unexplained anemia.
- **Bone Trial**, testosterone increased volumetric bone mineral density and the estimated strength of the spine and hip
- **Cardiovascular Trial**, testosterone **increased the coronary artery noncalcified plaque** volume

- Confusing
- Conflicting
- More data needed

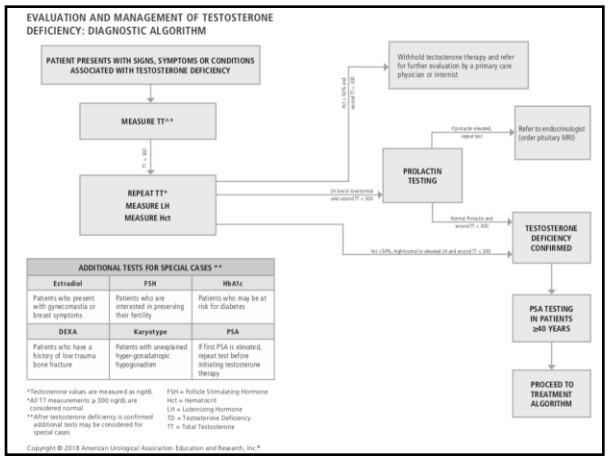
Evaluation and Management of Testosterone Deficiency AUA: Clinical Guidelines Published 2018

- Testosterone testing and prescriptions have nearly tripled in recent years
- Many men using testosterone without a clear indication
- Some studies estimate that up to 25% of men who receive testosterone therapy **do not have their testosterone tested prior to initiation of treatment**
- **Nearly half do not have their testosterone levels checked after therapy**

- A third of men who are placed on testosterone therapy **do not meet the criteria** to be diagnosed as testosterone deficient
- A large percentage of men in need of testosterone therapy fail to receive it due to clinician concerns, mainly prostate cancer development and cardiovascular events

TABLE 1: AUA Nomenclature Linking Statement Type to Level of Certainty, Magnitude of Benefit or Risk/Burden, and Body of Evidence Strength

	Evidence Strength A (High Certainty)	Evidence Strength B (Moderate Certainty)	Evidence Strength C (Low Certainty)
Strong Recommendation (Net benefit or harm substantial)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is substantial Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears substantial Applies to most patients in most circumstances but better evidence is likely to change confidence (rarely used to support a Strong Recommendation)
Moderate Recommendation (Net benefit or harm moderate)	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances and future research is unlikely to change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) is moderate Applies to most patients in most circumstances but better evidence could change confidence	Benefits > Risks/Burdens (or vice versa) Net benefit (or net harm) appears moderate Applies to most patients in most circumstances but better evidence is likely to change confidence
Conditional Recommendation (No apparent net benefit or harm)	Benefits = Risks/Burdens Best action depends on individual patient circumstances Future research unlikely to change confidence	Benefits = Risks/Burdens Best action appears to depend on individual patient circumstances Better evidence could change confidence	Balance between Benefits & Risks/Burdens unclear Alternative strategies may be equally reasonable Better evidence likely to change confidence
Clinical Principle	A statement about a component of clinical care that is widely agreed upon by urologists or other clinicians for which there may or may not be evidence in the medical literature		
Expert Opinion	A statement, achieved by consensus of the Panel, that is based on members clinical training, experience, knowledge, and judgment for which there is no evidence		



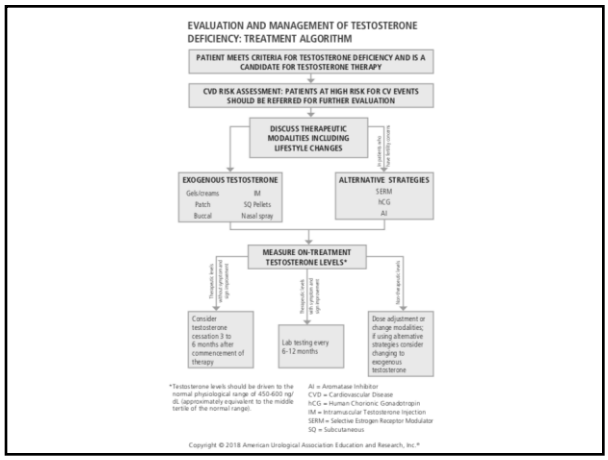


Table 3: Prevalence of Testosterone Deficiency

Author/Study	Number of Patients	Description of Population	Definition of Testosterone Deficiency	Method of Testosterone Deficiency Measurement	Prevalence of Testosterone Deficiency
Harman et al. 2000[5] *Baltimore Longitudinal Aging Study (BLAS)*	890	Generally healthy, middle class, 87% white Age range: 20-91 years (mean 63.8) Mean BMI: 25.6	TT <325 ng/dL or a FTI <0.153 Only one TT or FTI value needed to be in the deficient range to be considered testosterone deficient	Early morning samples from each subject's most recent and previous 3 visits as well as those from 10, 15, 20, 25, and 30 years prior were analyzed (3,565 samples total with a mean of 4 samples per patient). TT: RIA SHBG: RIA FT: FTI	50-59 years: 12% 60-69 years: 19% 70-79 years: 28% >80 years: 49%
Araujo et al. 2004[6] *Massachusetts Male Aging Study (MMAS)*	T1: 1,709 T2: 1,156	Patients were evenly divided among 40-49 years, 50-59 years, and 60-70 years; 95% white	TT<200 ng/dL combined with three or more symptoms (reduced libido, ED, depression, lethargy, inability to concentrate, sleep disturbance, irritability, and depressed mood), or a total testosterone level between 200- 400 ng/dL with three or more symptoms and a free testosterone level < 8.9 ng/dL	Patients were evaluated at 2 time points (T1: 1987-1989; T2: 1995-1997) separated by a mean of 8.8 years, all testing was done on single samples taken in the morning. TT: RIA SHBG: RIA FT: Sodergard equation assessment of patient symptoms	T1 40-49 years: 4.1% 50-59 years: 4.5% 60-70 years: 9.4% T2 40-49 years: 7.1% 50-59 years: 11.5% 60-70 years: 22.8%

Mulligan et al. 2006[7] *Hypogonadism in Males (HIM)*	2,098	All men ≥45 years (mean 60.5) undergoing routine evaluation by their primary care physicians, 82% white Mean BMI: 29.7	TT <300 ng/dL, or men who were previously diagnosed with testosterone deficiency and who were currently using testosterone therapy	All draws were performed between 8a.m. and noon. TT: RIA SHBG: RIA FT: equilibrium dialysis Bioavailable T: Ammonium sulfate precipitation	38.7% of study population Mean testosterone level 245 ng/dL 17% increase in testosterone deficiency per decade of life
Wu et al. 2010[8] *European Male Aging Study (EMAS)*	3,219	Age range: 40-79 years (mean 57.9)	TT <317 ng/dL along with the three sexual symptoms (sexual function [e.g., decreased frequency of morning erections, decreased frequency of sexual thoughts, ED, physical symptoms [e.g., inability to perform vigorous activity, inability to walk more than 1 km, inability to bend, kneel or stoop], and psychological symptoms [e.g., loss of energy, sadness, fatigue]	Men evaluated by primary care physicians had a single lab draw prior to 10a.m. and were administered a series of questionnaires. TT: GCMS SHBG: Immunoassay FT: Vermeulen equation	2.1% of study population

BMI: body mass index, ED: erectile dysfunction, FT: free testosterone, FTI: free testosterone index, GCMS: gas chromatography mass spectrometry, RIA: radioimmunoassay, SHBG: Sex hormone binding globulin, TT: total testosterone

- Age is a risk factor
- Variations in what is considered abnormal Testosterone
- Prevalence data is all over the place 2.1%- 49%

Testosterone Deficiency vs Low Testosterone

Low Testosterone

- Lab value
- total testosterone level below 300 ng/dL

Testosterone Deficiency

- Low testosterone
- Signs and symptoms

Physical Symptoms and Signs

- Reduced energy
- Reduced endurance
- Diminished work performance
- Diminished physical performance
- Loss of body hair
- Reduced beard growth
- Fatigue
- Reduced lean muscle mass
- Obesity

Cognitive Symptoms and Signs

- **Depressive symptoms**
- Cognitive dysfunction
- Reduced motivation
- Poor concentration
- Poor memory
- Irritability

Sexual Symptoms and Signs

- Reduced sex drive
- Reduced erectile function

*Take home message

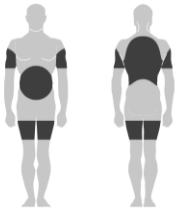
- Total testosterone level below 300 ng/dL
  (Moderate Recommendation; Evidence Level: Grade B)
- Two total testosterone measurements are taken on separate occasions with both in the early morning.
  (Strong Recommendation; Evidence Level: Grade A)
- Diagnosis of testosterone deficiency is only made when patients have low total testosterone levels plus symptoms and/or signs.
  (Moderate Recommendation; Evidence Level: Grade B)

Treatment

- Patches
- Gels
- Mouth Patch
- Injection/implants

Patches

- Androderm®
- Put on once daily in the evening



Gels

- **AndroGel:** (two 25 mg packets or one 50 mg packet) applied topically once daily to the shoulders and upper arms and/or abdomen area
- **Axiron:** (2 pump) applied once daily to the Axilla
- **Fortesta:** (4 pumps) applied once daily to the thighs in the morning
- **Natesto:** (1 pump per nostril) three times daily
- **Testim:** apply 5g (1 tube) once daily in the AM
- **Vogelxo:** (4 pumps) applied once daily to shoulders and upper arms

Mouth Patch

- **Striant:** one tablet on your gum q 12 hours

Injection/implants

TESTOPEL (testosterone pellets)

- **Aveed®:** 750mg injection at weeks 0, 4, and every 10 weeks thereafter
- **Testopel:** 6 -12 pellets every 3 to 4 month
- **T cypionate/enanthate:** 50-200mg every 7 -14 days IM
- **XYOSTED**: (testosterone enanthate) 75 mg subcutaneously in the abdominal region once weekly

Counseling Regarding Treatment of Testosterone Deficiency

- **Low testosterone is a risk factor for cardiovascular disease.** (Strong Recommendation; Evidence Level: Grade B)
- Testosterone therapy **may** result in improvements in erectile function, low sex drive, anemia, bone mineral density, lean body mass, and/or depressive symptoms. (Moderate Recommendation; Evidence Level: Grade B)
- **Evidence is inconclusive** whether testosterone therapy improves cognitive function, measures of diabetes, energy, fatigue, lipid profiles, and quality of life measures. (Moderate Recommendation; Evidence Level: Grade B)
- The **long-term impact of exogenous testosterone on spermatogenesis** should be discussed with patients who are interested in future fertility. (Strong Recommendation; Evidence Level: Grade A)
- Inform patients of the **absence of evidence linking testosterone therapy to the development of prostate cancer.** (Strong Recommendation; Evidence Level: Grade B)
- There is **inadequate evidence** to quantify the risk-benefit ratio of testosterone therapy with a history of prostate cancer. (Expert Opinion)
- It **cannot be stated definitively** whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., **myocardial infarction, stroke, cardiovascular-related death, all-cause mortality**). (Moderate Recommendation; Evidence Level: Grade B)
- Patients should be counseled regarding **lifestyle modifications** as a treatment strategy. (Conditional Recommendation; Evidence Level: Grade B)

Side-effects of Treatment

- Very common for the **testicles to shrink** while taking testosterone.
- Can cause statistically significant increased hemoglobin levels - **Polycythemia**
- Should not be prescribed to men who are currently trying to conceive
- Exogenous testosterone suppresses testicular function
  If and when they ever decide to discontinue testosterone supplements, their ***recovery from drug-induced "low T" may be highly symptomatic and prolonged.*** *In some cases, testicular function* ***may never return****, even to its pretreatment baseline* *Testosterone dependence: How real is the risk? | Urology Times July 23, 2014*

Follow-up of Men on Testosterone Therapy

- Measure an initial follow-up total testosterone level after an appropriate interval to ensure that target testosterone levels have been achieved. (Expert Opinion)
- Testosterone levels should be measured every 6-12 months while on testosterone therapy. (Expert Opinion)
- Clinicians should discuss the cessation of testosterone therapy three to six months after commencement of treatment in patients who experience normalization of total testosterone levels but fail to achieve symptom or sign improvement. (Clinical Principle)

Adjunctive Testing

- Serum **luteinizing hormone** levels
- Serum **prolactin levels** should be measured in patients with low testosterone levels combined with low or low/normal luteinizing hormone levels
- high prolactin levels of unknown etiology should undergo evaluation for endocrine disorders
- Serum **estradiol** should be measured in testosterone deficient patients who present gynecomastia
- **Baseline hemoglobin and hematocrit**
- **Baseline PSA**

Alternative Therapies

Table 6: Pharmacological Characteristics of Alternative Therapies

Selective Estrogen Receptor Modulators (SERMs)

Agent	Dosing	Pharmacokinetics	Mechanism of Action	Adverse Effects
Clomiphene citrate*	25- 50 mg orally every 1 -2 days	T Max = 5 hours T ½ = 5-7 days	Reduces negative feedback on pit gonadotropin release with a resultant increase in gonadotropins (LH, FSH)	Visual symptoms, flushing, headache, abdominal discomfort
Tamoxifen*	20 mg orally daily	T Max = 5 hours T ½ = 5-7 days	Inhibits hypothalamic and pituitary estrogen receptors, which blocks estrogen negative feedback on gonadotropin release. Thus, hypothalamic pituitary-gonadal gonadotropin release is increased.	Liver abnormalities, liver enzyme changes, ocular disturbances including cataracts, thromboembolic events including deep venous thrombosis and stroke

*Not FDA-approved for use in males
FSH: follicle-stimulating hormone, LH: luteinizing hormone, T Max: time to achieve max levels, T 1/2: half life

Aromatase Inhibitors (AIs)

Agent	Dosing	Pharmacokinetics	Mechanism of Action	Adverse Effects
Anastrozole*	0.05 - 1 mg every 1-3 days	T Max= 2-5 hours T ½ = 2 days	Inhibits conversion of testosterone to E2	Hot flashes, hypertension, nausea, back pain, bone pain, dyspnea, peripheral edema

*Not FDA-approved for use in males
#Discontinued in 2008. No longer available for medical
E2: estradiol, T Max: time to achieve max levels, T 1/2: half life

Human Chorionic Gonadotropin (hCG)

Agent	Dosing	Pharmacokinetics	Mechanism of Action	Adverse Events
hCG^	500-4000 IU units SQ or IM 2-3 times per week	T Max 12 hours T ½ = 2 days	Virtually identical activity to LH. Stimulated Leydig cells to make testosterone.	Headache, irritability, depression, fatigue, edema, gynecomastia, injection site pain.

^ FDA approved for use in males with hypogonadotropic hypogonadism and pediatric patients with cryptorchidism.
LH: luteinizing hormone, IM: intramuscular, SQ: subcutaneous, T Max: time to achieve max levels, T 1/2: half life

- Testosterone deficiency: a historical perspective https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3955324/
- AUA: Evaluation and Management of Testosterone Deficiency https://www.auanet.org/guidelines/testosterone-deficiency-(2018)
- Lessons From the Testosterone Trials: https://academic.oup.com/edrv/article/39/3/369/4924242
- US NEWS 2018: Why Are Older Men Bailing Out on Testosterone Therapy? https://health.usnews.com/health-care/patient-advice/articles/2018-08-29/why-are-older-men-bailing-out-on-testosterone-therapy
- Testosterone dependence: How real is the risk? | Urology Times July 23, 2014 https://www.urologytimes.com/modern-medicine-feature-articles/testosterone-dependence-how-real-risk