

Testosterone Replacement Therapy Update 2023

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Disclosures

I will be discussing the off-label use of
Clomid for men

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- **Primary Male Hormone**
 - Male development
- **Systems Affected**
 - Cardiovascular
 - Metabolic
 - Skeletal structure
 - Brain
 - Genitourinary

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Patient Care



1. Primary care physicians
2. Hormone replacement specialists
3. Endocrinologists
4. Urologists
5. Other

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Hypogonadism



ICD-10 E29
CPT 48723006

- 40% of men over 45
 - 60% of men over 65
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- 4.5 Million men in U.S. suffer from hypogonadism
 - 12.2% of men are being treated

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Testosterone Market

1988 - \$18 Million in RX

2013 - \$2 Billion in RX

- Increased awareness of
- Growth in senior population
- ↑↑ Levels of T Deficiency

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In 2023 the average ♂ has the average testosterone level of a 67-year-old ♂ in 2000

Level average ↓ 25-45% in the last 25 years

Age Years	Free Testosterone Average Range	Total Testosterone Average Range	Normal Total Testosterone
30 - 40	8.7 – 25.1 pg/mL	219 – 1009 ng/dL	600 – 675 ng/dL
40 - 50	6.8 – 21.5 pg/mL	201 – 993 ng/dL	500 – 550 ng/dL
50 - 60	7.2 – 24.0 pg/mL	170 – 918 ng/dL	400 – 450 mg/dL
Over 60	6.6 – 18.1 pg/mL	156 – 700 ng/dL	300 – 350 ng/dL

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Medical Use

- Hypogonadism
- Gender Dysphoria
- Types of Breast Cancer

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Diagnosis (Lab & Symptoms)

Lab:

- (M) Total Testosterone 300 – 1100 NG/DL
- (F) Total Testosterone 8 – 60 NG/DL

Free testosterone

Age 20-29 9.3 – 26.5 NG/DL
50-59 7.2 – 24 NG/DL

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Diagnosis Lab

- 2 morning draws
- Peak levels – Evening 9 p.m.

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Biologic Activity

- Lipophilic Hormone
 - Transported in water-based plasma
 - SHBG – Sex hormone binding globulin – binds testosterone
 - Unbound – Free Testosterone is active hormone

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Free Testosterone



Cytoplasm of target cells



Androgen receptor



Cell Nucleus



Chromosomal DNA

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Hormone Activity

- Two Important Human Tissues
 - Bones – Conversion to Estradiol
 - Brain → Estradiol Feedback to hypothalamus → LH

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Non-Steroidal Activity



- Testosterone – Modulates GABA receptor
- Affects on Neurotrophin nerve growth factor

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Brain

Testosterone $\xrightarrow{\text{Aromatase}}$ Estradiol
Sexual Differentiation

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- 
- Memory – Spatial ability
 - Importance in cognitive decline
 - Alzheimer – Dementia relationship

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Immune System



- T-Deficiency associated with metabolic syndrome
- Cardiovascular disease
- ↑ Mortality

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Testosterone Plasma concentration correlates inversely with multiple biomarkers of inflammation

- CRP
- Interleukin 1 beta
- Interleukin 6
- TNF ALPH
- Endotoxin concentration
- Leukocyte count

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In Androgen-deficient men with autoimmune thyroiditis substitution therapy with testosterone leads to decrease in thyroid auto antibody titers

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Testosterone is included in WHO List of Essential Medications

- It is available for men in topical gel, injection, intramuscular pellets
- Women have transdermal patches and sublingual tablets

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Clinical application of testosterone replacement therapy in men

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Men Under 40

- Do not start with testosterone
- Check LH Level – most have low testosterone due to hypopituitary function

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Treatment

- Clomid – 25-50mg Daily
- Recheck testosterone in 8 weeks

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Table 1. Causes of Hypogonadism in Men

Type	Laboratory values	Origin	Possible causes
Primary	Decreased total serum testosterone, increased LH and FSH	Congenital	Chromosomal abnormalities, cryptorchidism, FSH/LH receptor gene mutations, Klinefelter syndrome, myotonic dystrophy
		Acquired	Chemotherapy, hypothyroidism, orchitis/epididymo-orchitis (from mumps, gonorrhea, or chlamydia), radiation/trauma to testes, testicular torsion
Secondary	Decreased total serum testosterone, normal or decreased LH and FSH	Congenital	Kallmann syndrome, Prader-Willi syndrome, other genetic abnormalities
		Acquired	Chronic opioid use, hyperprolactinemia, pituitary tumors, sellar radiation, sleep deprivation, surgery, trauma
Mixed primary and secondary	Decreased total serum testosterone, variable LH and FSH	Acquired	Aging, cancer, chronic glucocorticoid use, chronic kidney disease, chronic obstructive pulmonary disease, cirrhosis, diabetes mellitus, hemochromatosis, human immunodeficiency virus infection, obesity

FSH = follicle-stimulating hormone; LH = luteinizing hormone.

Information from references 4 and 5.

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Table 3. Contraindications to Starting Testosterone Therapy

Absolute contraindications

Breast cancer
Polycythemia (hematocrit > 54%)
Prostate cancer
Prostate-specific antigen > 4 ng per mL (4 mcg per L) or presence of nodules/induration on digital rectal examination (referral to a urologist is required before considering testosterone therapy)

Relative contraindications

Baseline hematocrit > 50%*
Desire for fertility (testosterone therapy suppresses spermatogenesis)
Severe lower urinary tract symptoms
Uncontrolled congestive heart failure
Untreated obstructive sleep apnea

*—The criterion for discontinuing or decreasing testosterone therapy is a rise to a hematocrit of > 54%. A baseline hematocrit of > 50% predicts a likely rise to > 54% on therapy and is therefore a relative contraindication to starting therapy.

Information from references 9 and 11.

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Table 2. Signs and Symptoms of Hypogonadism in Men

Anemia (normocytic, normochromic)*
Breast discomfort, gynecomastia
Depressed mood*
Diminished bone density, low-trauma fractures
Diminished energy, sense of vitality, or sense of well-being*
Diminished muscle mass and strength*
Diminished physical or work performance*
Hot flashes, sweats
Impaired cognition*
Incomplete or delayed sexual development (in cases of prepubertal onset)
Increased body fat, body mass index*
Increased fatigue*
Infertility
Loss of body hair
Sexual symptoms (decreased libido, decreased spontaneous erection)
Very small testes

**—Less specific; may be associated with other conditions.*

Information from references 3, 8, and 9.

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**Goal is to raise
testosterone to 750-1000
and monitor symptoms
compared to start of
symptoms**

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Monitoring of Male Patients on Testosterone Therapy

Table 5. Monitoring of Male Patients on Testosterone Therapy

Test/examination	Frequency	Comment
History and physical examination	Three to six months following initiation of therapy, then annually	—
Total serum testosterone measurement	Baseline; three to six months after initiation of therapy, then annually if stable	Goal is to increase level to midnormal range, although there is no clear target level Endocrine Society recommends levels between 400 and 700 ng per dL (13.9 and 24.3 nmol per L) one week following injection with testosterone cypionate or enanthate, or at any time with other formulations
Complete blood count (hematocrit)	Baseline; three to six months after initiation of therapy, then annually if stable	If hematocrit is > 54%, therapy should be stopped, or dose lowered or changed to different formulation; it can be restarted at a lower dose once levels decrease
PSA and DRE	Baseline; three to six months after initiation of therapy, then discuss risks/benefits of ongoing screening with the patient given the evidence against routine screening	Only men older than 40 years with baseline PSA > 0.6 ng per mL (0.6 mcg per L) should be screened Refer to a urologist if PSA increases by > 1.4 ng per mL (1.4 mcg per L) over 12 months or there is an abnormality on DRE
Bone density	One to two years after initiation of therapy	In men with osteoporosis or low trauma fracture history

DRE = digital rectal examination; PSA = prostate-specific antigen.

Information from reference 9.

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BEST PRACTICES IN ENDOCRINOLOGY: RECOMMENDATIONS FROM THE CHOOSING WISELY CAMPAIGN

Recommendation	Sponsoring organization
Do not prescribe testosterone or testosterone products to men contemplating or attempting to initiate pregnancy.	American Society for Reproductive Medicine
Do not prescribe testosterone to men with erectile dysfunction who have normal testosterone levels.	American Urological Association
Do not prescribe testosterone therapy unless there is laboratory evidence of testosterone deficiency.	American Society for Clinical Pathology
Do not prescribe testosterone therapy unless there is biochemical evidence of testosterone deficiency.	The Endocrine Society/ American Association of Clinical Endocrinologists

Source: For more information on the Choosing Wisely Campaign, see <http://www.choosingwisely.org>. For supporting citations and to search Choosing Wisely recommendations relevant to primary care, see <http://www.aafp.org/aafp/recommendations/search.htm>.

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Testosterone therapy after treatment of prostate cancer

