HYPOGONADISM

Evaluation and Treatment in the Adult Male Patient

(The Endocrine Society Guidelines)

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OVERVIEW OF PRESENTATION

- **Take Home Points**
- **Definition of Hypogonadism**
- **Clinical Manifestations**
  - History and Physical Examination
  - Laboratory Studies
  - Imaging
- **Differential Diagnosis**
  - Hypergonadotropic Hypogonadism
  - Hypogonadotropic Hypogonadism
  - "Andropause"
  - Chronic Illness and Androgen Replacement
- **Therapeutic options, contraindications, side effects and guidance for surveillance.**
- **Take Home Points (again!)**

Take Home Points

- Measure T only if ***reliable*** symptoms are suggestive.
- Diagnose if symptoms are ***consisten***t and T levels are ***unmistakably*** low.
- Determine the cause.
- Consider secondary causes including use of performance enhancers and age related decline.
- Image only if indicated.
- Identify patients who are likely to benefit.
- Know contraindications and side effects.
- Educate about the lack of long term safety and efficacy data supporting diagnosis and treatment.

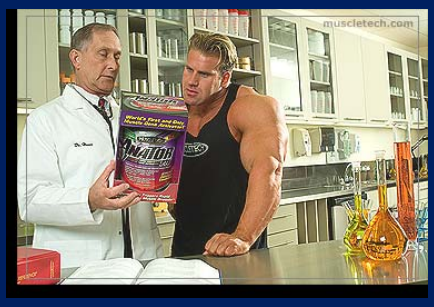
Hypogonadism; *The perspective in 1951*

"A person who complains of lifelong impotence or lack of libido does not suffer from hormonal lack; a patient with real (androgen) insufficiency does not complain of it but of something more trivial, such as being mistaken for a girl over the telephone."

Fuller Albright, 1951

Hypogonadism; *The perspective in 2018*

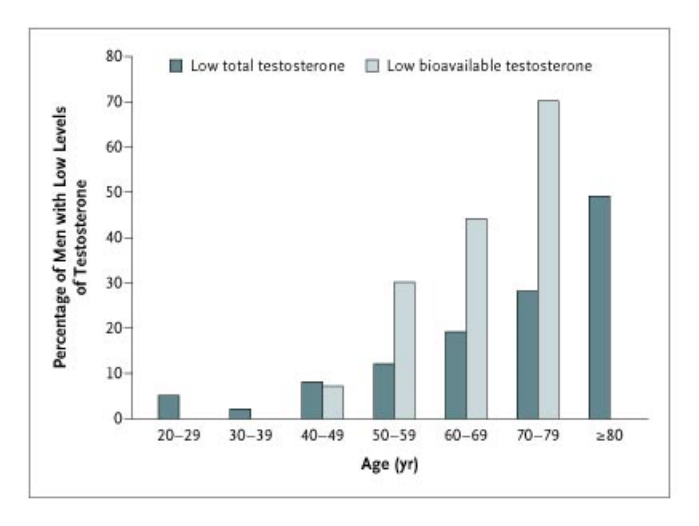
Lots of "Expert$" out There……



Definition of Hypogonadism

- Definition:
  - *" a clinical syndrome that results from failure of the testis to produce physiological concentrations of testosterone (T) and/or a normal number of spermatozoa due to pathology at one or more concentrations of the hypothalamic-pituitary-testicular axis."*

Prevalence of Low Levels of Total and Bioavailable Testosterone as an Index of Male Hypogonadism According to Decade of Life



Rhoden, E. L. et al. N Engl J Med 2004;350:482-492

The NEW ENGLAND JOURNAL of MEDICINE

Manifestations of Hypogonadism by Age of Onset

Age of onset:

- **In utero**
  - Varying degree of masculinity or pseudohermaphroditism
  - Defects in testicular descent or cryptorchidism
  - Microphallus
- **Prepubertal:**
  - Small testes, phallus, and prostate
  - Scant pubic and axillary hair
  - Eunochoid body habitus
  - Reduced male musculature
  - Gynecomastia
  - Persistently high pitched voice

A 17-day-old black neonate with hermaphroditism

Karam, J. A. et al. N Engl J Med 2004;350:393

Manifestations of Hypogonadism

- **Post pubertal adult male:**
  - Diminished libido, ED, or orgasmal difficulties
  - Increased fatigue, depressed mood.
  - Diminished muscle mass or strength and decreased physical performance
  - Low testicular volume
  - Anemia
  - Loss of body hair or decreased frequency of shaving
  - Menopausal hot flashes or sweats
  - Gynecomastia
  - WHEN SHOULD A BIOCHEMICAL SCREEN BE DONE?
  - WHAT LABS SHOULD BE ORDER?

Endocrine Society Position Statement on Literature Supporting Screening Tests for Men With High Likelihood of Hypogonadism

Endo Soc: Strength of recommendation: "WEAK"

Quality of evidence: "LOW"

Benefit:Risk Data: "NOT AVAILABLE"

When to Obtain Labs?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ORIGINAL ARTICLE

Identification of Late-Onset Hypogonadism in Middle-Aged and Elderly Men

- NEJM 2010;363:123-35.
- 3369 men age 40-79 years surveyed in Europe.
- Levels of total testosterone checked by mass spectroscopy and calculated.
- Univariate and multivariate analyses performed.
- Three symptoms consistently associated with lower testosterone levels in both analyses:
  - Poor morning erection
  - Low sexual desire
  - Erectile dysfunction
  - Physical performance

Table 3. Symptoms and Signs Suggestive of T Deficiency in Men

Specific symptoms and signs
Incomplete or delayed sexual development
Loss of body (axillary and pubic) hair
Very small testes (<6 mL)
Suggestive symptoms and signs
Reduced sexual desire (libido) and activity
Decreased spontaneous erections, erectile dysfunction
Breast discomfort, gynecomastia
Eunuchoidal body proportions
Inability to father children, low sperm count
Height loss, low-trauma fracture, low BMD
Hot flushes, sweats
Nonspecific symptoms and signs associated with testosterone deficiency
Decreased energy, motivation, initiative, and self-confidence
Feeling sad or blue, depressed mood, persistent low-grade depressive disorder
Poor concentration and memory
Sleep disturbance, increased sleepiness
Mild unexplained anemia (normochromic, normocytic)
Reduced muscle bulk and strength
Increased body fat, body mass index

J Clin Endocrinol Metab, May 2018, 103(5):1–30

Table 4. Conditions in Which There Is a High prevalence of Low T Concentrations and for Which We Suggest Measurement of Serum T Concentrations

Pituitary mass, radiation to the pituitary region, or other diseases of the sellar region
Treatment with medications that affect T production or metabolism, such as opioids and glucocorticoids
Withdrawal from long-term AAS use
HIV-associated weight loss
Infertility
Osteoporosis or low trauma fracture
Low libido or erectile dysfunction

J Clin Endocrinol Metab, May 2018, 103(5):1–30

Evaluation of the Hypogonad Male Patient/Labs

1. Serum Total Testosterone:

- Conditions:
  - Off of all performance enhancing supplements x 3mo
  - 2 fasting early morning samples drawn on 2 separate occasions (30% of men normalize on second test if first test is low).
  - Lower limit of normal range is not known; use institutional assay.
  - If near the lower limit or mildly low, consider ordering free T from equilibrium dialysis or calculating the free fraction:
    - (need alb, SHBG, total T) when near the lower limit of the normal range:
    - **www.issam.ch.freetesto.htm**

Evaluation of the Hypogonad Male Patient/Labs

2. Sex Hormone Binding Globulin (SHBG; 60% of T is bound)

- SHBG low causing ***false decrease*** in total T:
  - Obesity
  - Hypothyroidism
  - Acromegaly
  - Diabetes mellitus
  - **Glucocorticoids and androgenic steroids !**
  - Nephrotic syndrome
  - SHBG gene polymorphisms
- SHBG elevated causing *false* ***elevations*** in total T:
  - Hyperthyroidism
  - Liver disease (cirrhosis/ hepatitis)
  - Severe androgen deficiency
  - Use of Estrogens and Anticonvulsants
  - **Elderly men/ aging**
  - **HIV**

4. Thyroid Function Tests (Hypo/Hyperthyroid).

5. FSH, LH, Estradiol.

Evaluation of the Hypogonad Male Patient/Other Studies

- MRI Sella Turcica when indicated:
  - Hypogonadotropic hypogonadism (central cause).
  - Total testosterone < 150 ng/ml (w/low FSH and LH or inappropriately normal)
  - Panhypopituitarism
  - Persistent hyperprolactinemia (esp if >200)
  - Symptoms or signs of mass effect
- DEXA: baseline (no studies support!)
- Genetic studies and karyotyping
- Testicular ultrasound

Classification of the Biochemically Confirmed Hypogonad Patient

1. Hypergonadotropic Hypogonadism ?
2. Hypogonadotropic Hypogonadism ?

Classification of the Biochemically Confirmed Hypogonad Patient

Hypergonadotropic Hypogonadism

[↑ FSH ↑ LH ↓ Total Testosterone]

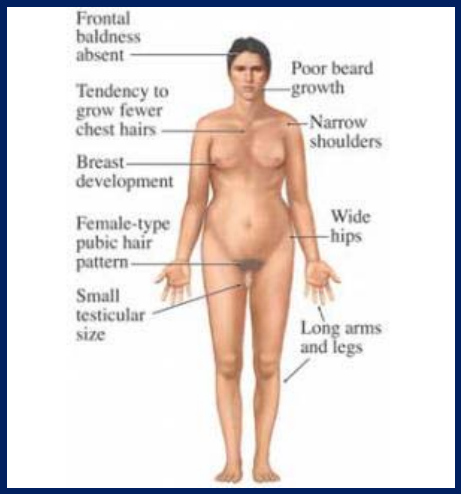
Hypergonadotropic Hypogonadism/Common Causes

[↑ FSH ↑ LH ↓ Total Testosterone]

- **Klinefelter's syndrome:**
  - Incidence: 1:400 male births; pubertal manifestation
  - 47 XXY or mosaicism
  - Reduction (~50%) in testosterone production.
  - **Small (<2.5cm) firm testes**
  - Arm span > height; crown:pubis/pubis:floor <0.92.
  - Taurodontism – early tooth decay
  - Partial virilization
  - **Gynecomastia – *20 X risk of breast cancer***
  - Learning disabilities and dyssocial behaviors

Hypergonadotropic Hypogonadism/Common Causes
[↑ FSH ↑ LH ↓ Total Testosterone]

- Klinefelter's syndrome:



Hypergonadotropic Hypogonadism/Common Subtypes

- **Others:**
  - **Hemochromatosis:**
    - Iron overload
    - Primary or secondary testicular failure
  - **External testicular insults:**
    - Testicular trauma or torsion
    - AIDS or mumps orchitis
    - Radiation or chemotherapy
    - Autoimmune syndromes
  - **Vanishing testes syndrome:**
    - Testicular insult during fetal life

Hypergonadotropic Hypogonadism/Other Subtypes

- **5 alpha reductase deficiency:**
  - Autosomal recessive
  - Female phenotype until puberty; then virilization
  - Elevated T:DHT ratio
- **Myotonic dystrophy**
  - Testicular failure after age 40
- **Cryptorchidism**
- **Androgen receptor defects:**
  - Partial resistance → Reifenstein's syndrome
    - *Male phenotype with pseudohermaphroditism*
  - Total resistance → testicular feminization
    - *Female phenotype with blind vaginal pouch*
- **47 XYY syndrome:**
  - 0.1 % of males ('supermales').

Classification of the Biochemically Confirmed Hypogonad Patient

Hypogonadotropic Hypogonadism
[↓FSH ↓LH ↓Testosterone]

Hypogonadotropic Hypogonadism/Subtypes [↓FSH ↓LH ↓Testosterone]

Etiology:

- Use of performance enhancing supplements
- Use of anabolic steroids.
- AIDS
- Malnutrition
- Critical illness
- ETOH dependence
- Glucocorticoids
- Chronic narcotics use.
- Hyperprolactinemia
- Hypothyroidism
- Large sellar masses
- Hemochromatosis
- Kallman's Syndrome: olfactory tract maldevelopment.
  - "anosmia, short stature, hypogonadism".

"Andropause" and the Elderly Male

No consensus on definition among Endocrine Society Expert Panel

Consider levels below <200 ng/dL with symptoms

"Andropause" and the Elderly Male:
(choose your role models wisely)

"Andropause" and the Elderly Male:

Endocrine Society position statement:

- "We recommend against a general policy of offering T to all older men with low T levels. We suggest offering T.....after explicit discussion of the uncertainty about risks and benefits."

American Association of Clinical Endocrinologists:

- "Treat if the benefit:risk ratio warrants it. We lack knowledge regarding benefit and we lack knowledge regarding risks".

"Andropause" and the Elderly Male

- If choose to treat, aim for low end of normal range for normal healthy young men (400-500 ng/dl).

- Sreekumaran, K; N Eng J Med; 355;16 19.
  - 87 elderly men with bioavailable testosterone in the 15th percentile of younger men.
  - Double blind study. Supplemented with testosterone, DHEA, or placebo and followed for 2 years.
  - Bioavailable testosterone significantly increased in treatment groups compared to the placebo group.
  - Statistically significant (yet small) increases in fat free mass and BMD in femoral neck in testosterone treated group.
  - No change in body composition, physical performance, insulin sensitivity, or quality of life.

Liu, P et al; Clinical Review 171. JCEM 89(10):4789-4796.

Chronic illness and low T

- Consider treatment if warranted:
  - HIV/AIDS with low T & weight loss
    - To induce/maintain body wt & lean mass gain
  - Glucocorticoid therapy
  - Chronic narcotic use (wounded warriors?)
    - If you choose to treat, attempt a wean off of androgen therapy after period requiring narcotics ends

Goals for Treatment with Testosterone

1. Restore sexual function, libido, well-being.
2. Produce and maintain virilization and fertility.
3. Increase hematopoiesis to normal levels.
4. Optimize bone density and prevent osteoporosis.
5. Minimize short term side effects
6. Minimize long term side effects.
    1. Unknown!

Contraindications for Androgen Therapy

- Prostate cancer.
    - Unless S/P radical prostatectomy, disease free x 2 years, and undetectable PSA.
- Breast cancer
- Elevated Hematocrit
- Severe lower urinary tract symptoms
- Palpable prostate nodule or induration
- Baseline PSA>4 or >3 AND higher risk population
- Uncontrolled congestive heart failure.
- MI, acute coronary event, unstable angina, or coronary revascularization procedure in prior 6 months.
- Thrombophilia
- Untreated severe obstructive sleep apnea
- Men planning fertility in near term

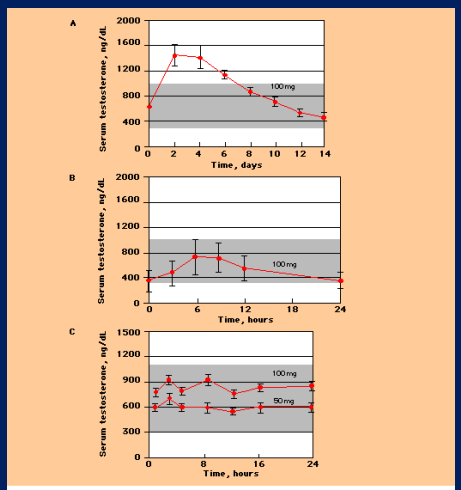
General Side Effects of Androgen Therapy

- General side effects associated with use of T:
  - Erythrocytosis
  - Acne and oily skin
  - Detection of subclinical prostate cancer
  - Growth of metastatic prostate cancer
  - Reduced sperm production and fertility
- Uncommon side effects:
  - Gynecomastia
  - Male pattern baldness (familial)
  - Growth of breast cancer
  - Induction or worsening of obstructive sleep ap**nea**

Androgen Therapy Options and Specific Side Effects

- Oral alkylated androgens (anabolics):
  - Alkylation retards degradation by the liver
  - Hepatotoxicity, dyslipidemia, testicular atrophy
  - Hepatomas, peliosis of the liver
  - Not aromatized to estrogen → osteoporosis
- Intramuscular preparations
  - Testosterone enanthate and cypionate.
  - 100-150mg IM q 2 weeks or 75-100mg q week.
  - Peak 2-5 days post tx; baseline at 10-14 days.
  - The "roller coaster" effect (well documented).
  - Pain at injection site
  - Excessive erythrocytosis
  - Cough (oil embolization? Rare….).

IM, Patch, and Gel Androgen Therapy Options and Serum Testosterone



Serum testosterone concentrations during the course of chronic administration of three different testosterone preparations to hypogonadal men A) During 14 days following the injection of 200 mg of testosterone enanthate. B) During the 24 hours after application of one or two testosterone patches that deliver approximately 5 mg of testosterone each. C) During the 24 hours after application of a testosterone gel containing 50 or 100 mg of testosterone. Data from: Snyder, PJ, Lawrence, DA. J Clin Endocrinol Metab 1999; 51:1335. Dobs, AS, Meikle, AW, Arver, S, et al. J Clin Endocrinol Metab 1999; 84:3469. Swerdloff, RS, Wang, C, Cunningham, G, Dobs, A. J Clin Endocrinol Metab 2000; 85:4500.

Androgen Therapy Options and Specific Side Effects

- **Transdermal preparations:**
  - Transdermal patch (skin irritation; 5% allergic)
  - Scrotal patch.
  - 1-2 5mg patches applied qhs to non pressured skin.
- Transdermal gel:
  - Potential risk for testosterone transfer to person in close contact. Ok to wash site 4-6h after application.
  - Skin irritation.
  - 5-10 grams of gel applied to a covered area of skin
- Transbuccal preparation:
  - 30mg bioadehesive buccal testosterone tablet applied to buccal mucosa q 12 hours.
  - Alterations in taste.
  - Irritation of gums and oral mucosa.
- Testosterone pellet preparation:
  - Subcutaneous implant Q3-6 mo.
  - Infection or expulsion of pellets.

Table 5. Clinical Pharmacology of T Formulations Approved in the United States and Europe

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
T enanthate or cypionate	150–200 mg IM every 2 wk or 75–100 mg/wk	After a single IM injection, serum T concentrations rise into the supraphysiological range, then decline gradually into the hypogonadal range by the end of the dosing interval	Relatively inexpensive, if self-administered; flexibility of dosing	Requires IM injection; peaks and valleys in serum T concentrations that may be associated with fluctuations in symptoms
T transdermal gels: 1%, 1.62%, or 2%	50–100 mg of 1% transdermal gel; 20.25–81 mg of 1.62% gel or 40–70 mg of 2% transdermal gel applied to skin; check package insert for application site and instructions	With appropriate dose, restores serum T and E2 concentrations to the physiological male range; less fluctuation of T concentrations than T enanthate or cypionate	Provides flexibility of dosing, ease of application, good skin tolerability; less erythrocytosis than injectable T	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
T Axillary Solution	60 mg of T solution applied in the axillae	Restores serum T and E2 concentrations to the physiological male range	Provides, good skin tolerability	Potential of transfer to a female partner or child by direct skin-to-skin contact; T concentrations may be variable from application to application skin irritation in a small proportion of treated men; moderately high DHT concentrations (of unknown significance)
Transdermal T patch	One or two patches, designed to nominally deliver 2–4 mg of T during 24 h applied every day on nonpressure areas	Restores serum T, DHT, and E2 concentrations to the physiological male range	Ease of application	Serum T concentrations in some T-deficient men may be in the low-normal range; these men may need applications of two patches daily; skin irritation at the application site occurs frequently in many patients
Buccal, bioadhesive T tablets	30-mg controlled release, bioadhesive tablets twice daily	Restores serum T, DHT, and E2 concentrations to the physiological male range; absorbed from the buccal mucosa	Convenience and discreet	Gum-related adverse events in 16% of treated men
T pellets	Pellets containing 600–1200 mg T implanted SC; the number of pellets and the regimen may vary with formulation	Serum T peaks at 1 month and then is sustained in normal range for 3–6 mo, depending on formulation	Requires infrequent administration	Requires surgical incision for insertions; pellets may extrude spontaneously; rarely, local hematoma and infection may occur
Injectable long-acting T undecanoate in oil	United States regimen: 750 mg IM, followed by 750 mg at 4 wk, and 750 mg every 10 wk	When administered at a dose of 750 mg IM, serum T concentrations are maintained in the normal range in most treated men	Requires infrequent administration	Requires IM injection of a large volume (3 or 4 mL); coughing episode reported immediately after injection in a small number of men

(*Continued*)

Table 5. Continued

Formulation	Typical Starting Doses	Pharmacokinetic Profile	Advantages	Disadvantages
Nasal T gel	11 mg two or three times daily	Serum T concentrations are maintained in the normal range in most treated men	Rapid absorption and avoidance of first pass metabolism	Multiple daily intranasal dosing required; local nasal side effects, not appropriate for men with nasal disorders

Adapted with permission from Bhasin *et al.* (7).

Abbreviations: DHT, dihydrotestosterone; E2, estradiol; IM, intramuscular(ly); SC, subcutaneous(ly).

Table 6. Testosterone Formulations Available Outside the United States, but Not Approved by the FDA

Formulation	Regimen	Pharmacokinetic profile	Advantages	Disadvantages
Oral T undecanoate	40–80 mg oral, two or three times daily with meals	When administered in castor oil, T undecanoate is absorbed hrough the lymphatics, bypassing the portal system; considerable variability in the same individual on different days and among individuals	Convenience of oral administration	Variable clinical responses; administration with fatty meal is required; fat content of meals affects bioavailability; variable serum T concentrations, high DHT:T ratio
T-in-adhesive matrix patch	Two 60-cm^2 patches delivering ~4.8 mg	Restores serum T, DHT, and E2 to the physiological range	Lasts 2 d	Some skin irritation

Abbreviations: DHT, dihydrotestosterone; E2, estradiol.

Other Less Common Options for Androgen Therapy

- Endocrinology/Urology Infertility:
  - Clomiphene.
  - Gonadotropin pumps.
  - HCG
  - GnRH pump.
  - Counseling
  - Assisted reproductive technology

Monitoring Testosterone-Replacement Therapy

- Check baseline T, hematocrit, and PSA (if PSA indicated).
  - If age 40yo or older obtain baseline PSA.
    - If baseline PSA >0.6ng/mL then digital rectal exam + PSA
    - Repeat PSA at 3 and 6 months and then defer to societal recommendations for monitoring PSA.
    - If PSA rises > 1.4 ng/ml in 12 months OR
    - If PSA velocity > 0.4 ng/ml in 6 months OR
    - Detection of prostate abnormality OR severe lower urinary tract sx.....
    - Discontinue testosterone and refer!
- Interval: Q3-6 months after initiation then annually.
- Aim for T levels 400-700 ng/dL after initiation.
  - Injectables: check T 2-3 days after the injection.

Take Home Points

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- Educate about the lack of long term safety and efficacy data supporting diagnosis and treatment.

QUESTIONS?