Testosterone Replacement Therapy: Risks and Benefits

Kay Colella, MSN, ANP-BC

Testosterone

- the major androgen in men, both in concentration and activity
- an anabolic steriod
- performance-enhancing drug
- schedule III controlled substance
- use has quadrupled since the turn of the century - but within the appropriate population ?
  (Those symptomatic from hormonal deficiency)

Testosterone Deficiency Syndrome

A clinical or biochemical syndrome associated with advancing age and characterized by typical symptoms and deficiency in serum testosterone levels.

- Andropause
- Male menopause
- ADAM (androgen deficiency in the aging male)
- Late onset hypogonadism
- Low T

Low T ? Not me !!

Two distinct roles of Testosterone

Androgenic

- Prenatal differentiation
- Effect on reproductive tract
- Secondary sex characteristics
- Libido
- Erection
- Ejaculation

Anabolic

- Growth-promoting effects on somatic tissue
- Bone formation
- Erythropoesis
- Prostate growth
- Muscle bulk

The Role of Sex Hormones, specifically Testosterone, during the Life Cycle:

Gestational: male/female differentiation beginning in 7th week by secretion of testosterone from Leydig cells; drives development of vas deferens, epididymis, seminal vesicles; masculinizes external genitalia.

Puberty: virilization, bone growth & epiphysial closure, laryngeal enlargement & vocal cord thickening, changes to body musculature & fat distribution, testicular growth, initiatic of spermatogenesis.

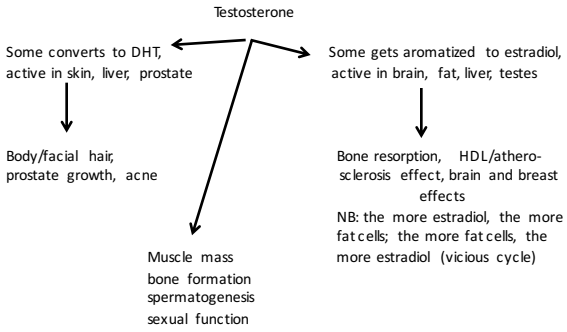
Adult: sustains spermatogenesis, maintains muscle bulk, maintains secondary sex characteristics, aids in erectile function.

Testosterone Regulation

The Hypothalamic - Pituitary - Gonadal (HGP) Axis:

1. Gonadotropin-releasing hormone secreted from the hypothalamus stimulates the anterior pituitary.
2. Anterior pituitary releases follicle stimulating hormone (FSH) and luteinizing hormone (LH).
3. LH stimulates Leydig cells in the testes to produce testosterone.
4. FSH stimulates Sertoli cells in the testes to produce sperm.

Testosterone Metabolism



Hypogonadism

❖**Primary:** aging (LOH), cryptorchism, infection, trauma, chromosome abnormalities (Klinefelters), orchitis (mumps), chemo/XRT

❖**Secondary:** obesity, pituitary disorders, Kallmann Syndrome, uremia, Cushings Syndrome

❖**Combined:** frequently the case

Hypogonadism (cont)

❖**Primary:** low T, elevated gonadotrophins (LH & FSH), impaired spermatogenesis

❖**Secondary:** low T, low or normal LH & FSH, impaired spermatogenesis

❖**Combined:** low T, variable LH & FSH, impaired spermatogenesis

❖13 million men have hypogonadism.

❖From ~age 30 to 35, 1% decrease in T every year.

❖40% of men >30 will have a T of <300 at some point, not all with symptoms.

❖Late onset hypogonadism is the most common form.

❖Big business since older male population increasing .
(Age >65 have 2-3x the rate of low T than <65.)

Signs & Symptoms:

❖Low libido
❖Erectile dysfunction
❖Irritability, mood disorders
❖Anemia
❖Sleep disorders
❖Weight gain
❖Loss of muscle mass
❖Fatigue/loss of energy

Many nonspecific symptoms, so TRT may not be answer, as low T may not be the cause, but rather one of many differential diagnoses.

Testosterone deficiency associated with poor general health –

- ❖Diabetes mellitus
- ❖Metabolic syndrome
- ❖Cardiovascular disease
- ❖Sleep apnea
- ❖Osteoporosis
  (Men globally do worse with osteoporosis than women.)

. . .and AGE:

31% of men over 45 yrs of age will have hypogonadism.

50% of men over 85 will have hypogonadism.

Overall prevalence is 38.6%

Patient Assessment:

Those with

- Diabetes
- ED
- HIV
- metabolic syndrome
- hx of long-term use of opioids
- hx of high use of corticosteroids
- OBESITY

And/or

- One or more of the symptoms we just discussed (irritability, low libido, fatigue, etc.)
- Consider his level of bother vs. his risks/benefits of treatment.

Patient Assessment (cont.)

❖**OBESITY**

-the single most powerful prediction of low T
-the most common cause of low T, second to aging

-weight loss is the ideal treatment to try to increase T.
-even a loss of 20 lbs may make a significant impact.
(along with the exercise this effort entails)

-In reality, co-morbidities may interfere with these wt loss efforts.

Diagnostic Laboratory Tests:

- ❖Must include two total testosterone levels, drawn in a.m.
  Diurnal variation in T, with highest reading in a.m.
  15% of healthy, young males will have a low T at some point in the day.
- ❖Free or bioavailable testosterone.
- ❖FSH
- ❖LH
- ❖Estradiol
- ❖Prolactin
- ❖Thyroid studies (if these are needed or done and abnormal, refer to Endocrinology)

FYI

❖Testosterone levels will also vary depending upon the point of focus of a man's relationship or lack thereof.

❖T Levels will be higher initially to ensure success in his obtaining a partner or fathering a child.

❖Once these have been established, the T level will decrease so as to ensure smoother success maintaining the partnerhood or fatherhood.

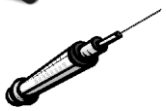
Normal Lab Values

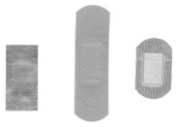
Total testosterone: 300 to 1000 or 1200 ng/dL, depending upon lab used

Free: 1-2.7%
SHBG-bound: 50-60%
Albumin-bound: 40-50%
FSH: 4-25 mIU/mL
LH: 6-23 mIU/mL
Prolactin: <20 ng/mL

Treatment Options for TRT:

- Oral supplement
- Injections
- Patches
- Gels
- Pellets



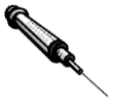

Oral Therapy:

- Over-the-counter preparations – little evidence of efficacy
- Methyltestosterone – hepatic toxicity, not in use, but still available
- Testosterone undecanoate -rejected by FDA due to concern about widespread use/misuse.
- TSX-200 -phase 2 trials; pro-lipisomal oral formulation of un-modified testosterone capable of absorption by the intestinal lacteals, thereby bypassing hepatic metabolism & toxicity.

Intramuscular Therapy:

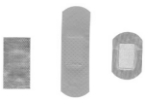
Short-acting: Testosterone cipionate or enthanate; given q 1-2 weeks; may result in supraphysiologic levels; wide peaks and troughs can exacerbate symptoms so best q 1 week; can be given at home.

Long-acting: Testosterone undecanoate (AVEED); given q 10 weeks, but early doses given 1 month apart; larger volume ; given in office due to concern about oil embolism (acute SOB), so monitor for at least 30 minutes after injection.



Patch Therapy:

- In use since 1994, first as scrotal patch (Testoderm)
- Later as non-scrotal patch (Androderm)
- Buccal mucosal patch (Striant), has to changed q 12 hrs.
- Daily dosing patches allow for normal circadian rhythms.



Transdermal Gel/Solution Therapy:

- Most common form of testosterone replacement treatment, used by 2/3 of TRT patients.
- Allows for dose titration.
- Androgel 1%, Androgel 1.62%, Testim, Fortesta, Axiron
- FDA warning of transference risk to those in close proximity with skin-to-skin contact. (Fortesta came out in answer to this risk, it is applied to inner thigh; Axiron to axilla).
- Nasal form -Natesto, approved in 2014, must be applied 2 to 3 times/day.

Implant Therapy:

- FDA approved since 2008.
- Testopel inserted into fat pads of lower back or buttocks.
- Initially may be 4 pellets, then adjusted to patients response and labs.
- Difficult to remove should there be adverse reaction.

Typical Dosing

- Testosterone enanthate or cypionate
  - 75-100 mg IM q wk or
  - 150-200 mg IM q 2 wks or
  - 300 mg q 3 wks or
  - 400 mg q month
- Patch (Androderm) 4 mg qhs
- Gel 50 mg (Androgel) 1% qam, 20.25 to 81 mg (1.62%) qam
- Buccal tablet (Striant) 30 mg q 12 hrs
- Transdermal spray (Fortesta) 4-7 sprays qam to inner thigh
- Transdermal solution/spray (Axiron) 30 – 90 mg (1-3 sprays) to axilla) daily
- Implantable slow release pellets (Testopel), 150 to 450 mg q 3-6 months.

TRT evaluation for formula-specific adverse events:

- Injectables: ask about mood swings or fluctuation in libido; cough after injection; evaluate Hct to detect erythrocytosis, particularly in older men.
- Patch: look for signs of skin irritation at application site.
- Gels: advise patients to cover site with clothing & wash site before having skin-to-skin contact to avoid transference of the residue to others, especially women/children.
- Buccal tablets: ask about alterations in taste; examine gums/oral mucosa for irritation.

Of note:

Testosterone replacement is synergistic with PDE5 inhibitors; but once on TRT and T regains eugonadal level, they can try functioning on TRT alone.

Monitoring treatment effects:

- Serum testosterone (total) = check q 2-3 months, for Testopel implants, check T at 6 weeks for peak and at 4 months for trough to determine how many implants to use at next insertion.
- PSA = may check one extra, unless hx of Prostate Ca or BPH symptoms, then check more often (q 3 months at least initially, then q 6 months if stable, especially in case of PCa).
- CBC = baseline, 3-6 months, then annually, to ensure no polycythemia.
- BMD = done after 1-2 yrs of TRT.

Benefits (and Goals) of TRT

- Improved libido
- Improved erectile function
- Improved lean body mass
- Decreased total body fat
- Improved bone density
- Improved energy level
- Improved psychological disposition, i.e., better mood or sense of well-being

Adverse Effects of TRT:

- Polycythemia (Hct >50)
- Gynecomastia
- Alopecia
- Edema
- Hepatoxicity
- Acne/oily skin
- Aggression - only with supraphysiologic values of T.

NB: The target goal of TRT is a level between 400 and 800.

TRT Risk/Considerations:

- **BPH** - may lead to further prostatic enlargement, though now evidence that T may improve prostate elasticity and thereby improve LUTS. Does increase prostatic volume, mostly in 1st 6 months. Studies show inconsistent rise in PSA.
- **Prostate Cancer** - no clear evidence that TRT increases risk of DEVELOPING prostate Ca - see next slide.
- **Fertility** - not for men with fertility issues since TRT will shut down the pituitary influence of T production (gonadotropins).
- **MI, CVA, DVT/PE** - due to erythrocytosis

TRT Contraindications:

- Untreated prostate or breast cancer (absolute)
- Suspicion of prostate cancer (until ruled out)
- Hematocrit > 50
- Unstable CHF
- Sleep apnea (relative)

TRT and Prostate Cancer:

- Again, no clear evidence indicating that TRT increases risk of DEVELOPING prostate cancer. PCa dx almost never seen during peak T levels, only when older and presumable hypogonadal.
- Limited data for TRT in patients previously treated for localized prostate cancer, with no evidence of recurrence.
- May be higher risk in patients who had XRT vs. surgery, so wait for PSA nadir, then if TRT started, check PSA q 3 months and stop TRT if PSA rises.

TRT and Cardiovascular Risk:

TIMELINE:

Nov. 2013 - JAMA article suggests 30% increased risk of cardiovascular events with TRT.

Jan. 2014 - FDA issues an alert recommending caution.

June 2014 - FDA issues general warning for DVT/PE risk.

Sept. 2014 - FDA advisory panel concludes there is no evidence for increased CV risk, but also calls for tighter Rx guidelines.

Oct. 2014 - European Medicines Agency releases similar statement.

TRT and Lipid Profile

- Inconsistent data
- Restoration to eugonadol range does not result in worsening lipid profile

TRT and Liver

❖Hepatotoxicity most common with oral forms of treatment.

❖Potential for benign and malignant tumors.

❖The need for LFT monitoring is questionable when using injectable and transdermal preparations.

TRT and Sleep Apnea

❖Development or worsening of sleep apnea possible.

❖Questionable central mechanisms that affect breathing patterns.

Conclusions?

❖Testosterone Deficiency Syndrome or Late Onset Hypogonadism is widespread and undertreated, but in some populations it is overtreated.

❖Diagnosis is easy but yet not, since many of its symptoms are nonspecific and may include a number of differential diagnoses.

❖Few clear contraindications; relatively low risk to treatment. Yet some providers recommend low dose ASA daily to counteract possible CV events.

Task force of The Endocrine Society:

"We recommend testosterone therapy for men with symptomatic androgen deficiency to induce and maintain secondary sex characteristics and to improve their sexual function, sense of well being, muscle mass and strength, and bone mineral density."

We recommend against starting testosterone in patients with breast or prostate cancer, a palpable prostate nodule or induration or PSA >4 or >3 in men at high risk for prostate cancer such as African-American or men with 1st degree relatives with prostate cancer without further evaluation, hematocrit >50%, untreated severe obstructive sleep apnea, severe LUTS with IPSS >19, or uncontrolled or poorly contolled heart failure."

The Endocrine Society (cont.):

"When testosterone is instituted, we suggest aiming at achieving testosterone levels during treatment in the mid-normal range with any of the approved formulations, chosen on the basis of patient preference, consideration of pharmacokinetics, treatment burden and cost. "

"When receiving testosterone therapy, patients should be monitored using a standardized plan."

-The Journal of Clinical Endocrinology and Metabolism, Vol 95, Issue 6, 2010.

Low T ? Not me !!

THANK YOU.

References:

Bassil, N. , et al. (2009). The benefits and risks of testosterone replacement therapy: a review. *Therapeutics and Clinical Risk Management.* 5, 427-448.

Garnick, M. (2015). Testosterone replacement therapy faces FDA scrutiny. *JAMA 313(6), 563.*

Harrison, Steve . (2014). Testosterone Deficiency. 45th Annual Conference, Society of Urologic Nurses and Associates.

Hillstrom, W., et al. (2014). Testosterone: diagnosis and management of the hypogonadol male. Annual Conference, American Urologic Association.

Kleier, J.A. (2014). Testosterone Therapy: The new drug seekers. *Urologic Nursing. 34(4), 162-163.*

Oefelien,M. et al. (2015). Phase 2 results of novel oral testosterone replacement therapy (TSX-002)in symptomatic hypogonadal men. Abstract, AUA University.

Position Paper on testosterone therapy. (2010). *Journal of Clinical Endocrinology & Metabolism. 95(6).*

Quallich, S. (2011). Male hypogonadism and testosterone replacement: current guidelines & controversies. 42nd Annual Conference., Society of Urologic Nurses and Associates.

Quallich, S. (2011). A nurse's perspective: patient education and the management of hypogonadism. Interview with Medscape Education.

SMSNA Concensus Statement and White Paper Executive Summary: Adult Onset Hypogonadism. 2015.