Men's Sexual Health: Testosterone Replacement

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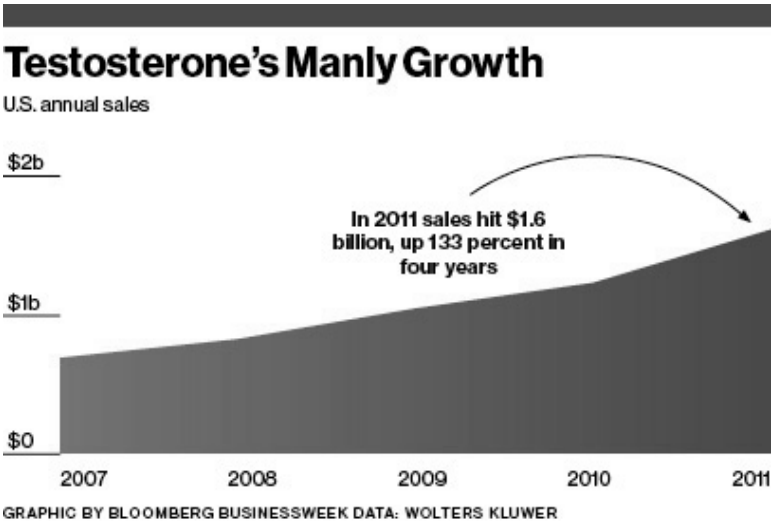
Business week



Objectives

- 1. Learn the factors predicting and associated with low testosterone.
- 2. Understand the factors used in diagnosing low testosterone.
- 3. Review the options available for testosterone replacement and the risk of prostate cancer.

Physiology of testosterone

- Produced and secreted by the testes
  - 95% from this source
  - 5-7 mg produced per day
  - Circadian rhythm
  - Circannual rhythm

Testosterone synthesis

- Leydig cell
- Produced cholesterol
- Regulated by:
  - Pulsatile GnRH
  - LH
  - Inhibited by inflammatory cytokines
- Metabolites
- Estradiol
- DHT

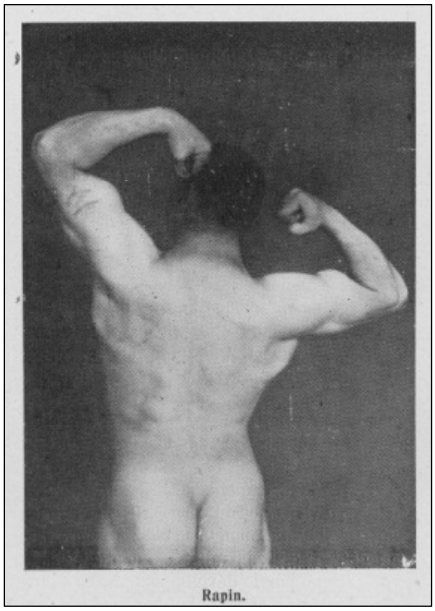
- Cholesterol
  - Via P450scc
- Pregnenolone
  - Via 3 beta-HSD
- Progesterone
  - Via P450c17
- 17 α-Hydroxypregesterone
  - Via P450c17
- Androstenedione
  - Via 17 beta-HSD
- Testosterone
  - Aromatase or 5 α reductase
- Estradiol or DHT

Circulation

- Biologically inactive
- Bound to SHBG (50-80%)
  - Strongly binds
  - Questionable biologic role
- SHBG
  - Decreased by obesity, insulin resistance, hypothyroid
  - Increased by estrogens, age, cirrhosis, HIV

- Biologically active
  - Bound to albumin (20-50%)
    - Freely dissociates
  - Free (2-3%)
    - Half life 10 minutes

Associations



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Diseases associated with testosterone deficiency

- Cardiovascular
- Cerebrovascular
- Respiratory
- Renal- especially ESRD
- Diabetes and metabolic syndrome
  - Longitudinal studies suggest TDS is independent predictor
- HIV
- Alzheimer's disease
- Autoimmune disorders

Prevalence low testosterone

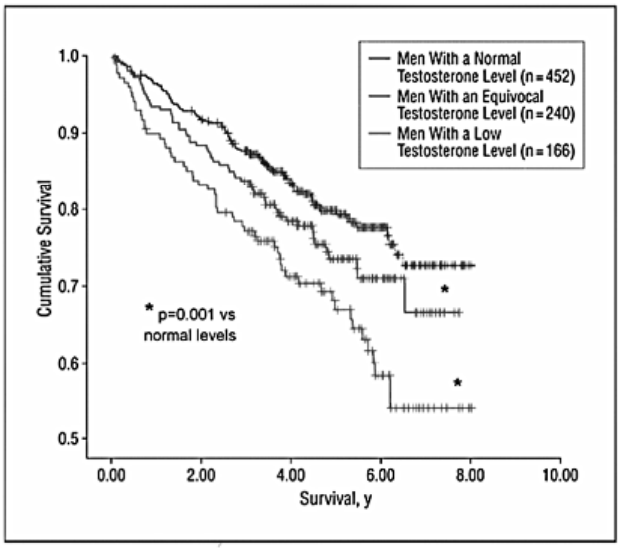
- Chronic opioid use – 74%
- Obesity – 52%
- Diabetes – 50%
- HIV/AIDS – 50%
- HTN – 42%
- Hyperlipidemia – 40%
- Erectile dysfunction – 36%

Mulligan et al. Int J Clin Pract 2006; 60:762.

Mortality

- Testosterone deficiency = doubled mortality risk
  - Shores et al. Arch Intern Med. 166:1660
  - Tivesten et al. J Clin Endocrinol Metab 94:2482
  - Primarily in older men
    - Few negative studies include younger men
- NEJM 2010 Basaria et al.
  - Stopped early due to increased cardiovascular events in testosterone treated arm
  - Frail older men

Reduced Survival in Men with Low Testosterone Levels



Unadjusted Kaplan-Meier survival curves for the three testosterone level groups in men aged 40 years or older.
Normal = ≥2 measurements of >250 ng/dL; Low = ≥2 measurements of <250 ng/dL
Equivocal = ≥1 low and ≥1 normal testosterone levels.
Shores MM, et al. Archives of Internal Medicine 2006;166:1660-5

Mortality

- **Shores et al. J Clin Endocrinol Metab 2012**
- **7 VA medical centers**
- **Observational study over time, comorbidity adjusted**
- **Outcome = mortality**
- **Two groups (testosterone less than 250 ng/dl)**
  - **Untreated (n=633)**
  - **Treated (n=398)**

- **Adjusted decreased risk of death**
- **HR 0.61, 95% CI 0.42-0.88**

Autoimmune disorders

- Improvements noted in RA and SLE
- Suppression of pro-inflammatory cytokines
  - Moderates antigen presenting cells
- Promotes anti-inflammatory cytokines
  - Shown in CAD and diabetes patients

Age

- Levels fall with age
  - Decrease 1-2% per year after age 40
  - Described as late onset hypogonadism when:
    - No cause found
    - 21% of 60-80 yo
    - 35% of 80+ yo
  - Decreased circadian rhythm

Obesity

- Aromatase activity proportional to adipose tissue
  - Metabolism of testosterone
  - Negative feedback of estradiol
- Metabolic syndrome
  - Testosterone helps improve insulin resistance
  - Cause or effect?

Cardiovascular disease

- Increased CAD in patients on androgen deprivation
- Testosterone associations on lipids:
  - Negatively on LDL, TG, and total cholesterol
  - Positively with HDL
- Increased diastolic blood pressure
  - Improved on testosterone treatment
- Endothelial dysfunction
  - Testosterone regulates flow and eNOS
- Metabolic syndrome effects

Heart failure

- Small studies suggest testosterone levels lower in patients with heart failure
  - Increased levels of inflammatory cytokines in HF
  - Improvements in these levels with testosterone supplementation

Osteoporosis

- Observational studies
  - Increase risk of fracture
    - Hip HR 1.88 95% CI 1.24-2.82
    - Nonvertebral HR 1.32 95% CI 1.03-1.68

Mood and Cognition

- Low testosterone associated with:
  - Irritability
  - Decreased short term recall
  - Poor spatial recognition tasks
  - Depression
- Mixed results with testosterone replacement

Sexual dysfunction

- Testosterone assists to regulate eNOS
  - May limit responsiveness to PDE5-inhibitors
- Decreased morning erections
- Low volume ejaculate
- Male infertility
  - Low sperm counts
- Decreased penile sensitivity
- Delayed orgasm or anorgasmia
- Delayed ejaculation

Low testosterone and PDE5-i

- Randomized study of testosterone gel as adjunctive therapy to sildenafil in hypogonadal men with erectile dysfunction who do not respond to sildenafil alone
  - Shabsigh, R. et al. J Urol 2004; 172:658-663.
- Observation of low serum testosterone associated with impaired cavernous vasodilation
- Placebo- controlled, double blind
  - Randomized 75 men to placebo vs 1% gel daily
  - Visits 1, 2 screening
  - Visit 3 first day sildenafil run in
  - Visit 4 baseline, day 1 of treatment groups
  - Visit 5 – 7 at 4 week intervals
  - No differences at baseline, all morning serum T < 400 ng/dl

Low testosterone and PDE5-i

- Responses to
  - difficulty maintaining erection to completion
  - feeling of orgasm
  - Overall sex life satisfaction
  - All remained significantly improved with testosterone gel
- Loss of significance for IIEF with time
  - At week 4 significant difference that was lost by week 12

PDE5-I failures

- All require sexual stimulation
- Sildenafil
  - Take 30-60 minutes prior, active 4-6 hours
  - High fat causes 29% reduction in max concentration
    - Take 1-2 hours after eating
- Vardenafil
  - Take 30-60 minutes prior, active 4-6 hours
  - Less reduction with fat
- Tadalafil
  - Max serum concentration 2 hours after dose, active 36 hours
  - Little to no effect by food

ACHIEVING TREATMENT OPTIMIZATION WITH SILDENAFIL CITRATE (VIAGRA®) IN PATIENTS WITH ERECTILE DYSFUNCTION

ANDREW R. MCCULLOUGH, JAMES H. BARADA, AHMED FAWZY, ANDRE T. GUAY, AND DIMITRIOS HATZICHRISTOU

• Urology 2002; 60:28-38.

- 6 double-blind, placebo-controlled flexible dose studies
- Sildenafil 654 pts : placebo 622 pts

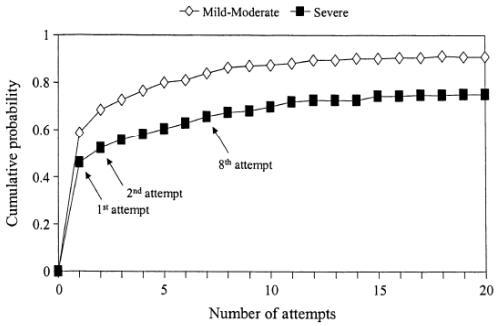
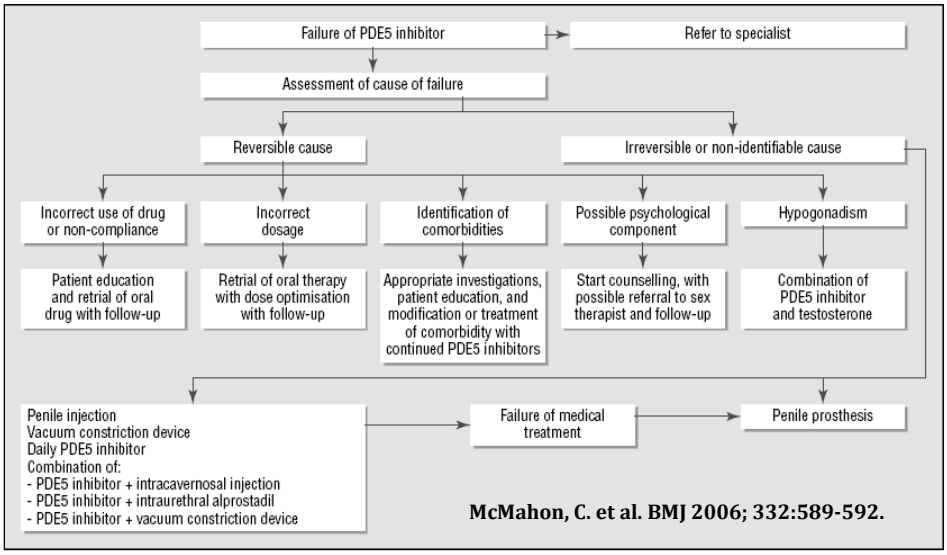


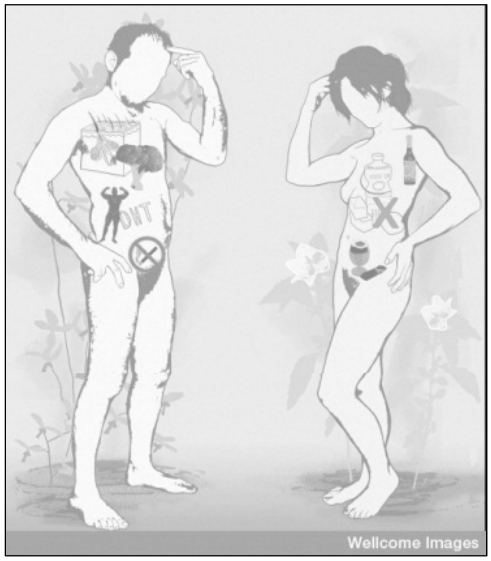
FIGURE 2. *Intercourse success rates, as determined from event log data, in men with erectile dysfunction taking sildenafil* (top). *Intercourse success rates in men stratified by erectile dysfunction severity* (bottom).

PDE5-I failures



McMahon, C. et al. BMJ 2006; 332:589-592.

Low Libido



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Diagnosis

“The trouble with testosterone”

Signs and symptoms of low testosterone[2]

- Decreased sexual desire (libido)
- Erectile dysfunction (ED)
- Fatigue or loss of energy
- Depressed mood
- Regression of secondary sexual characteristics
- Low bone mineral density
- Increased body fat
- Reduced muscle bulk and strength

Conditions associated with low testosterone in the HIM Study[1]

- Obesity
- Diabetes
- Hypertension
- Hyperlipidemia
- Asthma/COPD

Symptoms

- Fatigue
  - - generally feel refreshed upon awakening
- Sexual dysfunction
- Low libido
- Moodiness/Dysphoria/poor concentration
- Reduced physical endurance
  - Poor recovery after work-outs
- Infertility
- Failure to enter puberty

Image courtesy of http://images.wellcome.ac.uk

Signs

- Lack of facial hair
- Lack secondary sexual characteristics
- Underdeveloped muscles
- Truncal obesity
- Loss of height
- Wrinkling facial skin

- NO CONSISTENT SIGNS POST-PUBERTY
  - Even with Klinefelter's syndrome (XXY)

Aging Males Symptom Scale

AMS Questionnaire

Which of the following symptoms apply to you at this time? Please, mark the appropriate box for each symptom. For symptoms that do not apply, please mark "none".

Symptoms:	none	mild	moderate	severe	extremely severe
Score =	1	2	3	4	5
1. **Decline in your feeling of general well-being** (general state of health, subjective feeling)	☐	☐	☐	☐	☐
2. **Joint pain and muscular ache** (lower back pain, joint pain, pain in a limb, general back ache)	☐	☐	☐	☐	☐
3. **Excessive sweating** (unexpected/sudden episodes of sweating, hot flushes independent of strain)	☐	☐	☐	☐	☐
4. **Sleep problems** (difficulty in falling asleep, difficulty in sleeping through, waking up early and feeling tired, poor sleep, sleeplessness)	☐	☐	☐	☐	☐
5. **Increased need for sleep, often feeling tired**	☐	☐	☐	☐	☐
6. **Irritability** (feeling aggressive, easily upset about little things, moody)	☐	☐	☐	☐	☐
7. **Nervousness** (inner tension, restlessness, feeling fidgety)	☐	☐	☐	☐	☐
8. **Anxiety** (feeling panicky)	☐	☐	☐	☐	☐
9. **Physical exhaustion / lacking vitality** (general decrease in performance, reduced activity, lacking interest in leisure activities, feeling of getting less done, of achieving less, of having to force oneself to undertake activities)	☐	☐	☐	☐	☐
10. **Decrease in muscular strength** (feeling of weakness)	☐	☐	☐	☐	☐
11. **Depressive mood** (feeling down, sad, on the verge of tears, lack of drive, mood swings, feeling nothing is of any use)	☐	☐	☐	☐	☐
12. **Feeling that you have passed your peak**	☐	☐	☐	☐	☐
13. **Feeling burnt out, having hit rock-bottom**	☐	☐	☐	☐	☐
14. **Decrease in beard growth**	☐	☐	☐	☐	☐
15. **Decrease in ability/frequency to perform sexually**	☐	☐	☐	☐	☐
16. **Decrease in the number of morning erections**	☐	☐	☐	☐	☐
17. **Decrease in sexual desire/libido** (lacking pleasure in sex, lacking desire for sexual intercourse)	☐	☐	☐	☐	☐
Have you got any other major symptoms?	Yes ☐		No ☐		

The Saint Louis University Androgen Deficiency in Aging Males Questionnaire (ADAM)

<u>Do you have a decrease in libido (sex drive)?</u>
Do you have a lack of energy?
Do you have a decrease in strength and/or endurance?
Have you lost height?
Have you noticed a decreased "enjoyment of life"?
Are you sad and/or grumpy?
<u>Are your erections less strong?</u>
Have you noticed a recent deterioration in your ability to play sports?
Are you falling asleep after dinner?
Has there been a recent deterioration in your work recently?

The Massachusetts Male Aging Study/ Smith Questionnaire

What is your age?
60 years and older = 2 points
Have you ever been told by a health professional you have diabetes? If yes, are you receiving treatment?
Receiving treatment for diabetes = 3 points
Have you ever been told by a health professional you have asthma? If yes, are you receiving treatment?
Receiving treatment for asthma = 1 point
How much do you usually sleep?
Less than 5 hours per night = 1 point
Do you smoke cigarettes?
Formerly = 2 points
Never smoked = 2 points
Have you recently been bothered by headaches?
Yes = 2 points
Do you like directing other people's work?
No = 1 point
Height and weight- find you height and score for weight.
Not depicted
2 points for overweight and 3 points for obese

Utility of questionnaires

	ADAM		MMAS		AMS	
	Sensitivity	Specificity	Sensitivity	Specificity	Sensitivity	Specificity
Low Testo	97%	30%	60%	59%	83%	39%
< 300 ?						

Diagnosis

- Symptoms = non-specific
- Signs = non-consistent
- Questionnaires = non-specific

- Blood tests?

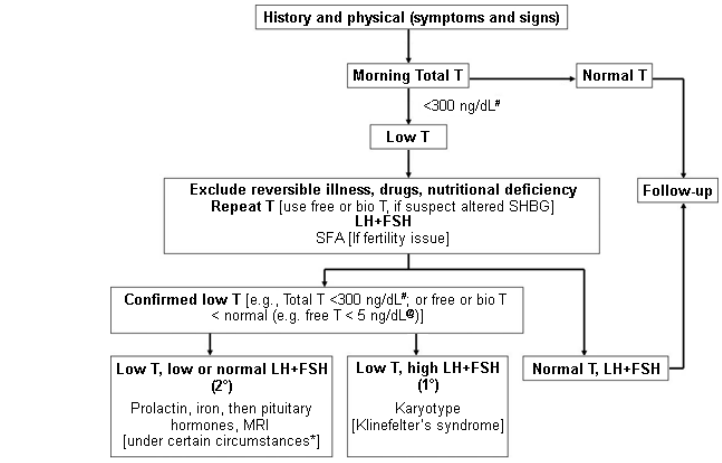
Testosterone assays

- Total testosterone
  - Measure between 7-10 AM
  - Preferably 2 separate days
  - No well defined range
    - Under 200 ng/dl likely hypogonadal and above 600 ng/dl likely eugonadal
  - Affected by illness, sexual activity, exercise
  - Assays usually fairly accurate

- LH, prolactin, TSH, FSH

Bioavailable and free

- Free testosterone
  - Only accurate with equilibrium dialysis
    - Difficult to do
  - Can calculate
    - Need SHBG and albumin levels
- Bioavailable testosterone
  - Calculated or ammonium sulfate precipitation
    - Labor intensive

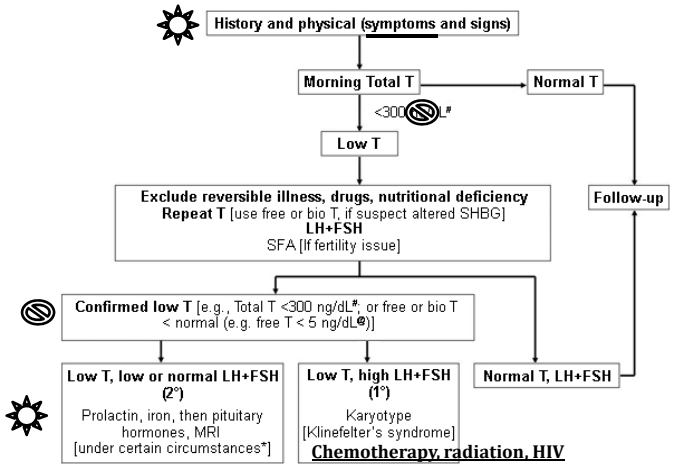


T = Testosterone; bio T = bio-available testosterone; SFA = seminal fluid analysis; 1° = primary testicular failure; 2° = secondary hypogonadism; SHBG = sex hormone-binding globulin; ng = nanograms; nmol = nanomol

: In some laboratories, the lower limit of the normal testosterone range in healthy young men is approximately 300 ng/dL (10.4 nmol/litre); however, this range may vary in different laboratories. Use the lower limit of the range established in your reference laboratory.

@ : In some reference laboratories, the lower limit of the normal free testosterone range in healthy young men is approximately 5 ng/dL (0.17 nmol/litre) (approximate lower limit of normal in three major commercial laboratories) using equilibrium dialysis or calculated from total testosterone and SHBG; however, this range may vary in different laboratories [approximate lower limits of normal ranging from 4 to 9 ng/dL (0.14 to 0.31 nmol/litre) in major commercial laboratories) using equilibrium dialysis or calculated from total testosterone and SHBG and the reference population used. Use the lower limit of the range established in your reference laboratory.

* : Perform pituitary imaging (MRI) to exclude pituitary and/or hypothalamic tumour or infiltrative disease, if severe secondary hypogonadism (serum T < 150 ng/dL), panhypopituitarism, persistent hyperprolactinaemia, or symptoms or signs of tumour mass effect, such as headache, visual impairment, or visual field defect, are present.



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Treatment options

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Supplementation

- Topical
  - Gel- Axiron, Androgel, Testim, Fortesta,
  - Patch- Androderm, Testoderm
- Oral
  - Clomid off-label
- Injection (IM)
  - Testosterone enanthate, testosterone cypionate
- Buccal
  - Striant
- Pellet
  - Testopel

Striant

- Buccal absorption
  - No risk transfer
  - First pass if swallowed
- Tmax 0.4-12 hrs
- Half life 5.7 hrs

- Side effects
  - 9% gum irritation
  - 4% taste bitter

Pellet (Testopel)

- Every 4-6 mo
- 75 mg pellets
- Tmax
  - 63 days
- Half life
  - 71 days
- Side effects
  - Pellet extrusion
  - infection

Gel

Axiron – under arm
Fortesta – internal thighs
Testim and Androgel – shoulders, chest, upper arm, upper back

Half life of 10 – 100 minutes
Tmax around 4 hours

Alcohol base
Risk of transfer to partner, chlidren

Intramuscular injection

- Altered form of testosterone to increase half life
  - Ester form
- Tmax 24 hours
- Half life 8 days
- Recommended starting dose:
  - 100 mg IM once per week or 200 mg every 2 weeks
- Inexpensive

Clomid

- Clomiphene citrate
  - Off-label but inexpensive
  - FDA approved for women
  - Selective estrogen receptor modulator
    - Increase FSH and LH
    - Maintain spermatogenesis
- Side effects
  - Headache, bloating, hot flashes, breast tenderness
  - ? DVT

Side effects of testosterone supplementation

- Polycythemia
  - Erythropoiesis stimulated
  - HCT increases more likely with supraphysiologic doses
- Suppress spermatogenesis
- Sleep apnea
  - Potential for worsening of untreated sleep apnea
- Gynecomastia
- Hepatotoxicity
  - Oral formulations except clomid

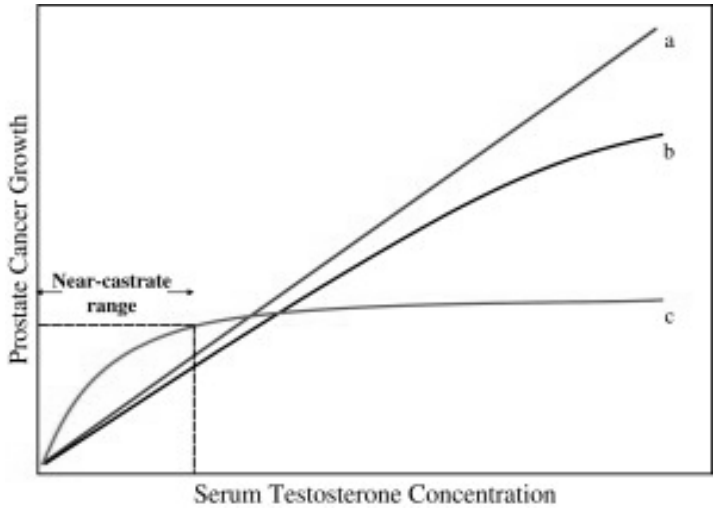
Prostate safety

- Currently no conclusive evidence testosterone therapy increases risk of prostate cancer or BPH
- PSA levels
  - Mixed clinical results
  - Tend to see initial rise that stabilizes
- BPH
  - Prostate events increased in meta-analysis
  - Mostly prostate biopsy

Prostate cancer

- No increased risk of prostate cancer in men with higher serum testosterone levels
- Meta-analysis of testosterone replacement trials do not show increased prevalence of prostate cancer
- Few small studies suggest increased risk of high grade cancer in hypogonadal men
- Risk of cancer with Prostatic Intraepithelial Neoplasia
  - Precancerous
  - After one year replacement, no increase prostate cancer

Saturation model



Replacement after prostate cancer treatment

- Few publications
  - Three retrospective studies after radical prostatectomy
    - No reported increase in PSA
    - Less than 100 patients
- Abstracts
  - No PSA recurrence in 133 pt, 21 high risk after prostatectomy
  - Two PSA recurrences after radiation therapy
  - Patients on surveillance
    - 12 of 14 men- no signs of progression on repeat biopsy

Khera, M. Curr Urol Rep (2010) 11:393-399

Following for prostate safety

- PSA prior to initiation of therapy
  - Biopsy for:
    - PSA velocity >0.4 ng/mL per year
    - PSA increase 1.4 ng/mL over 12 mo
    - PSA greater than 4 ng/mL
- PSA at 3 months
  - Consider addition of HCT, testosterone and estradiol

Contraindications to testosterone supplementation

- Metastatic prostate cancer
- Breast cancer
- Unevaluated prostate nodule or PSA >4 ng/ml
- HCT > 50%
- Severe BPH
- Poorly controlled CHF

Summary

- Testosterone is commonly associated with many chronic illnesses
  - CAD, DM, metabolic syndrome, ESRD, obesity, age, COPD
  - Low libido a key marker
- Diagnose base on symptoms PLUS low serum testosterone
  - Below 300 ng/dl
- Treatment options based on patient desire and cost
  - Repeat lab evaluation at 3 months