Hypogonadism: Who should get Testosterone Replacement?

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Objectives

• Review normal androgenic function in adult and aging men
• Discuss testosterone (T) deficiency (sometimes referred to as hypogonadism or andropause) in adult men
• Define treatment options for T deficiency in adult men including males who have undergone androgen deprivation therapy for prostate cancer

Learning Outcome

• At the end of this lecture the learner will:
  – Outline criteria for evaluation and management of adult males with symptomatic T deficiency.
Growing old, like comedy, is neither pretty nor for the faint of heart.
Androgens: What are they?

- Male sex hormones: substances that regulate 1º and 2º male sexual characteristics
- Role of androgens on male sexual characteristics and importance of production by testis recognized (in a rudimentary form) since antiquity; thus the historical record of eunuchs and various Biblical stories of David & Solomon

Androgens: Primary Players

- **Testosterone (T)**: acts as a hormone and a pro-hormone; primarily manufactured in the testis under influence of hypothalamic-pituitary-gonadal axis
- T is metabolized to form Dihydrotestosterone (DHT) under influence of the enzymes 5 α-reductase and estradiol, DHT is more metabolically active than T
- Adrenal glands also produce androgens; they exert much weaker androgenic effects than T or DHT
- The hormones Dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS) are manufactured in the adrenal, testes, liver, adipose tissue & brain; they act as pro-hormones for T

Androgens and the Male Life Cycle

- T secretion surges during 3 phases of a boy’s life
  - 1º trimester of embryogenesis
  - Early neonatal life
  - Puberty
- Levels established at puberty persist into adulthood
Gonadal Axis & Androgens

- Gonadal axis controls androgenic production
  - GnRH from hypothalamus stimulates LH & FSH
  - LH secretions increase T production in testes
  - T and inhibin from FSH provide negative feedback
- Testes produce about 95% of T; adrenals produce approximately 5%

(figure from chapter)

Androgens: Physiologic Effects

- Reproductive system
  - Spermatogenesis
  - Secondary sex characteristics (organs, skin, muscles)
- Non-Reproductive System Functions
  - Skeletal: promotes osteoblastic activity to maintain bone density & mass
  - Vascular system: T promotes vasodilation, DHT increases monocyte adhesion to endothelial cell


Androgens: Physiologic Effects

- Non-Reproductive System Functions
  - Nervous system: androgens protect neuronal cells from oxidative stress and possibly from cognitive decline such as Alzheimer’s disease, they alter expression of opioid receptors and may effect pain perception
  - Adiposity: fat cells aromatize T; (magnitude of effect equivalent to aging); effect partially reversed by weight loss among morbidly obese men
  - NOTE: Non-reproductive system receptors lack specificity of those in reproductive system

1. Pintana H et al. Metabolism and Brain Disease 2015; 30: 853-76.
**Obesity and T Deficiency as Public Health Issues**

- Limited evidence from MMAS suggests ↓ in circulating T over past 3 decades beyond age related expectations.
- Danish data also support this trend.
- Associated Factors include:
  - ↑ prevalence of obesity
  - Phthalate exposure from plastics
  - Measurement artifact (more sensitive assays available)


**Androgen Deficiency & Lipids**

Androgen Deficiency

- Triglycerides
- Total Cholesterol
- LDL-C
- Oxidized LDL
- HDL-C
- Oxidative stress
- Endothelial dysfunction
- Inflammation
- Proinflammation
- Atherosclerosis


**Androgens & Behavior**

- Sexual behaviors and orientation
  - Androgens exert profound influence on libido in both genders, no direct effect on single erectile event.
  - Limited evidence suggests prenatal androgenic influence on sexual orientation, but no apparent differences in adult homosexuals or genetic males identifying as transgender have been measured.

- Cognitive functions
  - May favor visual-spatial functions, but not verbal fluency.
  - Suppresses β-amyloid precursor peptide (may protect against Alzheimer’s disease).

- Mood
  - May protect against depression, T imparts feeling of energy, vitality and supports overall quality of life.

2. Osawa M. Neuroendocrinology 2011; 170-82.
Androgens & Aging

- **T** production declines with aging
  - Slow decline in testicular production of **T** by 0.5%–1.0% beginning around 40 years of age
  - Ratio of **T** to estradiol levels diminish (estradiol metabolized from **T** in peripheral tissues including fat)
  - Sex hormone binding globulin (SHBG) is synthesized in the liver; it ↑ with age, resulting in lower levels of **bioavailable** **T** (levels of bioavailable **T** diminish more sharply than overall **T** levels)
  - LH secretion unaffected


The prevalence of the syndrome in EMAS, overall and stratified by age, BMI and co-morbidity [1].


Androgens & Aging

- DHEA and DHEAS also decline with aging
- Effect exacerbated by cigarette smoking
- Also contribute to decline in bioavailable and total serum **T**

Aging and T Deficiency


Cut point in this study for low total T <325ng/dl

Androgens & Aging:

Summary of Adverse Effects

- ↓ libido, ↑ risk of sexual dysfunction
- ↑ risk for osteoporosis
- ↑ risk for hypercholesterolemia, hyperlipidemia
- ↑ risk for endothelial dysfunction, CV disease, HTN
- ↓ muscular mass and strength
- ↓ VO$_2$ max
- Impaired balance
- Impaired memory (may be related to Alzheimer’s risk)
- Impaired immune function
- ↑ risk for insulin resistance and DM


Androgens & Aging

• In women, there is a well recognized and precipitous, age-related decline in serum estrogen production that we label the climacteric or menopause
• Is there an analogous (and detectable) phase in men, ie: a “male menopause” or “andropause”? 
Androgenic decline in aging men: What is in a name?

- **Andropause (male menopause, male climacteric)**
  - First described as a clinical entity in 1939; implies an age-related, predictable decline with anticipated sequelae
- **Hypogonadism, T deficiency, ADAM (androgen deficit in aging male)**
  - Implies existence of a pathologic syndrome seen in some men rather than age-related change seen in all, definitions are based on symptoms and measurement of serum levels of testosterone (T) and secondary hormones


Andropause: Does it exist?

- **Arguments for ...**
  - Androgenic declines is associated with adverse physical and psychological events in many men
  - Replacement of T is a logical approach for alleviating or reversing adverse effects
  - Research shows promising in T replacement studies with short-term follow up
- **Arguments against...**
  - T decline is age related, but the incidence of symptoms with T deficiency is far lower
  - Multiple factors have been linked to andropause like symptoms
  - T replacement has not created the clinically dramatic effects we anticipated and is not well correlated to measureable changes in serum T levels


For purposes of this lecture I will label this condition **T deficiency**: I am implying this is specific disorder rather than age-related phenomenon

Decision based on current research, and consensus based expert opinion reflects in the recent Clinical Practice Guideline from the International Society for Sexual Medicine (ISSM)


**T Deficiency: Epidemiology**

- **Epidemiology**
  - Serum T deficiency steadily ↑ with age: affecting up to 5% at 40 years and as many as 70% at 60 years.

- **Prevalence of symptomatic T deficiency much lower:**
  - Best estimates are 2%-6%.

References:

**T Deficiency: Epidemiology & Natural History**

- Research also suggests symptom remission common
  - Study of 760 community dwelling men revealed found that 50% - 55% diagnosed with ADAM had remission of symptoms, usually coupled with ↑ bioavailable T within 10-15 years.
  - Remission associated with lower BMI and younger age at onset.

Travison TG et al. JAGS 2008; 56 (5): 831.

**T Deficiency: Classification System**

- ISSM identifies 4 subtypes of T deficiency
  - Hypergonadotropic or primary hypogonadism with reduced T synthesis and Leydig cell dysfunction
  - Hyponadotropic or secondary hypogonadism with reduction of T synthesis and inadequate stimulation of Leydig cells
  - Mixture of above causes
  - Compensated hypogonadism: normal T levels but ↑ levels of LH indicating need for hyperstimulation.

# T Deficiency

## Clinical Assessment

### T Deficiency: Epidemiology & Natural History

- I suggest starting with **symptoms**; most common clinical manifestations are:
  - Erectile dysfunction (37%)
  - Lethargy (28%)
  - Loss of libido (31%)
  - Sleep disturbances (27%)
  - Irritability (24%)
  - "Depressed Mood" (24%) (depression reported in <1%)

Travison TG et al. JAGS 2008; 56 (5): 831.

### T Deficiency: Associated & Co-Morbid Factors

- Assess for risk factors
  - Older age
  - Higher BMI (which is the cause and effect: metabolic syndrome vs. T deficit)
  - Type 2 DM
  - Hypertension
  - Heart Disease

T Deficiency: Symptom Score/Instrument

- Consider use of a validated questionnaire to identify associated symptoms; options include ADAM or AMS (aging male survey)\(^1\)\(^-\)\(^3\)
  - AMS has more robust psychometric testing; translated into 14 languages
  - ADAM more condition specific; use of Likert scale improves criterion validity
  - AMS designed for symptoms associated with aging due to multiple causes; it nevertheless correlates well with biochemical evidence of ADAM (r = .8-.9)

1. Morley JE et al. Metabolism: Clinical & Experimental 2000; 49(9): 1239
2. Daig I et al. Health and Quality of Life Outcomes 2003; www.hqlo.com/content1/1/77
Quantitative ADAM (qADAM)

- Updated version of ADAMq
  - Replaces original scale’s “yes” and “no” (bivariate) response system with 5 point Likert Scale where 5 represents absence of symptom and 1 indicates maximal symptom
  - Range of score is now 10 – 50 (↓ score = ↑ symptom)
  - Appears to improve criterion validity when compared to Sexual Health Inventory for Men (SHIM) and Expanded Prostate Cancer Index composite hormonal sexual domains (EPIC)


Quantitative ADAM questionnaire

- Questions Used as Part of the qADAM Questionnaire
  1. How would you rate your sexual desire? (1: extremely low to 5: extremely high)
  2. How would you rate your sexual interest? (1: extremely low to 5: extremely high)
  3. How would you rate your sexual activity? (1: extremely low to 5: extremely high)
  4. How would you rate your sexual desire? (1: extremely low to 5: extremely high)
  5. How would you rate your sexual interest? (1: extremely low to 5: extremely high)
  6. How would you rate your sexual activity? (1: extremely low to 5: extremely high)

T Deficiency: Medication Review

- Review Medications; among the many agents known to impair gonadal function include
  - Thiazide diuretics
  - Long-acting oral opiates
  - Antiepileptic drugs
  - Specific antipsychotics including risperidone (Risperdal) and olanzapine (Zyprexa)
  - Androgen deprivation therapy (LHRH agonists and antagonists for prostate cancer)

T Deficiency: Physical Examination

- General inspection including breast examination
- Body and facial hair; evaluate for androgenic alopecia vs 'man-scaping'; note T deficiency does not usually affect beard growth or thickness
- Genital examination including penile length and testicular examination (should be 4-5cm x 2-3cm)


T Deficiency: Physical Examination

- BMI: height and body, waist circumference, assess for central obesity
- Breast examination for gynecomastia vs central obesity

T Deficiency: Physical Examination

- Digital rectal examination is not considered essential for initial assessment for T deficiency

Biochemical Diagnosis

• Measure serum T in all cases
  – Start by measuring total T, consider SHBG (serum hormone binding globulin) in older and obese men
  – Radio-immunoassay or chemiluminescence assays (RIA/IA) usual used to measure T; liquid chromatography-tandem mass spectrometry is gold standard, but it is not widely available

• ISSM recommends systematic screening of these groups:
  – Obese men
  – Men with Type 2 Diabetes mellitus
  – Men with metabolic syndrome


T Deficiency: Biochemical Diagnosis

• Criteria for Diagnosing T Deficiency (ISSM CPG/AUA White Paper)
  – No universally accepted cut points: ISSM and AUA recommend:
  – Measurement in morning usually recommended 0800-1200; afternoon values tend to be lower
  – Most common cut point for “normal” (no T deficiency) is 350 ng/dL or ≥ 12 nmol/L; additional evaluation needed if levels are lower than this cut point
  – Historic alternative to this cut point is:
    • > 400 ng/dL: normal; no further evaluation
    • 200-399 ng/dL: treat when symptoms present
    • > 200 ng/dL: hypogonadal; treatment indicated


T Deficiency: Biochemical Diagnosis

• Step 2: obtain bound and bioavailable (free) T levels
  – Schedule 0800-1200, at least 1 week later
  – Obtain serum LH (luteinizing hormone) to identify subtype of T deficiency
  – Prolactin to evaluate for hypogonadotropic (secondary) hypogonadism, hemochromatosis (look for elevated ferritin)
  – Obtain SHBG in all older and obese men (cut points not identified in published CPG)

T Deficiency: Biochemical Diagnosis

- Interpreting results of laboratory studies
  - Serum T is > 350 ng/dL: no treatment indicated; look for other causes of symptoms
  - Serum T is < 231 ng/dL: treatment clearly indicated; especially in younger men
  - Serum T is 232ng/dl to 345 ng/dl and/or SHBG is elevated; consider 6-12 month trial of treatment after other causes have been evaluated and alternative or complementary treatments considered


T Deficiency: Treatment Options
T Deficiency: Nonpharmacologic Interventions

- **Lifestyle modification**: ↑ exercise (transiently raises T and SHBG), heart healthy diet, weight loss for many
- **Treat sleep apnea** (CPAP raises ADAMq scores but no effect on gonadal function in men with T2DM in 1 study)
- **Discontinue opioids** (daily use suppresses T in men)
- **No adverse SE; first line treatment of choice in men when fertility concerns are in play**


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T Deficiency: Pharmacologic Treatment Overview

- **Testosterone replacement**
  - Is the only USFDA approved pharmacologic intervention for management of T deficiency currently available
  - The goal of treatment is to establish midrange normal values of serum T in order to **relieve symptoms**
  - Men who wish to maintain fertility and testicular volume **must** be counseled that TR is expected to suppress spermatogenesis and fertility and reduce testicular volume; referral to a specialist for men with fertility concerns is strongly recommended


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Testosterone Replacement

- **Management: Testosterone Replacement**
  - Intramuscular agents
    - Testosterone cypionate
    - Testosterone enanthate
  - Transdermal agents
    - Androderm (patch)
    - Testoderm (patch)
    - Androgel (gel applied to skin)
    - Axiron (transdermal/axillae)
  - Transmucosal (Buccal) Agents
    - Oral agents
    - Fluoxymesterone
    - Methyltestosterone
    - Testosterone undecanoate (not available in US)
Testosterone Replacement

- **Intramuscular preparations**
  - T. cypionate: 50-400mg, dosed every 2-4 weeks or every week based on response
  - T. enanthate: 50-400mg monthly; dosed every 2-4 weeks or weekly
  - Most men can be taught to self-inject
  - Maximum serum levels at 72 hours, gradually declines to nadir over following days to weeks before repeating cycle
  - May need to alter diabetic medications or insulin, T alters insulin sensitivity
- Long acting formulations in Canada and Europe but not US


Testosterone Replacement

- **Adverse Side Effects**
  - Emotional lability (peaks and valleys) and variable libido (↑ injection frequency to weekly to reduce these adverse SE)
  - Pain at injection site
  - Facial flushing
  - Polycythemia, blood clots
  - Gynecomastia
  - Exacerbation of sleep apnea
  - Exacerbation of acne
  - Fluid retention
  - Prostate enlargement resulting in lower urinary tract symptoms


Testosterone Replacement

- **Testosterone implants: Testopel**
  - Pellets as seen in figure contain crystalline T
  - Implanted into the subdermal fat of lower abdominal, deltoid, proximal thigh or buttocks wall via wide-bore trocar under local anesthesia
  - Outpatient procedure requires about 15 minutes with experience
  - Provides stable T levels for 3 months in most
  - Improves long-term adherence to TR when compared to topicals: 19% at 1 year for transdermal preparations vs 72% with T pellets

Testosterone Replacement

**Adverse side effects**
- Inflammation and pain at injection site
- Polycythemia, blood clots
- Gynecomastia
- Exacerbation of sleep apnea
- Exacerbation of acne
- Fluid retention
- Prostate enlargement resulting in lower urinary tract symptoms

Testopel package insert:
http://www.endo.com/File%20Library/Products/Prescribing%20Information/Testopel_prescribing_information.html

Testosterone Replacement

* Transdermal preparations
  - Testoderm: oldest transdermal preparation; non-adhesive patch must be applied to shaved scrotum with jock strap type brief (off market due to newer approaches)
  - Testoderm-TTS: adhesive patch applied to clean, dry skin on arms, back or upper buttocks daily; doses vary from 4,5 & 6 mg doses; patch varies accordingly; usually start with 4 mg patch
    - 65% achieve physiologic serum levels with regular use, change product if levels not achieved within 6-8 weeks
    - Most commonly reported side effects: rash or erythema at application site in 15% to as high as 66%; may advise patients to rotate sites and use topical steroid as preventive measure


Testosterone Replacement

* Transdermal preparations
  - Androderm patches: 2.5-5.0gm patches apply as shown
  - Patches contain central reservoir of alcohol based gel that breaks down dermal barrier and promotes drug absorption
  - Adverse Side Effects: skin irritation at application site, advise patients to rotate site, apply skin barrier for mild to moderate irritation

Testosterone Replacement

• **Transdermal preparations: gel**
  - Delivers 5-10 mg of T daily
  - Single use sachets deliver 1.5 mg gel and pump preparations usually deliver 2% gel; all are applied daily
  - Applied to shoulders, upper arms or abdomen after bathing or shower
  - Several head to head trials generally show greater efficacy than patches with fewer adverse skin reactions
  - **NOTE:** T gels and solutions can be transmitted to partner, especially within 15 minutes of application; advise men to wear clothing to cover application area and wash hands (newer more concentrated gel, 1.62% formulation available that reduces volume and skin exposure)

  Abadilla KA, Doleh AS. Drugs 2012; 72 (12): 1586-1603.

Testosterone Replacement

• **Transdermal solution: Axiron**
  - Axillary delivery system newer; T is first agent to be delivered using this system
  - Applied in meter dosed pump that delivers 1.5 ml of solution and 30 mg T; recommended to start at 60 mg, may be escalated to 120 mg
  - Alcohols evaporate leaving T and octisalate, a thickening agent that promotes transdermal absorption of T
  - Compatible with regular deodorant or antiperspirant; recommend applying these products prior to T


Testosterone Replacement

• **Buccal Testosterone: Striant**
  - Adhesive tablets applied to gums above the incisors
  - Release T over 12 period; must be applied twice daily; delivery is transdermal avoiding first pass metabolism; this is not an oral formulation
  - Unique adverse side effects for buccal formulation
    - Irritation, tenderness or pain of gums
    - Change in taste perception or bitter taste in mouth

Testosterone Replacement

• Ongoing Monitoring for Men Receiving TR
  – Assess for effect of treatment at 3, 6, 12 months and annually for duration of treatment
  – Routinely obtain serum T, CBC, lipid profile at each follow up visit
  – Injection therapy: morning trough level 1-2 weeks before 4th injection; short term therapy – draw T and midpoint of cycle 3-4
  – Transdermal or buccal therapy: draw T 0800-1200 following application of T dose


Testosterone Replacement

• Adverse Side Effects for transdermal or transbuccal preparations
  – Skin irritation (erythema, rash) in 10-12%
  – Polycythemia, blood clots
  – Gynecomastia
  – Exacerbation of sleep apnea
  – Exacerbation of acne
  – Fluid retention
  – Prostate enlargement resulting in lower urinary tract symptoms

Testosterone Replacement

• Oral Agents
  – Not recommended in ISSM guideline
  – T is inactivated in liver; chemical modification bypasses this effect but results in hepatotoxicity
  – T, undecanoate avoids first pass metabolism – it is largely absorbed via lymphatics; must be taken 2-4 times daily with meal
  – Available in Europe and Canada, but not in US

Testosterone Replacement: Ongoing Monitoring

- Annual History and Physical Examination
  - Symptom inventory, response to treatment
  - Evaluate body habitus, body weight, hair pattern growth
  - Breast inspection for gynecomastia
  - Digital rectal examination for prostatic nodules


Testosterone Replacement: Ongoing Monitoring

- PSA and TR
  - Serum PSA will rise slightly with TR; physiologic response in most cases
  - ISSM recommends referral for additional evaluation if PSA levels rise more than 1.4 ng/mL within any 12 month period

- CBC and TR
  - Monitor for evidence of polycythemia

- Lipid profile and TR
  - Dyslipidemia may improve after therapeutic T levels have been attained

- Routine monitoring of liver function not indicated


Testosterone Replacement: Are there adverse long-term consequences?
Testosterone Replacement: Does it influence Prostate CA Risk?

- In most cases, prostate cancer is hormone sensitive; reducing T levels to “castrate” (<50ng/dl) is an effective treatment option.
- This begs the question...does TR “feed” (increase the risk for or growth of) malignant cells within the prostate?
- ANS: The theoretical risk is not borne out by empiric evidence.


Testosterone Replacement: Does it influence Prostate CA Risk?

- Endogenous Hormones and Prostate Cancer Collaborative Group pooled data from 18 prospective studies with 3886 men with prostate cancer and 6438 controls:
  - No association between prostate cancer risk and serum T levels: (RR in the highest vs lowest fifth = 0.86, 95% confidence interval = 0.75 to 0.98; P_trend = .01)
- Muller et al. reported outcomes of 3255 men in REDUCE trial (finasteride for prevention of prostate CA) at 2 and 4 years and found no association between prostate CA incidence and serum T levels.


Testosterone Replacement: Does it influence CV disease risk?

- Evidence concerning influence of TR on risk of cardiovascular disease is mixed:
  - Initial research found no increased risk, and they found association between T deficiency and endothelial disease.
  - Vigen et al reported findings from observational study of 8709 men that linked CV risk with T levels >300ng/dl; AR 5.8%; 95%CI -1.4% to 13.1%; multiple problems with statistical analysis (absolute occurrences in men receiving T was half that of those not receiving T; excluded men who started T after MI; 10% of subjects were women).

Testosterone Replacement: Does it influence CV disease risk?

- Evidence concerning influence of TR on risk of cardiovascular disease is mixed.
  - Finkle et al. also completed an observational study and reported an ↑ risk of nonfatal MI 3 and 12 months after beginning T replacement compared with 12 months prior to TR initiation; this study was based on insurance claims with no control for CV risk factors as confounding variables; in addition the rate of incident MI was lower than anticipated using the Heart Attack Risk Calculator, actual risk was 1 CV event for every 1,000 years of T use.


Testosterone Replacement: Does it influence CV disease risk?

- ISSM goes on to argue that TR improves CV health and/or ameliorates risk for CV disease.
  - CV disease is a risk factor for T deficiency; studies that fail to control for this may suffer from selection bias.
  - T Replacement improves CV risk factors including reduced fat mass, improved lean muscle mass, improved glycemic control and insulin sensitivity.
  - T Replacement has been shown to reduce mortality in younger men.
- For both controversies; additional research is needed.


Testosterone Replacement and Bone Health

- TR ↑ Bone Density in men.
  - Bone Mineral Density increased in 8 of 8 studies; 4 published 4 derived from grey literature (abstracts, proceedings).
  - N=76; sample sizes varied from 4-29; treatment time varied from 3-14 months.
  - Outcomes varied: biochemical measurements of bone turnover or imaging techniques looking at lumbar spine; none measured most direct outcome – fractures or clinical outcomes.

Testosterone Replacement and Polycythemia

- Raises hematocrit & hemoglobin to polycythemic levels in 7%–20% of older men

<table>
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<th>Duration of Most % change in Hgb/HEC, mg/day</th>
<th>No. change</th>
<th>Right or Ict</th>
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</table>


Testosterone Replacement and Obesity

- TR ↑ lean body mass, ↓ central obesity
  - 5 studies, 4 published and one from gray literature
  - N=108 subjects, treatment from 3-18 months
  - Various outcomes: CT scan for body fat distribution, as part of bone density examination, bioimpedance plus CT, hydrostatic (underwater mass displacement)

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<td>12</td>
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<td>2.0%</td>
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</tbody>
</table>

Strength of Evidence: Weak (Mixed results: generally favorable)


Testosterone Replacement

- Argument for TR in men: ↑ strength & performance
  - 8 studies, 6 published and 2 from grey literature (Sih et al subsequently published)
  - N=107; 4 used changes in grip strength, 2 used LE strength changes and 2 used subjective perceptions of strength and/or energy
  - Length of treatment varied from 3-24 months
  - 7 of 8 showed positive change in at least one parameter; grip strength improved more dramatically than LE strength

Testosterone Replacement and Cognitive Function/AD Risk

- Evidence is insufficient for definitive conclusions
  - Literature review using MEDLINE reveals no large cohort study and no systematic reviews published since 2000.
  - Research suggests neuroprotective effect of T and positive benefits of T replacement but additional research is needed before recommending T as beneficial for prevention of AD.


Potential Benefits of T Replacement

- **↑ bone density** *(evidence favors TR)*
- **↑ lean body mass, fat distribution** *(mixed evidence)*
- **↑ CV health and prevent CVD** *(evidence favors TR)*
- **↑ strength & performance** *(evidence favors TR)*
- **Health Related QOL** *(evidence shows no benefit)*
- **↑ mood, protects from depression** *(evidence shows no benefit)*
- **↑ libido and sexual function** *(evidence favors TR)*
- **↑ cognitive function & memory** *(mixed evidence)*

Testosterone Replacement

- The argument against
  - **Liver toxicity**: potential greatest for some oral agents, not seen with transdermal or IM preparations.
  - **Gynecomastia** (painful breast enlargement) occurs in 1%-2%, usually with injectable formats due to supraphysiologic surges.
  - **Sleep apnea**: mixed evidence raises possibility that it may exacerbate condition.

T Replacement and Men with Prostate Cancer History

- T has the very real potential to exacerbate existing prostate cancer but...
  - T replacement has been deemed safe in men who have undergone radical prostatectomy and who have undetectable PSA levels; meta-analysis suggest recommend non-injectable formulations safest¹
  - T replacement has been deemed safe in men following radiation therapy who have undetectable PSA levels²
  - I strongly recommend referral to a urologist with expertise in T replacement in both cases

¹ Kang SY, Li HG. Medicine 2015; 94(3): e410.

Pharmacotherapy in Men with T deficiency: Alternatives to TR

- Several medications are used by specialists in men with fertility concerns; none are approved for this indication by the US FDA
  - Clomiphene citrate: enhances endogenous T production
  - Anastrozole: blocks conversion (aromatization) of T to estrogens, resulting in higher serum T and lower estradiol
  - Human chorionic gonadotropin: enhances endogenous T production
- I strongly recommend referral to urologist with expertise in andrology when treating any men with T deficiency who wishes to preserve fertility


Conclusions

- A gradual decline in T levels is an age related phenomenon in men
- T deficiency is a clinically relevant syndrome affecting some men with various causes of hypogonadism
- Assessment focuses on combination of biochemical evidence of T deficiency and clinical symptoms
- Treatment primarily focuses on TR; long-term follow up in these men is essential