Hypogonadism and Testosterone
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, andropause, androgen deficiency in aging men) 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

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**Androgens: Primary Players**

- **Testosterone (T):** acts as a hormone and a pro-hormone; it is primarily manufactured in the testis under influence of the hypothalamic-pituitary-gonadal axis
- **T** is metabolized to form Dihydrotestosterone (DHT) under influence of the enzymes 5α-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**

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**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**

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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%


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 obese and 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

- 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 gay males or genotypic 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.


Androgens & Behavior

- Sexual behaviors and orientation:
  - Androgens exert profound influence on libido in both genders, no direct effect on single erectile event.
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Androgens & Aging

- T production declines with aging¹,²
  - 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; ↑ with age, resulting in lower levels of bioavailable T diminish more sharply that overall T levels
  - LH secretion unaffected


Androgens & Aging

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

(Figure from article)

Aging and T Deficiency


(Figure from article)
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
- ↓ VO₂ 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 males, 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 these 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 measurable changes in serum T levels

Androgenic decline in aging men: What is in a name?

- For purposes of this lecture I will label this condition T deficiency; I am implying this is a specific disorder rather than an 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 rises 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%

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
  - Hypogonadotropic 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

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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)
  - AMS has more robust psychometric testing; translated into 14 languages
  - ADAMq 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)

ADAM Questionnaire

Quantitative ADAM (qADAM)

- Updated version of qADAM
  - 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

*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

*Figure: NCIS visuals, https://visuals.nci.nih.gov/*


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**Biochemical Diagnosis**

- **Always Measure serum T**
  - Start by measuring total T, consider SHBG (serum hormone binding globulin) in older and obese men
  - Radio-immunoassay or chemiluminescence assays (RIA/IA) usually 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 mg/dL: hypogonadal; treatment indicated


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)


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 232 ng/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

- **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

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


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

Abadilla KA, Dobbs AS. Drugs 2012; 72 (12): 1591-93.

Testosterone Replacement

◆ Transdermal preparations
  - Androderm patches: 2.5-5.0 gm 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% 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, Dobbs AS. Drugs 2012; 72 (12): 1591-1603.
**Testosterone Replacement**

- **Transdermal solution: Axiron**
  - Axillary delivery system newer; T is first agent to be delivered using this system
  - Apply at least 2 minutes after antiperspirant/regular deodorant
  - Prime pump with 3 productive pumps before initial use
  - Apply cover and avoid direct contact with women or children
  - Applied in metered dose 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


- **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


- **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 Examination1,2
- Recommend follow up at 3, 6 & 12 months, then annually
- Administer symptom inventory and compare score to baseline
- Evaluate body habitus, body weight, hair pattern growth, inspect breasts gynecomastia, tenderness
- Digital rectal examination for prostatic nodules
- Effects variable: ↑ libido within 3 weeks, will plateau by 6 weeks, maximum effect of QoL and depressive mood with 1 month, maximal effect on ED within 6 months

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 with regular follow up
- **Lipid profile and TR**
  - Dyslipidemia may improve after therapeutic T levels have been attained, monitor with regular follow up
- 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 be empiric evidence1,2

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).


- 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.
- Anderson et al. evaluated outcomes in 4736 men and used Cox proportional analyses to adjust for risk factors, TR was not associated with higher likelihood of MACE (major adverse cardiovascular event).

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
  - Androgens protect against development of osteoporosis in aging men
  - Bone Mineral Density increased in 8 of 8 studies; 4 published 4 derived from grey literature (abstracts, proceedings); pooled N=76 sample sizes varied from 4-29; treatment time varied from 3-14 months
  - ↓ bone density considered one of the multiple related conditions used to justify need for TR in selected men


Testosterone Replacement and Polycythemia

- Polycythemia is well known adverse side effect of TR
  - Analysis of 179 patients median 7 month follow up in world class andrology clinic
  - 49 (27%) had 10% or greater change in hematocrit
  - Erythrocytosis (hematocrit ≥ 50% rise) developed in 36 (20.1%)
  - Men with polycythemia had significantly higher DHT levels than those without; researchers suggested possible role for 5α-reductase inhibitor

Testosterone Replacement and Obesity

- Obesity strongly linked to T deficiency, especially in morbidly obese men
- TR interruption associated with ↑ BMI in study of 262 men
- The corollary clinical question is: does TR ↑ lean body mass and ↓ central obesity
  - 5 studies, 4 published and one from gray literature; pooled N =108 subjects, treatment from 3-18 months
  - Various outcomes used: CT scan for body fat distribution, as part of bone density examination, bioimpedance plus CT, hydrostatic (underwater mass displacement); evidence is weak but 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)*

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


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