MALE HYPOGONADISM

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Notes about handout vs. lecture

- There are more slides included in handout than will be covered in the lecture, thus more reference information in this handout
- Slides which have been omitted in the lecture are marked in left lower corner with an “X”
- Slides which have been modified for the lecture are marked in left lower corner with an “M”
Definition of Hypogonadism

Decrease in either or both of the two major functions of the testes: Sperm production, Testosterone (T) production

“Hypogonadism in men is a clinical syndrome that results from failure of the testis to produce physiologic levels of testosterone (androgen deficiency) and a normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-testicular axis” – TES CPG
Prevalence of Hypogonadism

- 13.8 million men with hypogonadism
- Baltimore Longitudinal Study of Aging
- Only 9% treated
Hypothalamic-Pituitary-Gonadal Axis

- Hypothalamus: pulsatile GnRH secretion
- Pituitary: pulsatile FSH and LH secretion
- LH stimulates Leydig cells to produce T
- FSH acts on Sertoli cells to stimulate spermatogenesis
- (-) feedback via T and Inhibin B
**T Synthesis**

- Similar to other adrenal hormones
- Cholesterol is first key precursor
- Requires several enzymatic steps
- Other androgens produced en route

![Chemical diagram of steroid synthesis]

1. **Cholesterol**
   - **CYP11A1** (cholesterol side chain cleavage enzyme)

2. **Pregnenolone**
   - **3β-HSD** (3β-hydroxysteroid dehydrogenase/isomerase)

3. **Progesterone**
   - **CYP17** (17α-hydroxylase)

4. **17-OH-Progesterone**
   - **CYP17** (17, 20-lyase)

5. **Androstenedione**
   - **17β-HSD** (17β-hydroxysteroid dehydrogenase)

6. **Testosterone**
   - **5α-Reductase**
   - **CYP19** (aromatase)

7. **Estradiol**
   - **Dihydrotestosterone**
T Metabolism

- Dihydrotestosterone (DHT) has > affinity than T at androgen receptor (AR)
- $5\alpha$-reductase: prostate, skin, reproductive tissues
- Aromatase: adipose, liver, certain CNS nuclei
Diurnal Circadian Rhythm

- Peak levels in early a.m.
- Night/swing shift different
- Lost with aging
- Wide inter-individual variation
Effects of Aging on T Levels

- 1-2% ↓ T levels per year after age 30
- Gradual/more subtle loss than ♀
- Free > total
- Individual variability
- Chronic disease
T Circulation

- 1-2% unbound or free
- 54-68% loosely bound to other proteins e.g. albumin
- 30-44% tightly bound to sex hormone binding globulin (SHBG)
- Acts directly on target cells or converted to dihydrotestosterone (DHT) via 5α-reductase or estradiol via aromatase
Biologic Effects: Reproductive

- Testes, penis, epididymis, seminal vesicles, and prostate:
  - Stimulate prenatal differentiation
  - Stimulate pubertal development
  - Maintenance in adults
- ↓ prostate size and PSA in hypogonadal ♂
- Initiation and maintenance of spermatogenesis
- Stimulation and maintenance of sexual function

X
Biologic Effects: Reproductive

- DHT-dependent masculinization:
  - Enlargement of external male genitalia
  - Prostate enlargement

- T-dependent processes:
  - Male pattern hair growth
  - Muscle mass
  - Voice deepening
Biologic Effects: Musculoskeletal

- **Muscle:**
  - ↑ nitrogen retention, lean body mass (LBM), and body weight
  - Anabolic cannot be dissociated from androgenic properties

- **Bone:**
  - Stimulate proliferation of bone cells
  - Estrogen effects > androgen (conversion)
Biologic Effects:
Skin and Hair

- Sebum production is androgen-dependent (DHT > T)
- Hair growth depends on androgens:
  - Higher concentrations for face, chest, and upper pubic area
  - Lower concentrations for axilla and lower pubic area
Biologic Effects: Cardiovascular

- **Cardiac:**
  - Hypogonadal ♂ > risk CAD than eugonadal
  - ? vasodilatory effects on coronary vessels
- **Altered lipid levels vs. pre-menopausal ♀:**
  - Lower HDL-C
  - Higher triglycerides, LDL-C, VLDL-C
  - May reflect reason for ↑ CAD risk
**Biologic Effects:**

**Hepatic**

*Increased synthesis*
- Clotting factors
- Triglyceride lipase
- Sialic acid
- $\alpha_1$-antitrypsin
- Haptoglobin

*Decreased production*
- SHBG
- Hormone-binding globulins
- Transferrin
- Fibrinogen
Biologic Effects

- **Metabolic:**
  - Predisposes to insulin resistance
  - Association w/ metabolic syndrome and DM 2

- **Hematologic:**
  - Stimulates erythropoietin production
  - Alkylated androgens stimulate production of C1 esterase inhibitor

- **Immune ?:** > # of autoimmune diseases in ♀
Clinical Presentation

- Impaired T secretion varies based on age
  - 1\textsuperscript{st} trimester \textit{in utero} depends on degree
  - 3\textsuperscript{rd} trimester \textit{in utero} typically with normal \textbullet male sexual differentiation with micropenis
  - Incomplete puberty otherwise

- Impaired spermatogenesis:
  - Infertility
  - ↓ testicular size
Prepubertal Presentation

- Eunuchoid appearance
  - Crown to pubis length < pubis to floor length
  - Arm span > height
    - Long bones grow out of proportion to axial skeleton under the influence of IGF-1
  - Small testis
  - Decreased hair
  - Small penis
- Most common diagnosis is Klinefelter’s
<table>
<thead>
<tr>
<th>Physical/Metabolic</th>
<th>Sexual</th>
<th>Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased bone mineral density</td>
<td>Diminished libido</td>
<td>Depressed mood</td>
</tr>
<tr>
<td>Decreased muscle mass &amp; strength</td>
<td>Erectile dysfunction</td>
<td>Diminished energy, sense of vitality, or well-being</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Difficulty achieving orgasm</td>
<td>Impaired cognition and memory</td>
</tr>
<tr>
<td>Decreased 2° sexual characteristics</td>
<td>Decreased erections</td>
<td></td>
</tr>
<tr>
<td>Frailty</td>
<td>Infertility</td>
<td></td>
</tr>
<tr>
<td>Increased body fat</td>
<td></td>
<td>Laboratory</td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td>Anemia (NCNC)</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td></td>
<td>Oligo/azoospermia</td>
</tr>
</tbody>
</table>

**Laboratory**

- Anemia (NCNC)
- Oligo/azoospermia
### Primary Hypogonadism (1)

<table>
<thead>
<tr>
<th><strong>Gonadal defects</strong></th>
<th><strong>Testicular</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic diseases (e.g. Klinefelter’s)</td>
<td>Trauma, torsion, tumors, resection</td>
</tr>
<tr>
<td>Anatomic defects (anorchia, cryptorchidism)</td>
<td>Orchitis (e.g. Mumps)</td>
</tr>
<tr>
<td>Toxin-mediated</td>
<td><strong>Hormone resistance</strong></td>
</tr>
<tr>
<td>Medication-related</td>
<td>Androgen insensitivity</td>
</tr>
<tr>
<td>Enzyme defects</td>
<td>LH insensitivity</td>
</tr>
</tbody>
</table>
Klinefelter’s Syndrome

- 1:1000 live births
- Testes:
  - Small
  - Firm
- Gynecomastia
- Eunuchoid
- Azoospermia
- 50% ↓ T levels

- 93% 47XXY
- 7% mosaic
  (46XY/ 47XXY)
Primary Hypogonadism (2)

<table>
<thead>
<tr>
<th>Toxin-mediated</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiation</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Chemotherapy (esp. alkylating agents)</td>
<td>Spironolactone</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Radioactive iodine</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Environmental</td>
<td>Flutamide</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
</tbody>
</table>
Androgen Insensitivity

- AKA “Testicular Feminization”
- X-linked recessive disorder
- Normal male karyotype 46,XY
- Defect in AR → T resistance → failure to develop male characteristics dependent on testosterone, so phenotypic ♀
- Incomplete form with some androgen effects
Primary Hypogonadism (3)

- Enzyme defects: CAH, 5α-reductase
- Noonan syndrome (~ Turner’s phenotype)
- Autoimmune syndromes
- Sertoli-cell only syndrome
- Less common genetic defects: 47, XYY, myotonic dystrophy
Central Hypogonadism

**Hypothalamic**
- Kallmann syndrome
- Infiltrative diseases
- “Eugonadal sick”
- Functional
- Constitutional delay

**Pituitary**
- Sellar masses
- Hypopituitarism
  - Trauma
  - Iatrogenic
  - Infarct/apoplexy
- Hyperprolactinemia

**Gonadotropin suppression**: Gonadal steroids, GnRH analogs, chronic opiates
Hormonal Deficiencies

- Isolated GnRH:
  - Idiopathic
  - Kallmann syndrome:
    - AD or X-linked recessive trait
    - Prepubertal hypogonadism, anosmia, midline defects, congenital deafness, cryptorchidism
- Isolated LH = fertile eunuch syndrome
- Isolated FSH or LH/FSH $\beta$-subunits
Combined/Dual HPT Axis Causes

Hemochromatosis
Sickle cell disease
Thalassemia
Glucocorticoid treatment
Anabolic steroid use/abuse
Alcoholism
Chronic disease: CKD, cirrhosis, HIV
Historical Points

- Sexual development
  - Phenotypic presentation
  - Milestones
- Etiologic
  - Behavioral changes
  - Chemo, XRT, EtOH, surgery, trauma
  - Pituitary symptoms
  - Anosmia
Physical Examination (1)

- Age consistency important
  - Descended testes w/o hypospadias
  - Tanner staging
- 20-25 mL = normal adult testes volume (orchidometer)
- Adult penile length
  - 4-7 cm flaccid
  - 12-16 cm stretched flaccid
Question

What is the name of this measuring device?

Orchidometer

X
Physical Examination (2)

- Testicular masses
- Male musculature
- Hair distribution
- Gynecomastia
  - Seen in $1^\circ > 2^\circ$ hypogonadism
- Eunuchoid proportions (lower body $> 2$ cm longer than upper body)
- Regression of $2^\circ$ sexual characteristics delayed
Conditions Warranting Screening

Sellar mass, radiation to or diseases of sella
Medications that affect T production or metabolism (e.g. opioids, glucocorticoids)
HIV-associated weight loss
ESRD on maintenance dialysis
Infertility
Moderate to severe COPD
Osteoporosis or low-trauma fracture
DM type 2
Total T (TT) Measurement

- Morning sampling given diurnal changes
- Repeat testing necessary
  - Crucial if abnormal, borderline, or inconsistent with clinical suspicion
- Measure during healthy/non-ill state
- Labor-intensive assays more accurate & sensitive (e.g. LC/MS)
- Generally, level < 200 ng/dL diagnostic
Free T (FT) Measurement

- Useful if:
  - Abnormal SHBG levels suspected
  - Inconsistent or borderline TT levels
- Calculated via SHBG and TT levels as free androgen index (www.issam.ch/freetesto.htm)
- Equilibrium dialysis only reliable direct measurement (not analog displacement)
- Lack of consensus on threshold parameters
T Assay Difficulties

- Vary depending on age and presence of comorbid conditions
- Vary with time of day
- Interference from other circulating steroids
- Vast majority of hospitals use total T assays neither certified by CDCP testosterone standardization program nor calibrated to NIST or CAP standards

# SHBG Levels

<table>
<thead>
<tr>
<th>Elevated</th>
<th>Decreased</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advancing age*</td>
<td>Obesity*</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Cirrhosis*</td>
<td>Acromegaly</td>
</tr>
<tr>
<td>Estrogen excess/use</td>
<td>Nephrotic syndrome*</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Androgenic steroid, progestin, or glucocorticoid use*</td>
</tr>
<tr>
<td>Anticonvulsants*</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Levothyroxine use</td>
<td>Cachexia/malnutrition</td>
</tr>
</tbody>
</table>

* indicates risk factors that are also associated with liver disease.
Take-Home Points

- Morning levels (7-10 a.m.)
- Multiple samples needed
- Repeat if abnormal or discrepant
- Full panel testing often necessary:
  - Obesity $\rightarrow$ ↓ SHBG $\rightarrow$ ↓TT/normal FT level
  - ↑ age $\rightarrow$ ↑ SHBG $\rightarrow$ normal TT/↓FT level
- Use reliable reference laboratory/assays
FSH/LH (Gonadotropin) Levels

- Supranormal levels = primary disease
- (Inappropriately) normal or low levels = central
- FSH has longer T½ so more accurate
- Consider LH only, unless fertility concerns
- Spermatogenic problems $\rightarrow \uparrow$ FSH with normal LH and T levels but $\downarrow$ sperm counts
- $\uparrow$ Prolactin $\rightarrow \downarrow$ pulse frequency of both
Other Endocrine Tests

- Prolactin and TSH in ~ 100%
- Estradiol and/or hCG levels:
  - Gynecomastia present
  - Testicular tumor suspected
- Karyotyping if suspect Klinefelter’s
- Anterior pituitary function if central process
MRI Sella

- Perform if …
  - Other pituitary hormone abnormalities/hypopituitarism
  - Persistent hyperprolactinemia
  - Tumor effects (headache, visual field change)
- Finding mass lesion more likely if younger and lower T level
  - T < 250 ng/dL for younger male
  - T < 150 ng/dL for older male
Ancillary Testing

- CBC (H/H) and PSA – see later
- Semen analysis if infertility concerns
- Systemic disease-specific tests e.g. iron
- Testicular ultrasound for mass/hydrocele
- Mammogram/breast ultrasound for mass
- BMD assessment via DXA after 1-2 yrs
- Sleep apnea evaluation, if symptoms
Diagnosis & Evaluation: TES CPG 2010

- No widespread screening
- Screening questionnaires not recommended
- Morning TT by reliable assay with repeat
- Measure FT or BT, using accurate & reliable assay, if borderline TT or SHBG alteration
- Do not measure during acute/subacute illness

Golden Rules for Diagnosis

- Use accurate assays, CDC-certified lab, and rigorously-derived reference range
- Do NOT diagnose based on single T level
- Do NOT diagnose based only on T level
- Measure free T using an accurate method when suspect binding protein abnormality
- Use ancillary data (testicular volume, FSH/LH levels) to aid in diagnosis
Bone Mineral Density

- 3-6% of ♂ >50 have osteoporosis
- 28-47% of ♂ >50 have osteopenia
- Risk of fracture 22% for ♂ >60
- ↑ risk with aging occurs 7-10 years after ♀
- ↓ with age correlates with estradiol > T levels
- Insights from conversion enzyme deficiencies:
  - Estradiol > T to prevent bone resorption
  - Estradiol = T for bone formation
Treatment of Hypogonadism

- Clear and widely recommended that patients with primary or secondary hypogonadism, presenting with symptoms, should be treated with testosterone replacement therapy (TRT)
- Neither long-term benefits or risks established in middle-aged/older males with age-related decline in T levels
- 3 month trial if borderline levels/symptoms
Potential Benefits of TRT

- Restores libido and erectile function
- Produces &/or maintains virilization
- Increases energy and improves mood
- Improves body composition
  - ↓ fat mass, ↑ lean body mass & muscle strength
- Stabilizes or increases bone density

- Benefits in young >> elderly hypogonadal ♂
Specific Points

- Improvement in libido has a low threshold without dose effect based on T level obtained
- Erectile function improved with libido if no concomitant neuro/vascular disease
- TTrials: inaugural report just published\(^1\)
  - Modest, waning improvement in sexual function but less than PDE5-I treatments
  - Limited physical function and psychologic benefits

Contraindications

- Clinical prostate cancer, unexplained ↑ PSA or prostate abnormality, BPH w/severe LUTS
- Male breast cancer or Prolactinoma
- Erythrocytosis (Hct >50%)
- Family/personal history of VTE/thrombophilia
- Class III or IV CHF
- Undiagnosed/untreated sleep apnea or edema
- MI or CVA within last 6 months
# Testosterone Formulations

(All schedule III drugs due to abuse potential)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dosage and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Injectable</strong></td>
<td></td>
</tr>
<tr>
<td>Cypionate/enanthate</td>
<td>50-400 mg every 1-4 weeks</td>
</tr>
<tr>
<td>Undecanoate</td>
<td>750 mg baseline, @4 wks, then q10 wks</td>
</tr>
<tr>
<td><strong>Topical</strong></td>
<td></td>
</tr>
<tr>
<td>Patch system</td>
<td>2-8 mg daily</td>
</tr>
<tr>
<td>Gel (upper body)</td>
<td>12.5-100 mg daily</td>
</tr>
<tr>
<td>Gel (thigh)</td>
<td>10-70 mg daily</td>
</tr>
<tr>
<td>Axillary solution</td>
<td>30-120 mg daily</td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>2-6 pellets implanted SC q 3-6 mo</td>
</tr>
<tr>
<td>Buccal system</td>
<td>30 mg every 12 hrs</td>
</tr>
<tr>
<td>Nasal gel application</td>
<td>5.5 mg each nostril TID (total 33 mg)</td>
</tr>
</tbody>
</table>
## Formulations: Pros & Cons (1)

<table>
<thead>
<tr>
<th>Type</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cypionate, enanthate</td>
<td>Inexpensive, Effective symptom relief</td>
<td>Peak/trough issues, Risk polycythemia</td>
</tr>
<tr>
<td>undecanoate</td>
<td>Ultra long-acting</td>
<td>? Decrease HDL, IM injections, ? Painful</td>
</tr>
<tr>
<td>Transdermal</td>
<td>T levels mimic circadian rhythm, Low incidence of polycythemia</td>
<td>Moderate cost, Visible, not discrete, Difficulty achieving adequate T levels, Skin irritation, Lack of adhesiveness, Daily administration</td>
</tr>
</tbody>
</table>
T Undecanoate

- Int’l approval 12 yrs; NDA 8/07 → approval 3/14
- Efficacy proven – 94%
- Consistent post-injection reactions:
  - Pulmonary oil microembolism (POME) due to castor oil
  - Anaphylaxis due to castor oil or benzyl benzoate
  - No deaths, but resuscitations and hospitalizations
- REMS program for prescribers/clinics
## Formulations: Pros & Cons (2)

<table>
<thead>
<tr>
<th>Type</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transdermal gel/liquid</td>
<td>T levels maintained over 24-hr period</td>
<td>Expensive</td>
</tr>
<tr>
<td></td>
<td>High patient compliance</td>
<td>Transference concerns</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Drug accumulation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Variable absorption</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Messy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin irritation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Daily administration</td>
</tr>
<tr>
<td>Pellets</td>
<td>Longest duration of action</td>
<td>Procedural implantation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Local side effects, extrusion</td>
</tr>
<tr>
<td>Buccal system</td>
<td>Physiologic range levels</td>
<td>Expensive, oral irritation, altered taste, BID dosing</td>
</tr>
<tr>
<td>Nasal gel</td>
<td>Convenient, quick</td>
<td>Rhinorrhea, epistaxis, nasal discomfort, URT infections</td>
</tr>
<tr>
<td></td>
<td>Minimal transference risk</td>
<td></td>
</tr>
</tbody>
</table>

- **Transdermal gel/liquid**
  - Pros: T levels maintained over 24-hr period, high patient compliance
  - Cons: Expensive, transference concerns, drug accumulation, variable absorption, messy, skin irritation, daily administration

- **Pellets**
  - Pros: Longest duration of action
  - Cons: Procedural implantation, local side effects, extrusion

- **Buccal system**
  - Pros: Physiologic range levels
  - Cons: Expensive, oral irritation, altered taste, BID dosing

- **Nasal gel**
  - Pros: Convenient, quick, minimal transference risk
  - Cons: Rhinorrhea, epistaxis, nasal discomfort, URT infections
AndroGel® (testosterone gel) 1.62%]
Designed with a man in mind™

The Authorized Generic of Testim contains the identical formulation of testosterone gel contained in Testim with the same efficacy and safety profiles.

Distributed by Phesto Laboratories

Distributed by Auxilium Pharmaceuticals, Inc.
Oral T Agents

- 17α-methyl testosterone not recommended
  - 1st pass effects → ↑ risk hepatotoxicity
  - Potential liver toxicity, including neoplasms
  - Dyslipidemia via ↓ HDL and ↑ LDL
- Oral testosterone undecanoate*
  - Bypasses first pass metabolism
  - No adverse hepatic side effects
  - Not available in U.S.
    - Sept 18th – FDA advisory panel votes against 18-3

* Not available in U.S.
# Potential Class Adverse Effects

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate cancer</td>
<td>Controversial; no conclusive evidence</td>
</tr>
<tr>
<td>Benign prostatic hyperplasia</td>
<td>Infrequently worsened in mild or moderate LUTS; avoid if severe LUTS</td>
</tr>
<tr>
<td>Testicular atrophy or infertility</td>
<td>Common, especially in young men; usually reversible when treatment stops</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>Infrequent; controversial</td>
</tr>
<tr>
<td>Acne and oily skin</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Fluid retention/edema</td>
<td>Rarely of clinical significance; concern if class III or IV CHF, CKD, or cirrhosis</td>
</tr>
<tr>
<td>Erythrocytosis</td>
<td>Injectable &gt;&gt; Transdermal/other</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Infrequent, injectable &gt; others</td>
</tr>
</tbody>
</table>
Adverse Events with TRT

**Evidence of Association**
- Acne, oiliness of skin
- Erythrocytosis
- Testicular atrophy, infertility
- ↑ risk of detection of prostate events
- ↑ growth of metastatic prostate cancer
- Formulation-specific

**Weak or Inconclusive Evidence of Association**
- Gynecomastia
- Prostate cancer
- Obstructive sleep apnea
- Lower urinary tract symptoms (LUTS)
- Cardiovascular events
Topical Label Change

- Reports of secondary T exposure in children
- Adverse events: inappropriate genitalia enlargement, premature pubarche, advanced bone age, increased libido, aggressive behavior
- Boxed warning label change for topical therapies
- Precautions suggested to minimize potential for secondary exposure
  - Wash hands thoroughly after exposure
  - Avoid skin contact until dried completely
  - Keep application site covered

http://www.FDA.gov/NewsEvents/Newsroom/PressAnnouncements/ucm149580.htm
General Label Updates

- Risk of venous thromboembolism (VTE)
  - Previous labeled as erythrocytosis consequence
  - Thrombosis warning added to label of all products
  - Inquire about personal/family VTE history before
  - But, NO routine thrombophilia screening suggested
- Spring 2015: TRT use limited to ♂ who have low T levels in conjunction with an associated medical condition
Cardiovascular Risk (1)

✧ Epidemiologic studies suggest hypogonadism a/w CV events and all-cause mortality
✧ TRT favorably changes many CV risk factors
✧ To date, no RCTs to evaluate CV risk concern
✧ Recent published studies raised concerns
   ✧ Retrospective with “diseased” males
   ✧ Important methodologic limitations
CV Risks of TRT

Biological Plausibility: Consistent Evidence

Potential CV Risks
- Hematocrit
- HDL cholesterol
- Platelet aggregation
- Sodium retention
- Smooth muscle proliferation
- VCAM expression

Potential CV Benefits
- Vasodilator effect – increased coronary and penile blood flow
- ↓ whole body fat (visceral and subcutaneous)
- Vascular reactivity
- Shortened QTc interval
Mixed Results from Recent Studies on TRT and CVD

- Retrospective analyses with conflicting results
- Limitations
  - Heterogeneity of study populations, intervention duration, and study designs
  - Variable definitions & ascertainment of CV outcomes
  - Unclear treatment indications, treatment regimens, T levels, and exposure
  - Residual confounding: study groups differed on CV risk factors
Cardiovascular Risk (2)

- 9/14 FDA: need further studies to evaluate CV risk associated with TRT
- Injectable TRT show greater MI and stroke risk\(^1\)
- AACE/ACE Position Statement affirms all points\(^2\)
- TEAAM: no significant difference in CV risk using CIMT and CAC\(^3\)
- TEAAM and TTrials\(^4\): not powered for CV events

Take-Home Points about TRT

- Thorough diagnostic work-up necessary
- Cautious approach to TRT in elderly/aging
- Inform patients that long-term risks not known with possibility that TRT may be harmful
- Although cost may be lower, “older” injectable preparations are NOT easier to use and have increased risks of side effects vs. others
Monitoring

- Evaluate symptom response 3-6 months after start, then each clinic visit
- If 1° hypogonadism, follow LH levels
- H/H:
  - Baseline, 3-6 months, then annually
  - If Hct >54%, stop tx and re-evaluate
- BMD measurement via DXA after 1-2 yrs
- Adverse effects at each visit
## Assessing Response to T

- T levels at 2-3 months after initiation
- Aim to raise to mid-normal range

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Application Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable cypionate/enanthate</td>
<td>Midway b/w injections, then peak/trough</td>
</tr>
<tr>
<td>Injectable undecanoate</td>
<td>Just prior to next injection</td>
</tr>
<tr>
<td>Transdermal patches</td>
<td>3-12 hours after application</td>
</tr>
<tr>
<td>Buccal system</td>
<td>Immediately before fresh application</td>
</tr>
<tr>
<td>Transdermal gels/liquid</td>
<td>After use for at least 1 week,</td>
</tr>
<tr>
<td></td>
<td>At least 2 hours after application</td>
</tr>
<tr>
<td>Testosterone pellets</td>
<td>At end of dosing interval</td>
</tr>
<tr>
<td>Nasal gel application</td>
<td>Not labeled at present</td>
</tr>
<tr>
<td>Oral undecanoate*</td>
<td>3-5 hours after ingestion</td>
</tr>
</tbody>
</table>

* Not available in U.S.
Monitoring: Prostate Issues

- Men > 40 yrs
  - DRE/PSA @ baseline, 3-6 months, then per CPGs
  - Prostate symptom assessment
- Urology consultation/biopsy if:
  - Abnormal baseline DRE or PSA > 4.0 ng/mL
  - ↑ PSA > 1.4 ng/mL in 12-month period
  - PSA velocity > 0.4 ng/mL/yr after 6 month tx
  - AUA/IPSS score >19
Other Therapies

- Clomiphene citrate for secondary disease*
  - Recent study completion with 79% T normalization as main goal
  - Non-inferiority for sperm count
  - Well-tolerated
- Anti-estrogens not recommended/routinely used

* Not approved to date in U.S.
Gonadotropin or GnRH Therapy

- Only for secondary disease
- Initiate and maintain spermatogenesis for fertility purposes
- hCG (~LH) +/- hMG (~FSH)
- GnRH via pump
- Monitor gonadotropins, T levels, and semen analyses