Androgen Replacement Therapy in the Aging Male

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Objectives
1. List 3 effects of androgens on normal male physiology.
2. Describe 2 controversial issues surrounding androgen replacement in the older male.
3. Outline an appropriate testosterone replacement algorithm in hypogonadal men.

Androgen Effects on the Normal Male

- Blood-clotting, Lipids
- Heart-vasodilation
- Liver-serum proteins
- Fat-reduction
- Muscle-anabolic
- Bone marrow-stem cells

Behavior/mood
Body Hair
Kidney-erythropoietin
Male sex organs-maintenance
Bone-growth, density
What Happens to Testosterone with Age?

It falls… but gradually.

Also known as:
- Male Menopause
- Late Onset Hypogonadism (LOH)
- Andropause
- Viropause
- Male Climacteric

ADAM-Androgen Deficiency in the Aging Male

Age and Testosterone Levels

Baltimore Longitudinal Study of Aging
Prospective, 40 year study to date.
N=890 men evaluated

Age and SHBG Levels

Y ounger Older

Bioavailable T

SHBG-T

Bioavailable T

SHBG-T

SM Harman et al. JCEM. 86: 724, 2001
Androgen Replacement Therapy

Aging and Testosterone

Androgen Replacement: Benefits and Risks

IOM 2003: What Have We Learned?

When and What to Give

Symptoms/Findings with ADAM

1. Decreased libido/erectile dysfunction
2. Mood changes, fatigue and depression
3. Memory loss
4. Decreased lean body mass and muscle loss
5. Increase in visceral fat
6. Decreased body/facial hair and skin thinning
7. Decreased bone mineral density - osteoporosis
* 8. Infertility and testis atrophy
* 9. Gynecomastia

* Conditions specific to hypogonadism

Androgen Replacement: Benefits

<table>
<thead>
<tr>
<th>Symptom/Finding</th>
<th>Evidence?</th>
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</thead>
<tbody>
<tr>
<td>Libido/erectile function</td>
<td>Yes/Maybe</td>
</tr>
<tr>
<td>Mood changes/fatigue/depression</td>
<td>Yes</td>
</tr>
<tr>
<td>Increased body mass and muscle</td>
<td>Yes</td>
</tr>
<tr>
<td>Decreased body/visceral fat</td>
<td>Yes</td>
</tr>
<tr>
<td>Cardiovascular benefit</td>
<td>Maybe</td>
</tr>
<tr>
<td>Increased bone mineral density</td>
<td>Yes</td>
</tr>
<tr>
<td>Improved cognition</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Androgen Replacement Therapy: Risks

➢ Obstructive Sleep Apnea

➢ Infertility

➢ Polycythemia

➢ CV disease

➢ Prostate Health
Institute of Medicine Statement - November 2003

What? The NIA (National Institutes of Aging) and NCI (National Cancer Institute) requested the IOM to conduct a 12-month study to:

1) Review and assess current knowledge about the risks and benefits of testosterone therapy in older men.
2) Prepare an evidence-based report and make recommendations regarding the design, safety, and ethics of clinical trials of this intervention, if warranted.

Why? Due to growing concern about an increase in the number of older men using testosterone replacement in the absence of adequate scientific information about risks and benefits.

Who? The committee consisted of prominent scientists in epidemiology, endocrinology, geriatrics, urology, oncology, psychiatry and other relevant fields.

And…?

Institute of Medicine Statement - November 2003

Androgen Replacement Therapy

- "Critical gaps in knowledge"
- Unclear if lower testosterone concentrations affect health outcomes in older men
- Evidence suggests benefits of testosterone replacement, but it is generally mixed and inconclusive
- No definitive evidence of risk associated with replacement


Androgen Replacement Therapy

Aging and Testosterone
Androgen Replacement: Benefits and Risks
IOM 2003: What Have We Learned?
When and What to Give
**Prostate Health**

No clear link between testosterone level and BPH

Association between testosterone replacement and prostate cancer still inconclusive, but:
- Lower endogenous T may = worse cancer
- No obvious increased risk of prostate cancer in men on T replacement
  - Meta-analysis N=651, OR 1.09


**Androgen Replacement and PSA**

Contemporary studies have confirmed (non-comparative)

Hypogonadal likely have lower PSA

**Androgen Replacement: PSA and Prostate Cancer**

*Current Recommendations*

1. Before Rx: PSA, DRE, voiding history.
2. If normal, consider testosterone.
3. If either abnormal, TRUS biopsy. Positive biopsy - No testosterone, Negative biopsy - Consider testosterone.
4. During Rx: continued monitoring q3-6 mos.

**Prostate Health**

No evidence of cancer recurrence after treatment for organ-confined or locally advanced CaP.

No increased risk of CaP in hypogonadal men with PIN treated with testosterone.

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Metabolic syndrome (MS)

1. Insulin resistance
2. Obesity
3. Abnormal lipids
4. Hypertension
5. Hypogonadism

HIM Study: 31% prevalence of DM in hypogonadal men
17% prevalence of DM in eugonadal men


Non-Diabetic men 4-fold more likely to develop MS if hypogonadal


Cardiovascular health

IOM: “no clear link” between T and CV outcomes

Testosterone replacement may:
• Improve CV parameters and QOL
• Improve Coronary artery vaso-reactivity
• Does not negatively influence markers of coagulation

Physical function

IOM: “inconclusive evidence” linking T and body composition; decreased T may contribute to frailty

Testosterone replacement may:
• Improve bone mineral density and muscle mass/strength
• Increase lean body mass and performance and decrease fat and leptin

Mental function

Testosterone replacement may lead to:
• Improvements in VERBAL and SPATIAL memory
• Relationship between total/free testosterone and Alzheimer’s disease.
  Free testosterone falls more precipitously in men who develop Alzheimer’s Disease
  Men with Alzheimer’s have lower testosterone levels than age-matched controls
Sexual function
Massachusetts Male Aging Study:
- Serum T did not correlate with ED
- ED is multifactorial in older men; only 6.6% is due to hypogonadism; Only 1/3 of these men will respond to T.

Improved libido and sexual function: yes!
Testosterone plus PDE-5 inhibitors: maybe
Shabsigh R. J Urol 2004; 172: 658-63

Androgen Replacement Therapy
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When and What to Give

Androgen Replacement Therapy: When and What?
1. Assess patient symptoms. Appropriate Sx's present.
2. Measure total testosterone. If:
   - <200ng/dL Consider Rx
   - 200-350ng/dL Repeat Total and Free T
   - >350ng/dL Normal; No Rx

Androgen Replacement: Contraindications
- Known or suspected prostate cancer.
- Known or suspected breast cancer.
- Elevated hematocrit.
- Pre-existing obstructive sleep apnea.
Androgen Replacement Therapy: What?

<table>
<thead>
<tr>
<th>Available preparation</th>
<th>Formula</th>
<th>Dose</th>
<th>Specific risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
<td>Methyltestosterone</td>
<td>10-50mg/day</td>
<td>High first pass inactivation, multiple daily dosing, hepatotoxicity</td>
</tr>
<tr>
<td></td>
<td>Flutamide</td>
<td></td>
<td></td>
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<tr>
<td>Parenteral</td>
<td>Testosterone</td>
<td>200-250mg</td>
<td>Deep intramuscular injection, supraphysiologic peaks and troughs</td>
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<tr>
<td></td>
<td>cypionate</td>
<td>IM every 2-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Testosterone</td>
<td>weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>enanthate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transdermal patch</td>
<td>Testoderm(scrotal)</td>
<td>4-6mg/day</td>
<td>Scrotal: poor absorption, daily shaving</td>
</tr>
<tr>
<td></td>
<td>Testoderm TTS</td>
<td>5mg/day</td>
<td>dermatological reactions</td>
</tr>
<tr>
<td></td>
<td>Androgel</td>
<td>2.5-5mg/day</td>
<td></td>
</tr>
<tr>
<td>Transdermal gel</td>
<td>Androgel</td>
<td>5mg=5mg/day</td>
<td>Transference to partner</td>
</tr>
</tbody>
</table>

Androgen Replacement: Conclusions

1. Very appropriate for truly hypogonadal men.
2. Highly questionable for eugonadal but symptomatic older men.
3. Long, term prospective trials needed to truly define risk (benefits observed in short trials).