An Update on Men’s Health and Sexual Function

Lawrence Jenkins, MD, MBA
Assistant Professor – Clinical
Department of Urology
The Ohio State University Wexner Medical Center

Outline

• Testosterone Deficiency
  – Definition
  – Pathophysiology
  – Prevalence
  – Disease modification
  – Diagnosis
  – Treatment options
  – Risks
  – Treatment alternatives

• Men’s Sexual Health
  – Premature ejaculation
  – Delayed orgasm
  – Erectile dysfunction
• AOH is a clinical and biochemical syndrome characterized by a deficiency of testosterone with signs and symptoms that can be caused by testicular and/or hypothalamic-pituitary dysfunction
• AOH is clinically distinct from classical primary and secondary hypogonadism
• AOH more often occurs in men who have chronic medical conditions


Pathophysiology

• GnRH levels decrease with age
• Sex hormone binding globulin (SHBG) levels increase with age
• Testosterone levels begin to decline by 0.3% - 1.4% per year beginning at 20 – 30 years of age
• Many chronic illnesses are associated with low T levels

Araujo et al. 2011; Feldman et al. 2002; Wu et al. 2008
• AOH is often overlooked because patients ignore their symptoms.
  – Hypoactive sexual desire
  – Reduced nocturnal/morning erections
  – Delayed ejaculation
  – Reduced semen volume

• The Endocrine Society suggests measuring T levels in men with any symptoms or conditions in the table.

<table>
<thead>
<tr>
<th>Conditions in which serum T measurement is suggested</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>Osteoporosis, low trauma fracture</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Glucocorticoids, ketoconazole, opioid medications that affect T metabolism/production</td>
</tr>
<tr>
<td>Moderate to severe COPD</td>
</tr>
<tr>
<td>Sellar mass, radiation to the sellar region</td>
</tr>
<tr>
<td>End-stage renal disease</td>
</tr>
<tr>
<td>HIV-associated weight loss</td>
</tr>
</tbody>
</table>

Dandona et al 2010; Bhasin et al 2010

---

Prevalence

• European Male Aging Study (EMAS)
  – 3369 participants
  – Aged 40 – 79
  – Total testosterone cutoff 300 ng/dL
  – LH cutoff 9.8 U/L
  – 13.8% Hypogonadism
    • 2% Primary hypogonadism
    • 11.8% Secondary hypogonadism
  – 9.5% Compensated hypogonadism
    • Meaning elevated LH with normal T

• Hypogonadism in Males (HIM) study
  – Overall prevalence 39% in males >45
    • 34% – 45-54
    • 50% – >80

• Massachusetts Male Aging Study (MMAS)
  – Symptomatic prevalence increased somewhat with age
    • 4.1% - 40 – 49 years
    • 4.5% - 50 – 59 years
    • 9.4% - 60 – 69 years

Tajar et al 2010; Mulligan et al. 2006; Araujo 2004
Prevalence in Other Conditions

- 74% - Chronic opioid use
- 52% - Obesity
- 50% - Diabetes
- 50% - AIDS
- 42% - Hypertension
- 40% - Hyperlipidemia
- 30% - HIV
- 19% - ED

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>2.38</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.09</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.84</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.47</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>1.41</td>
</tr>
<tr>
<td>Asthma/COPD</td>
<td>1.40</td>
</tr>
</tbody>
</table>

High BMI, central adiposity and metabolic syndrome are associated with low serum total T and free T levels

Bodie et al. 2003; Daniel et al. 2002; Wang et al. 2011; Mulligan et al 2006; McLachlan et al 2010

Disease Modification

- Treatment can be started with disease modification
  - Obesity
  - Diabetes
  - Hypertension
  - Hyperlipidemia

  - Diet and exercise
  - Improved glycemic control
  - Weight loss
  - Improved sleep
  - Stress reduction
  - Varicocele repair
Fifty-two-Week Treatment With Diet and Exercise Plus Transdermal Testosterone Reverses the Metabolic Syndrome and Improves Glycemic Control in Men With Newly Diagnosed Type 2 Diabetes and Subnormal Plasma Testosterone

AEMIN E. HEUPELDER,* FARID SAADE†, MATTHIAS C. RINCK‡ AND LOUIS GOREN

From (Hamburg) Univ Primary Care, Men's Health Care, Scientific Affairs, Bayer Schering Pharma AG, Berlin, Germany; chief Medical University, Amag, Clinical Dept Endocrine, and the Department of Endocrinology, Free University Medical Center, Amsterdam, the Netherlands. Dr Heufelder is in private practice in Hamburg, Germany.

32 men with metabolic syndrome
• 16 diet + exercise
• 16 diet + exercise + testosterone

• 81% diet + exercise + testosterone no longer with metabolic syndrome
• 31% diet + exercise alone no longer with metabolic syndrome

CLINICAL STUDY
Age-associated changes in hypothalamic–pituitary–testicular function in middle-aged and older men are modified by weight change and lifestyle factors: longitudinal results from the European Male Ageing Study


• Longitudinal survey – 2,736 men
• Assessed changes in weight and T levels
• >10% decrease weight = 85 ng/dL increase in T
CLINICAL STUDY

Body weight loss reverts obesity-associated hypogonadotrophic hypogonadism: a systematic review and meta-analysis

Giovanni Corsia¹,², Giulia Rustelli¹, Matteo Monari¹, Furid Saud³, Michaela Luconi¹, Marcello Lucchese⁴, Enrico Fucchiano⁵, Alessandra Storna⁶, Gianni Forti², Edoardo Mannuzzi¹ and Mario Maggi³

• Meta-analysis of 24 articles

• Mean percent weight loss:
  – 32% with surgery
  – 9.8% with diet

• Bariatric surgery being more effective in comparison with the low-calorie diet
  – TT increase:
    • 252 ng/dL for bariatric surgery
    • 83 ng/dL for the low-calorie diet
    • both p<0.0001 vs baseline

Subnormal serum testosterone levels in male internal medicine residents

Frank Singer²,³, *, Barnett Zumoff

• The consequences of sleep deprivation and stress in residency training
• Unexpectedly observed a significant (P < 0.005) and marked depression of serum testosterone levels in healthy male internal medicine residents (340 ng/dL) compared with other hospital personnel (594 ng/dL)
  – 254 ng/dL difference
• Testosterone concentrations in the two groups were entirely nonoverlapping, while luteinizing hormone levels were not significantly different.
## Varicocele Repair Impact on Testosterone

- **Retrospective, 53 men underwent varicocele repair**
  - Mean testosterone values increased from 319 +/- 12 to 409 +/- 23 ng/dL (p<0.0004)

- **Prospective, 200 men**
  - Varicocele vs observation
  - Mean improvement 80 ng/dL

- **Meta-analysis of 9 studies**
  - 814 patients
  - Mean improvement 100 ng/dL


## Diagnosis Recommendations

- **The International Society of Andrology (ISA), International Society for the Study of Ageing Male (ISSAM), European Association of Urology (EAU), European Academy of Andrology (EAA), American Society of Andrology (ASA) recommendations:**
  - Total testosterone - 230 ng/dl is a limit below which patients will usually benefit from testosterone replacement treatment

- **Endocrine Society**
  - Total testosterone - approximately 280–300 ng/dl
  - Free testosterone - approximately 5–9 ng/dl

  An evaluation of androgen deficiency should not be made during an acute or subacute illness.
A telephone survey of 12 academic, 12 community medical laboratories, and one national laboratory.

Eight different assays were used to measure TT and four for FT.

Of the 25 labs, there were 17 and 13 different sets of reference values for total and free testosterone, respectively.

<table>
<thead>
<tr>
<th>Reference value</th>
<th>Range</th>
<th>Variation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Testosterone</td>
<td>Lower Value</td>
<td>130 – 450 ng/dL</td>
</tr>
<tr>
<td>Total Testosterone</td>
<td>Upper Value</td>
<td>486 – 1593 ng/dL</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>Lower Value</td>
<td>5.0 – 13.5 pg/mL</td>
</tr>
<tr>
<td>Free Testosterone</td>
<td>Upper Value</td>
<td>19.0 – 54.7 pg/mL</td>
</tr>
</tbody>
</table>

All reference values were based on a standard statistical model without regard for clinical aspects of hypogonadism.

Free vs Total Testosterone and Sex Hormone Binding Globulin

- Approximately 40% to 50% of the circulating T in men is SHBG-bound.
- Because SHBG binds T with high affinity, the level of SHBG is a major determinant of the circulating total T level, and the level of SHBG and its affinity for T are used to calculate the free or “bioavailable” T concentration.

<table>
<thead>
<tr>
<th>Increased SHBG concentrations</th>
<th>Decreased SHBG concentration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>Hypothyroidism</td>
</tr>
<tr>
<td>Hepatic cirrhosis</td>
<td>Obesity; metabolic syndrome</td>
</tr>
<tr>
<td>Use of anticonvulsants</td>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Use of estrogens</td>
<td>Nephrotic syndrome</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>Use of steroids (glucocorticoids, progestin, anabolic)</td>
</tr>
<tr>
<td>HIV infection</td>
<td>Malnutrition; malabsorption</td>
</tr>
</tbody>
</table>
In men with secondary hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic and/or pituitary dysfunction. This evaluation may include measurements of serum prolactin and iron saturation, pituitary function testing, and magnetic resonance imaging of the sella turcica.

### Symptoms of Low Testosterone

<table>
<thead>
<tr>
<th>Sexual</th>
<th>Constitutional</th>
<th>Cognitive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low sexual desire</td>
<td>Anemia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>Delayed orgasm</td>
<td>Decreased muscle</td>
<td>Irritability</td>
</tr>
<tr>
<td>Erectile dysfunction</td>
<td>Decreased bone</td>
<td>Depression</td>
</tr>
<tr>
<td>Decreased nocturnal erection</td>
<td>Hot flashes</td>
<td>Lethargy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Short-term memory loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased motivation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Decreased sense of overall well-being</td>
</tr>
</tbody>
</table>
• Total Testosterone (ng/dL)
  • 577
  • 433
  • 346
  • 288
  • 231
• Loss of libido
• Loss of vigor
• Obesity
• Feeling depressed
• Disturbed sleep
• Lacking concentration
• Diabetes mellitus type 2
• Hot flashes
• Erectile dysfunction

**Increasing prevalence of symptoms with decreasing testosterone levels**

**Treatment options**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Dose</th>
<th>Precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intramuscular injections</td>
<td>75–100 mg weekly or 150–200 mg every 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Transdermal gels</td>
<td>5–10 g applied daily to upper arms/shoulders, or abdomen (5–10 mg testosterone systemically absorbed)</td>
<td>Gel transference to partner or children</td>
</tr>
<tr>
<td>Transdermal patches (non-scrotal)</td>
<td>2.5–7.5 mg applied nightly for 24 h</td>
<td>Skin reaction</td>
</tr>
<tr>
<td>Subcutaneous pellets</td>
<td>6–16, 75 mg pellets implanted subcutaneously every 4–6 months</td>
<td></td>
</tr>
<tr>
<td>Long-lasting intramuscular injection</td>
<td>750 mg every 10 weeks</td>
<td>Pulmonary oil microembolization</td>
</tr>
<tr>
<td>Buccal tablets</td>
<td>30 mg tablet applied to the buccal mucosa every 12 h</td>
<td>Inflammation of the gums</td>
</tr>
</tbody>
</table>
Monitoring – Endocrine Society recommendations

- Follow-up at 3 and 6 mo, then annually; signs/symptoms, weight, TT, Hct, PSA; at 6 mo; if total T<400 ng/dL and no improvement, then consider dose increase with reassessment in another 3-6 mo;
- If hematocrit >54%, then stop TRT until Hct decreases to safe level; evaluate for hypoxia and sleep apnea; reinitiate TRT at reduced dose
- Measure BMD of lumbar spine and/or femoral neck after 1-2 y of TRT in men w/ osteoporosis or low trauma fracture
- In men aged ≥40 years w/ baseline PSA >0.6 ng/mL, perform DRE and check PSA before TRT, at 3 to 6 mo, and then based on prostate cancer screening guidelines
- Evaluate formulation-specific adverse events at each follow-up visit

Risks and Safety of Testosterone

- Challenges:
  - Lack definitive evidence derived from properly-designed studies
  - Mixed evidence that is not definitive from literature that is available
- Patients must be monitored for adverse events
- Cardiovascular risks
- Prostate cancer risks
- Erythrocytosis
- Benign Prostatic Hypertrophy (BPH)/Lower Urinary Tract Symptoms (LUTS)
- Rises in estrogen levels
Cardiovascular risks

• “There are multiple published meta-analyses that evaluated possible CVD risks associated with T treatment. Challenges to interpreting findings across meta-analyses include that these publications varied in study inclusion criteria, outcomes evaluated, and data analytic strategies. In addition, most authors report that the methodological quality of the included trials was poor to moderate.”


• “7486 patients not receiving testosterone therapy, 681 died, 420 had MIs, and 486 had strokes. Of the 1223 patients receiving testosterone therapy, 67 died, 23 had MIs, and 33 had strokes. The Kaplan-Meier estimated cumulative percentages with events among the no testosterone therapy group vs the testosterone therapy group at 1 year after coronary angiography were 10.1% vs 11.3%; at 2 years, 15.4% vs 18.5%; and at 3 years, 19.9% vs 25.7.”

<table>
<thead>
<tr>
<th></th>
<th>No T (n=7486)</th>
<th>T (n=1223)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Died</td>
<td>681</td>
<td>67</td>
</tr>
<tr>
<td>MI</td>
<td>420</td>
<td>23</td>
</tr>
<tr>
<td>Stroke</td>
<td>486</td>
<td>33</td>
</tr>
<tr>
<td>Total</td>
<td>1587</td>
<td>123</td>
</tr>
<tr>
<td>Absolute rate</td>
<td>1587/7486=21.2%</td>
<td>123/1223=10.1%</td>
</tr>
</tbody>
</table>
A retrospective cohort study was conducted within an integrated health care delivery system.

The cohorts consisted of 8808 men (19.8%) ever dispensed testosterone (ever-TRT) (mean age, 58.4 years; 1.4% with prior cardiovascular events) and 35,527 men (80.2%) never dispensed testosterone (never-TRT) (mean age, 59.8 years; 2.0% with prior cardiovascular events).

Among men with androgen deficiency, dispensed testosterone prescriptions were associated with a lower risk of cardiovascular outcomes over a median follow-up of 3.4 years.
Prostate Cancer risks

- Although no appropriately designed and powered study has been conducted to assess prostate cancer related risks of TT, the available evidence suggests that T treatment does not increase prostate cancer risk.

- Low T levels are associated with higher rates of prostate cancer as well as more advanced prostate cancer tumor grade, stage, and volume compared with men who are not hypogonadal.

- Observational studies also suggest that men taking T do not have an increased risk of developing prostate cancer. A large longitudinal study evaluating roughly 10,000 men found no association between androgen levels and prostate cancer risk.

Roddam et al 2008; Bhasin et al 2010; Isom-Batz et al 2005
Androgen Hypothesis 1941 - 2006

- High T causes Prostate cancer
- Low T protects against Prostate cancer
- T administration in men with known Prostate cancer is like “pouring gasoline on a fire” or “feeding a hungry tumor”

Morgentaler slide

- No evidence of increased risk for Prostate cancer with testosterone therapy

The Saturation Model describes a steep T-dependent curve at T concentrations at or below the near-castrate range, with a plateau representing little or no further growth above this concentration.
Post prostatectomy
- 103 hypogonadal men
  - 26 (25%) high risk
- 49 eugonadal controls
  - 15 (31%) high risk
- Mean follow-up – 27 mo
- Biochemical recurrence
  - 4 (4%) T group
  - 8 (16%) control group

All men on active surveillance for prostate cancer
- 28 hypogonadal men with Testosterone therapy
- 96 hypogonadal men no Testosterone therapy
- 3 yr median f/u
- No difference in progression between groups
Erythrocytosis

• Testosterone is a known stimulant of erythropoiesis, so a rise in hematocrit is not unusual and it needs to be monitored.

• During TT, levels of Hb and Hct rise for the first 5 to 6 months, then tend to plateau; levels decline to baseline within 3 to 12 months after TT discontinuation.

• Intramuscular formulations are most commonly associated greatest increases


BPH...

• Several studies demonstrate either no change or improvement in BPH/lower urinary tract symptoms with T administration.

• Placebo-controlled trials of exogenous administration of dihydrotestosterone (DHT) and T resulted in no changes in prostate DHT or T in blood sampling or prostate biopsy specimens.

• Bone mineral density measurement should also be tested at baseline because hypogonadism is an important cause of male osteoporosis.

Contraindications

- Infertility
  - various alternative options
- Male breast cancer
- Controversial
  - Stroke
  - Spontaneous Venous Thromboembolism

Testosterone Alternatives

- To preserve fertility
- Preserve testicular volume
- Concern for safety of testosterone products

- Medical therapies
  - Selective Estrogen Receptor Modulators (SERMs)
  - Aromatase Inhibitors (AIs)
  - Human Chorionic Gonadotropin (HCG)
Medical therapies

- **SERMs**
  - Act as estrogen receptor agonists and antagonists depending on location
  - In the brain, acts as an antagonist
  - Clomiphene (Clomid) 50 mg every other day
  - OFF LABEL

- **AIs**
  - Block conversion of testosterone to estrogen via aromatase
  - Anastrozole (Arimidex) daily, Letrozole

---

HCG

- Placental glycoprotein homologue of LH
- Able to stimulate testicular testosterone production like LH
- Needs to be injected 3 times/week
- Brands: Novarel, Ovidrel, Pregnyl, A.P.L., Profasi, Chorex, Gonic, HCG, Chorigon, Choron-10
Future Options

- Stem cell therapies

- New formulations of testosterone
  - Oral
  - Preloaded injections

- Updates on testosterone alternatives
  - More selective SERMs
  - Long acting HCG

Conclusion

- Disease modification should be considered in patients with reversible co-morbidities
  - Diet, exercise, weight loss, improved glycemic control, sleep, stress reduction, and varicocele repair

- Obtain 2 early morning levels to make diagnosis
- Treat symptomatic patients who meet criteria
- Monitor all patients on therapy
- Do not use testosterone when trying to preserve fertility
  - Risk should be discussed with patients prior to initiation of testosterone
- Trial of therapy is an option
In men with secondary hypogonadism, we suggest further evaluation to identify the etiology of hypothalamic and/or pituitary dysfunction. This evaluation may include measurements of serum prolactin and iron saturation, pituitary function testing, and magnetic resonance imaging of the sella turcica.
Delayed Orgasm and Anejaculation

Erectile dysfunction

- 3rd International Consultation on Sexual Medicine:
  - ED is the consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual performance
- Intercourse or masturbation
- Rigidity, presence of spontaneous morning/night erections
- Psychological factors
- Questionnaires
  - IIEF, IIEF-5, EPIC, EDITS, Hardness scale, Fullness score....

Mechanics of an erection

Effects of Castration and Androgen Replacement on Erectile Function in a Rabbit Model

ABDULMAGED M. TRAISH, KWANGSUNG PARK, VINITA DHIR, NOEL N. KIM, ROBERT B. MORELAND, AND IRWIN GOLDSTEIN

- Castration resulted in a statistically significant loss of trabecular smooth muscle ($P < 0.02$)
- Testosterone treatment prevented the loss of smooth muscle induced by castration
- Estradiol treatment did not prevent the loss of trabecular smooth muscle ($P < 0.02$).
Princeton III Consensus Conference Guidelines on Cardiac Evaluation for the ED Patient

Nehra et al. 2012

Process of care model for ED

<table>
<thead>
<tr>
<th>Diagnose</th>
<th>Modify reversible causes</th>
<th>Educate</th>
</tr>
</thead>
<tbody>
<tr>
<td>History</td>
<td>Diet</td>
<td>Diet</td>
</tr>
<tr>
<td>Physical</td>
<td>Exercise</td>
<td>PDE5 inhibitors</td>
</tr>
<tr>
<td>Labs</td>
<td></td>
<td>Counseling</td>
</tr>
</tbody>
</table>

First Line Therapies

- PDE5 inhibitors
- Counseling

Second Line Therapies

- Penis Injections
- Intraurethral Suppositories
- Vacuum Erection Device

Third Line Therapies

- Penile Implant Surgery
**Oral Medications**

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Highest dosage</th>
<th>Trade name</th>
<th>Peak absorption (hours)</th>
<th>Serum half-life (hours)</th>
<th>Take on empty stomach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>100 mg</td>
<td>Viagra®</td>
<td>1-2</td>
<td>3-5</td>
<td>Yes</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>20 mg</td>
<td>Levitra®</td>
<td>1-2</td>
<td>3-5</td>
<td>Yes</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>20 mg</td>
<td>Cialis®</td>
<td>2-4</td>
<td>18</td>
<td>No</td>
</tr>
<tr>
<td>Avanafil</td>
<td>200 mg</td>
<td>Stendra®</td>
<td>0.3 - 0.5</td>
<td>3</td>
<td>No</td>
</tr>
</tbody>
</table>

**Vacuum Erection Device**
Intraurethral Suppository

Penile Injection Therapy
Penile Implant Surgery

- 92% Patients reported sexual activity with the implant to be excellent or satisfactory
- 96% Partners reported sexual activity with the implant to be excellent or satisfactory
- 95% Patients reported no change or better orgasm following the surgery
- 98% Patients reported satisfactory or excellent erections following the surgery

Image courtesy of Coloplast A/S, Humlebæk, Denmark

Montorsi et al 2000

Men’s Sexual Health

- Identify patients who need further cardiovascular evaluations
- Educate patients that there are more options beyond pills
- Focus patients on long-term goals to help minimize anxiety
- Identify barriers to treatment
- Make sure pills are maximized and taken appropriately before considering failure
- Penile implant surgery provides a safe-effective option for the right patient