Testosterone Alternatives

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Testosterone Testing and Initiation

A  Testosterone testing

B  Testosterone initiation

Layton et al. J Clin Endocrinol Metab 2014; 99(3):835-842
Why Testosterone Alternatives?

• Preserve fertility
• Preserve testicular volume
• Desire “natural” testosterone production
• Avoiding “treatment for life”
• Concern for safety of testosterone products
Discussion: Testosterone Alternatives

- **Medical** Alternatives to TTh
- **Natural** Alternatives to TTh
- **Future** Alternatives to TTh
Testosterone Alternatives: Medical Therapies

- Human Chorionic Gonadotropin (hCG)
- Aromatase inhibitors (AIs)
- Selective Estrogen Receptor Modulators (SERMs)
HUMAN CHORIONIC GONADOTROPIN (hCG)

- Placental glycoprotein homologue of LH
- Because of its similarity to LH, hCG can be used to induce testosterone production in the testes
- Sources
  - Urine: Pregnyl®, Follutein, Profasi, Choragon and Novareel
  - Recombinant: Ovidrel®
AROMATASE INHIBITORS (AI)

- Aromatase inhibitors block the conversion of $T \rightarrow E_2$
  - $\downarrow$ The negative feedback of $E_2$
  - $\uparrow$ GNRH, LH, FSH $\rightarrow$
    $\uparrow$ intratesticular $T$
- Increase $T/E$ ratio by 77%
- Arimidex, Letrozole
Selective Estrogen Receptor Modulators (SERMs)

- SERMS act as estrogen receptor antagonists and agonists depending on their location in various tissues
- In the brain they act as antagonists
Higher Centers

GnRH

Hypothalamus

Anterior Pituitary

Inhibin

Germinal Epithelium

Sertoli Cells

Leydig Cell

FSH

LH

Testosterone

Higher Centers

GnRH

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Higher Centers

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LH

Inhibin

Testosterone

Estrogen

Germinal Epithelium

Sertoli Cells

Leydig Cell

SERMs: Clomiphene
Outcomes of clomiphene citrate treatment in young hypogonadal men

Darren J. Katz, Omar Nabulsi, Raanan Tal and John P. Mulhall
Male Sexual and Reproductive Medicine Programme, Urology Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

- 86 men aged 22-37 years
- T<300 ng/dL
- Mean follow-up 19 months
- CC 25 to 50 mg every other day
The Effect of Clomiphene Citrate on Serum Hormone Profiles

<table>
<thead>
<tr>
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<th>Baseline, mean (SD)</th>
<th>After Treatment, Mean (SD)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total testosterone, ng/dL</td>
<td>192 (87)</td>
<td>485 (165)</td>
<td>&lt; 0.01</td>
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<tr>
<td>Free testosterone pg/mL</td>
<td>22 (16)</td>
<td>95 (35)</td>
<td>&lt; 0.01</td>
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<tr>
<td>Estradiol pg/mL</td>
<td>26 (22)</td>
<td>39 (18)</td>
<td>&lt; 0.05</td>
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<tr>
<td>LH, IU/mL</td>
<td>2.6 (2.2)</td>
<td>6.8 (2.8)</td>
<td>&lt; 0.01</td>
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<tr>
<td>FSH, IU/mL</td>
<td>1.9 (1.7)</td>
<td>7.6 (1.9)</td>
<td>&lt; 0.01</td>
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</table>


<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline %</th>
<th>After Treatment %</th>
<th>p</th>
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<tbody>
<tr>
<td>Decreased Libido</td>
<td>72</td>
<td>32</td>
<td>&lt; 0.01</td>
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<tr>
<td>Lack of energy</td>
<td>65</td>
<td>40</td>
<td>&lt; 0.01</td>
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<tr>
<td>Decreased strength/endurance</td>
<td>28</td>
<td>21</td>
<td>0.18</td>
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<tr>
<td>Lost height</td>
<td>4</td>
<td>5</td>
<td>0.45</td>
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<tr>
<td>Decreased life enjoyment</td>
<td>85</td>
<td>40</td>
<td>&lt; 0.001</td>
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<tr>
<td>Sad/grumpy</td>
<td>60</td>
<td>30</td>
<td>&lt; 0.01</td>
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<tr>
<td>Erections weaker</td>
<td>12</td>
<td>8</td>
<td>0.29</td>
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<tr>
<td>Decreased sports performance</td>
<td>55</td>
<td>25</td>
<td>&lt; 0.001</td>
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<td>Sleep after dinner</td>
<td>34</td>
<td>28</td>
<td>0.17</td>
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<tr>
<td>Decreased work performance</td>
<td>45</td>
<td>38</td>
<td>0.28</td>
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FDA Drug Safety Communication: FDA cautions about using testosterone products for low testosterone due to aging; requires labeling change to inform of possible increased risk of heart attack and stroke with use

This information is an update to the FDA Drug Safety Communication: FDA Evaluating Risk of Stroke, Heart Attack, and Death with FDA-Approved Testosterone Products issued on January 31, 2014.

Safety Announcement

[03-03-2015] The U.S. Food and Drug Administration (FDA) cautions that prescription testosterone products are approved only for men who have low testosterone levels caused by certain medical conditions. The benefit and safety of these medications have not been established for the treatment of low testosterone levels due to aging, even if a man’s symptoms seem related to low testosterone. We are requiring that the manufacturers of all approved prescription testosterone products change their labeling to clarify the approved uses of these medications. We are also requiring these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone. Health care professionals should prescribe testosterone therapy only for men with low testosterone levels caused by certain medical conditions and confirmed by laboratory tests.
Specific Medical Conditions Associated with Hypogonadism

- 89.1% Unknown
- 10.9% Specific medical conditions
- Genetic: 3.4%
- Empty sella: 1.1%
- Drugs: 1.7%
- Radiotherapy: 2.4%
- Surgery: 1.1%
- PRL-adenomas: 0.1%
- Trauma: 1.1%

Specific Medical Conditions Associated with Secondary Hypogonadism

Concomitant metabolic disease (Obesity, T2DM or MetS) 71.8%
Specific medical conditions 28.2%
Unknown 10.9%
Unknown 89.1%

• 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
Initial Treatment of Many Conditions Associated with AOH

Start with Disease Modification

• Obesity
• Diabetes
• Hypertension
• Hyperlipidemia

1. Should disease modification also be initiated in hypogonadal patients?

2. Can patients who start TTh + disease modification later discontinue TTh?
Testosterone Alternatives: Natural Therapies
(Disease Modification)

- Diet and exercise
- Improved glycemic control
- Weight loss
- Improved sleep
- Stress reduction
- Varicocele repair
52 week randomized trial

32 men with MetS and T2DM
  - 16 diet + exercise
  - 16 diet + exercise + testosterone

Results:
  - Diet and exercise alone significantly improved serum testosterone levels

Metabolic Syndrome Reversed After 52 Weeks

- Adult Treatment Panel III $P = .004$
- International Diabetes Federation $P = .003$

Low Testosterone Levels and Diabetes/Metabolic Syndrome

Androgen deficiency "hypogonadism"

Obesity  Hypertension  Dyslipidemia  Hyperglycemia  Insulin resistance

Metabolic syndrome
Relationship Between Total Testosterone and the Number of MS Components

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

E M Camacho, I T Huhtaniemi¹, T W O’Neill², J D Finn, S R Pye², D M Lee², A Tajari²*, G Bartfai³, S Boonen⁴, F F Casanueva⁵, G Forti⁷, A Giwercman⁸, T S Han⁹, K Kula¹⁰, B Keevil¹¹, M E Lean¹², N Pendleton¹³, M Punab¹⁴, D Vanderschueren¹⁵, F C W Wu and the EMAS Group†

- Longitudinal survey of 2,736 men
- Assessing changes in weight and T levels
- > 10% decrease in weight = 2.9 nmol/l (85 ng/dl) increase in T
Weight Loss Reverts Obesity-Associated Secondary Hypogonadism: Systematic Review and Meta—Analysis:

• Meta-analysis of 22 studies on the effect weight loss (diet or surgery) on T levels
  • Mean percent weight loss:
    • Low calorie diet = 9.8%
    • Bariatric surgery = 32%
  • RESULTS:
    • Both diet and bariatric surgery are associated with a significant increase in both TT and FT (p<0.0001)
    • Low calorie diet = 83 ng/dl increase in T
    • Bariatric surgery = 250 ng/dl increase in T

Sleep

Obstructive Sleep Apnea

Sleep Deprivation
Obstructive Sleep Apnea

- Men with OSA have a higher prevalence of secondary HG than age-matched controls
- Greater degrees of nocturnal hypoxia predict lower T due to blunting of LH levels

- **Prospective controlled trial of 12 men with OSA:**
  - uvulopalatopharyngoplasty therapy (UPP)
  - 3 months post-op
  - T levels increased from 13.31 +/- 1.07 to 16.59 +/- 0.72 nmol/l (p<0.02) (95 ng/dl improvement)

Sleep Deprivation

- Restriction of sleep for 8 nights to 5 h (00:30–05:30 hours) a night decreased testosterone levels by 10%–15%¹

- When sleep is restricted during the first half of the night and permitted from 0400–0800 for 5 nights there was no significant change in testosterone²

¹Leproult et al JAMA 2011; 305: 2173–4.
Stress and Testosterone

ACTH = adrenocorticotropic hormone
is being produced by the
pituitary gland at the
base of the brain and controls
the production of cortisol
the cortex (outer ring around the
adrenaline gland which is
located above the kidney)

vegetative nervous system

Disease

- rapid shallow breathing
- rapid heartbeat
- cardiovascular system
  high blood pressure
- liver muscles
  high blood sugar
  & excess stored body fats
- hormones
  sexuality dysfunctions
- immune system,
  thymus, spleen, skin,
  lymph immune deficiency
- virus
- tumor cells
- bacteria

neuropeptide

hypophysis

adrenaline gland
Stress and Testosterone

• Healthy internal medicine residents (means = 11.8 +/- 1.1 nmol/L, n = 7) significant decrease in T levels in compared with other hospital personnel (means = 20.6 +/- 5.3 nmol/L, n = 18) (approx. 250ng/dl)¹

• Hypogonadism significantly associated with 4 factors:²
  • hypertension (P<0.025)
  • tobacco abuse (P<0.0059)
  • sleep apnea (P<0.0001)
  • work stress (P<0.041)
    • long work hours (> 50 h per week)
    • multiple jobs (> 1 job)
    • long daily commutes (>1 h each way)
    • quotas or deadlines to meet, and/or
    • feared losing employment because of layoffs and mergers

¹Singer F and Zmoff T. Steroids. 1992 Feb;57(2):86 –9
Varicocele Repair and Testosterone
Testosterone Improves After Varicocele Repair

- Retrospective review of 53 infertile men undergoing varicocele repair
- Mean testosterone values increased from \(319 +/ - 12\) to \(409 +/ - 23\) ng/dl (\(p < 0.0004\))
- Men with at least 1 firm testis preoperatively had a greater increase in serum testosterone (\(p < 0.005\))


Mean serum testosterone levels (ng/dL) increased after varicocelectomy, n=53 in each group \(p < 0.0004^{(*)}\)
Testosterone Improves After Varicocele Repair

• Prospective, 200 men
  • varicocelectomy vs. observation
  • T increased average 80 ng/dl after varicocelectomy
  • Normalization of T:
    • Treatment- 78%
    • Controls- 16%

• Meta-analysis of 9 studies
  • 814 patients
  • Approximate 100 ng/dl increase in serum T after varicocelectomy
  • Most of these studies retrospective

Testosterone Alternatives: Future Therapies

Stem Cells
Exposing Leydig stem cells to LH in vitro from human testis biopsies, we can differentiate them to adult Leydig cells that can express 3β-HSD and make testosterone.
• **Medical** therapies used to increase natural T production include hCG, SERMS and AI

• **Natural** therapies to increase T production include diet and exercise, weight loss, improved glycemic control and sleep, stress reduction, and varicocele repair

• Disease modification should be considered in hypogonadal patients with reversible co-morbid conditions

• Patients initiating TTh should be counseled on disease modification and the possibility of discontinuing TTh in the future

• The **future** of TTh may include increased endogenous T production through stem cells
Thank you for your attention

Medical Center  Houston, Texas
Men 20-45 yrs have a 3-8% incidence of hypogonadism = ~ 2.5 million men

Prevalence of Diabetes in USA

CDC Diabetes Data and trends,
www.cdc.gov/diabetes/statistics/prev/national/figbyage.htm
Obesity and Aging

Obesity by Age Group -- 2008 vs. 2012

Gallup-Healthways Well-Being Index

GALLUP
Visceral Fat: the Vicious Circle

T ↓

Prevalence of the Metabolic Syndrome Among US adults

Estimate of the prevalence in the US as defined by the NCEP. Analysis of data on 8814 men and women

Autografting Leydig Cells in Mouse Testis: A study to Increase Serum Testosterone without affecting HPG axis

1: Bilateral orchiectomy and isolate seminiferous tubules

2: Isolate Leydig stem cells by enzymatic digestion and centrifugation

3: Culture stem cells in “expansion medium”

Mouse Autograft cells cultured in new DIM for up to 7 Days

Relative expression changes upon DIM

Arora &
Are Lifestyle Changes Alone Sufficient for Improvement of Erectile Function?

Recidivism: The tendency to relapse into a previous condition or mode of behavior
CLOMIPHENE CITRATE EFFECTIVELY RAISES SERUM T LEVELS

- Raise serum T levels comparable to gels
- May improve semen parameters, but the effect is inconsistent
- Side effects: gynecomastia, weight gain, hypertension, cataracts, acne

Relative Risk for Hypogonadism According to the Number of MS Components

803 patients with sexual dysfunction (29.4%) diagnosed as having a MS

Relative risk for hypogonadism

Corona G et al Eur Urol. 2006; 50: 595-604
Prevalence of Low Testosterone in Other Conditions

HIV = 30%.
ED = erectile dysfunction.