Options for Treatment of Hypogonadism in Men Desiring Fertility Preservation

Natan Bar-Chama MD
Director Male Reproductive Medicine and Surgery
The Mount Sinai School of Medicine New York NY

American Association of Clinical Endocrinologists (AACE)
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Growth of Testosterone Market

- Aging population
- Low T associated with osteoporosis, DM, CVD
- Reduced concern of TRT and prostate cancer
- New entries with increased promotion
- Direct to consumer advertising
FDA Concerns Have Decreased Use of TRT

- Risk of CVD, VTE and stroke – FDA requires boxed warning on all TRT products since 6/14, 3/15.
  - Decision made based on 4 trials (Vigen, Finkle, Basaria, Xu).
  - All with methodological flaws or misleading results.
  - Concern with inappropriate use and use in aging men

REASONS FOR INCREASED INCIDENCE OF HYPOGONADISM IN YOUNGER MEN

- Increased opioid use
- Increased incidence of co-morbidities
  - Obesity
  - DM
  - HIV/AIDS
- Increased steroid abuse
- Stress
MEN ARE FATHERING CHILDREN AT AN OLDER AGE

• In 1970, less than 15% of all men fathering children were over 35.

• Today that percentage has risen to almost 25%.

• Even among men in the 50 to 54 age group, there has been a notable increase in fatherhood.


Testosterone: Adult Physiological Effects
Signs and Symptoms Associated with Low Testosterone

- Loss of muscle mass and strength
- Loss of libido and erectile function
- Depression
- Fatigue
- Osteoporosis
- Some regression of secondary sexual characteristics
- Oligospermia or azoospermia

TRT and Weight Loss

Reduction in BMI in hypogonadal men in response to TRT over the course of 60 months

- TRT in hypogonadal men for up to 5 years duration appears to be safe and effective in facilitating weight loss, reduction in waist circumference and reduced BMI


Association Between Metabolic Syndrome and Hypogonadism

Androgen deficiency/hypogonadism

Obesity  Hypertension  Dyslipidemia  Hyperglycemia  Insulin resistance

Metabolic syndrome

**Relationship Between Total Testosterone and the Number of MetS Components**

803 patients with sexual dysfunction, 236 (29.4%) diagnosed as having metabolic syndrome

![Graph showing the relationship between total testosterone and the number of MetS components.](image)


**Hypogonadism in Diabetic Men**

*A Concerning Prevalence*

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mulligan</td>
<td>2006</td>
<td>50</td>
</tr>
<tr>
<td>Rhoden</td>
<td>2005</td>
<td>34-46</td>
</tr>
<tr>
<td>Dhindsa</td>
<td>2004</td>
<td>33</td>
</tr>
</tbody>
</table>

**Testosterone Therapy Effects on Diabetes TIMES2 Study:**

Mean Change from Baseline HOMA/IR in All Patients with T2DM

![Graph showing mean change from baseline in HOMA/IR index for 6 months and 12 months.](image)

- **6 months:**
  - Mean change from baseline: 0.16
  - Improvement: P < 0.05

- **12 months:**
  - Mean change from baseline: 0.33
  - Improvement: P < 0.01

<table>
<thead>
<tr>
<th>Mean change from baseline 6 months</th>
<th>Placebo</th>
<th>Testosterone</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean change from baseline 12 months</td>
<td>0.33</td>
<td>-0.58</td>
<td>0.010</td>
</tr>
</tbody>
</table>

HOMA/IR – homeostasis model assessment of insulin resistance

Jones TH et al. Diab Care 34: 828-837 (2011)

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**Skeletal Muscle, Amino Acids and Protein Synthesis**

![Diagram showing the relationship between amino acids, insulin, testosterone, IGF-1, catecholamines, and muscle cell protein synthesis.](image)
Effect of Exercise and Testosterone on Muscle Size

Testosterone Dose = 600 mg IM/Week x 10 Weeks

Change in Muscle Size (mm²)

- No exercise/Placebo
- No exercise/Testosterone
- Exercise/Placebo
- Exercise/Testosterone

Triceps M.

Quadriceps M.

Hypogonadism Adversely Affects Bone Quality

Control

Well-connected, predominantly platelike trabecular network of the control

MicroMRI of Tibia

Hypogonadal man

More disconnected, predominantly rodlike architecture of the hypogonadal man

J Clin Endocrinol Metab. 2003;88:1497-1502.

Testosterone and Depression

An overview of older studies shows mixed results regarding the relationship between testosterone levels in men and depression. However several well-controlled studies indicate that endogenous testosterone levels are lower in depressed aging men than in healthy subjects. In particular, low bioavailable testosterone levels in aging men correlate strongly with depression.


Testosterone and Cognitive Function

Cognitive measures demonstrate significant correlation with plasma bioavailable testosterone levels in some, but not all studies. Plasma testosterone levels influence the performance of cognitive tasks with positive correlations with spatial tests and negative correlations with verbal tests. Plasma testosterone is lower in men with Alzheimer’s Disease than in healthy men.

## Low Testosterone and Increased Mortality

<table>
<thead>
<tr>
<th>Recent Studies</th>
<th>HR (95% CI)</th>
<th>Nature</th>
<th>Men, n</th>
<th>Follow-Ups, yrs</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shorey, 2006</td>
<td>1.88 (1.34–2.65)</td>
<td>Retrospective</td>
<td>855</td>
<td>8</td>
<td>All-cause</td>
</tr>
<tr>
<td>Laughlin, 2008</td>
<td>1.36 (1.02–1.85)</td>
<td>Prospective</td>
<td>794</td>
<td>20</td>
<td>CVD</td>
</tr>
<tr>
<td>Khaw, 2007</td>
<td>2.29 (1.60–3.26)</td>
<td>Prospective</td>
<td>2364 of 11,664</td>
<td>10</td>
<td>All-cause/CVD</td>
</tr>
<tr>
<td>Viring, 2010</td>
<td>2.32 (1.38–3.89)</td>
<td>Prospective</td>
<td>1954</td>
<td>7.2</td>
<td>CVD</td>
</tr>
<tr>
<td>Melin, 2010</td>
<td>2.27 (1.45–3.06)</td>
<td>Prospective</td>
<td>930</td>
<td>6.9</td>
<td>All-cause in men with CAD</td>
</tr>
<tr>
<td>Vester, 2009</td>
<td>1.65 (1.29–2.12)</td>
<td>Prospective</td>
<td>3014</td>
<td>4.5</td>
<td>All-cause</td>
</tr>
<tr>
<td>Menke, 2010</td>
<td>1.43 (1.09–1.87)</td>
<td>Prospective</td>
<td>1114</td>
<td>9</td>
<td>All-cause</td>
</tr>
<tr>
<td>Vikan, 2009</td>
<td>1.24 (1.01–1.54)</td>
<td>Prospective</td>
<td>1168</td>
<td>31.2</td>
<td>All-cause</td>
</tr>
<tr>
<td>Pop, 2014</td>
<td>2.3 (1.4-3.2)</td>
<td>Prospective</td>
<td>2199</td>
<td>4.3</td>
<td>All Cause/CVD</td>
</tr>
<tr>
<td>Jones, 2013</td>
<td>2.02 (1.2-3.4)</td>
<td>Prospective</td>
<td>561</td>
<td>5.8</td>
<td>All-cause</td>
</tr>
<tr>
<td>Corona, 2010</td>
<td>7.1 (1.8–28.4)</td>
<td>Prospective</td>
<td>1887</td>
<td>4.3</td>
<td>CVD</td>
</tr>
<tr>
<td>Muraleedharan et al, 2013</td>
<td>2.02 (1.3–3.4)</td>
<td>Prospective</td>
<td>561</td>
<td>5.8</td>
<td>All-cause</td>
</tr>
<tr>
<td>Hyde et al, 2012</td>
<td>1.62 (1.20–2.19)</td>
<td>Prospective</td>
<td>4249</td>
<td>5.1</td>
<td>All-cause/CVD</td>
</tr>
<tr>
<td>Lerchbaum et al, 2012</td>
<td>2.11 (1.60–2.79)</td>
<td>Prospective</td>
<td>2069</td>
<td>7.7</td>
<td>All-cause/CVD</td>
</tr>
</tbody>
</table>

## Testosterone and Cardiovascular Disease
Low Testosterone and SHBG May Be Predictors of Other Conditions

Low Total Testosterone and Low SHBG

METABOLIC SYNDROME

Coronary Heart Disease (CHD)

Type 2 Diabetes

Low TT and SHBG levels independently predict development of the metabolic syndrome and diabetes in middle-aged men.¹

Metabolic syndrome prospectively identifies risk for CHD and even more strongly predicts new-onset diabetes.²


Prior Articles Demonstrating Beneficial Effects of T Against CVD

<table>
<thead>
<tr>
<th>Type of Article</th>
<th>Number of Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low levels of endogenous testosterone and increased mortality</td>
<td>8</td>
</tr>
<tr>
<td>Low testosterone levels and increased incidence of coronary artery disease</td>
<td>6</td>
</tr>
<tr>
<td>Low testosterone level correlates with increased severity of coronary artery disease</td>
<td>4</td>
</tr>
<tr>
<td>Low endogenous testosterone level and increased carotid intima-media thickness</td>
<td>8</td>
</tr>
<tr>
<td>TRT decreases obesity</td>
<td>6</td>
</tr>
<tr>
<td>TRT improved cholesterol levels (meta-analysis)</td>
<td>3</td>
</tr>
<tr>
<td>TRT improves glycemic control</td>
<td>6</td>
</tr>
<tr>
<td>TRT decreases markers of inflammation</td>
<td>8</td>
</tr>
</tbody>
</table>

Total studies= 49
TRT Causes CVD

- Basaria et al. NEJM 2010
  - RPCT frail elderly men
  - 15 grams of testosterone
  - CVD not an endpoint
  - Treatment arm greater CV risks
  - 5 vs 2 major CV events (ie MI)
  - No difference if exclude CHF

- Vigen et al. JAMA 2013
  - No randomization or placebo
  - 2 major corrections
  - "Absolute risk" of MI (19.9 vs 25.7%) vs (21 vs 19%)
  - Exclusion of 3132 men
  - RETRACTION 29 societies

  - No randomization or placebo
  - No control group or clinical info
  - Health insurance database
  - 90 days after start testosterone
  - PDE5I Control Group inherently healthier (no nitrates)
  - Pre-prescription MI rate 3.48/1000
  - Post-prescription MI rate 4.75/1000

- Xu et al. BMC 2013
  - Meta-analysis of CV events in 27 PC studies of >12 weeks
  - 2 studies provided 1/3 of all CV events in T treat arm
  - If exclude 2 studies CV events in T and placebo are identical

Corona Meta-analysis of TRT and CV events (MACE)

- Available evidence “does not support a causal role between testosterone supplementation and adverse CV events when hypogonadism is properly diagnosed and replacement therapy correctly performed”.

American Association of Clinical Endocrinologists and American college of Endocrinology

- There is no compelling evidence that testosterone therapy either increases or decreases cardiovascular risk.

- Large-scale prospective randomized controlled trials on testosterone therapy, focusing on cardiovascular benefits and risks, are clearly needed.

- As with therapeutics in general, common sense, experience, and an individualized approach are recommended

Endocr Pract. 2015;21:1066-1073

The treatment of hypogonadism in men of reproductive age

Edward D. Kim, M.D., a Lindsey Crosnoe, B.S., a Natan Bar-Chama, M.D., b Mohit Khera, M.D., b and Larry I. Lipshultz, M.D. c

a University of Tennessee Graduate School of Medicine, Knoxville, Tennessee; b Mount Sinai Medical Center, New York, New York; and c Scott Department of Urology, Baylor College of Medicine, Houston, Texas

- Exogenous T supplementation decreases sperm production.
- Studies of hormonal contraception indicate that most men have a return of normal sperm production within 1 year after discontinuation.
- SERMs, Aromatase Inhibitors and hCG are a safe and effective therapies for men who desire to maintain future fertility.

“Of concern is that 25% of respondents use exogenous testosterone, a medication known for its contraceptive potential, for male infertility treatment.”


The Hypothalamic-Pituitary-Gonadal Axis
**Testicular Leydig Cell Production of Testosterone**

Testosterone is the primary circulating androgen in the male.

3 to 10 mg of testosterone is secreted daily by the testis.

95% of circulating testosterone is produced by the Leydig cells, with its secretion under the control of LH also modulated by a number of paracrine factors (e.g., IGF-I, inhibins, activins, TGF-α, GnRH, and vasopressin).

Testosterone secretion is diurnal, with the highest concentrations observed in the morning.

Testosterone is converted in many peripheral tissues into its active metabolites, estradiol 17-β and 5-α DHT.

**Testosterone: Role in Spermatogenesis**

Either alone or in concert, FSH and testosterone act in a stage-dependent manner in order to optimize spermatogenesis.

- progression of meiosis
- regulation of the apoptotic process
- maturation (spermiation)

INTRATESTICULAR TESTOSTERONE (ITT) AND SPERMATOGENESIS

- ITT concentration is 50-100x higher than in serum
- Exogenous T suppresses ITT production
- Spermatogenesis is dramatically compromised at ITT concentrations <20 ng/ml

Intratesticular T (ITT) is an absolute prerequisite for normal spermatogenesis.

TESTOSTERONE USE IN MALE CONTRACEPTION

<table>
<thead>
<tr>
<th>Reference</th>
<th>Number of Subjects</th>
<th>Androgen Dose</th>
<th>Azoospermia n (%)</th>
<th>Severe Oligospermia &lt;1mil/mL n (%)</th>
<th>Oligospermia &lt;3mil/mL n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WHO, 1996</td>
<td>225</td>
<td>TE 200mg IM/ wk</td>
<td>157 (70%)</td>
<td>29 (13%)</td>
<td>8 (4%)</td>
</tr>
</tbody>
</table>

Suppression of spermatogenesis with weekly IM-TE resulted in sustained, reversible contraception with good efficacy and minimal short-term side effects.

DISCONTINUATION OF IM-TESTOSTERONE CAN RESTORE SPERM PRODUCTION

- 93% developed azoospermia
  Median time of 108 days
- Method failure rate of 6.1%
- Median time to recovery was 3.5 months

>99% of men had spermatogenesis return to normal fertile range by 15 months after T discontinuation


Hormonal male contraceptive regimens show full reversibility within a predictable time course.

Men in Contraceptive T Studies Were Not Hypogonadal Males

- Contraceptive studies:
  - Men with no concerns regarding fertility
  - Normal T at baseline
  - Normal sperm production at baseline
  - Different (higher) doses of T administered & often with additional agent

The consistency of spermatogenesis recovery in clinical practice may not be as predictable as seen in contraceptive studies.

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 Novarel
  - Recombinant: Ovidrel®
Can low-dose hCG maintain ITT and spermatogenesis during TRT?

Low-Dose Human Chorionic Gonadotropin Maintains Intratesticular Testosterone in Normal Men with Testosterone-Induced Gonadotropin Suppression


Testosterone enanthate 200mg/week
AND
hCG 0, 125, 250 or 500 IU qod

• Measure serum and intratesticular testosterone (ITT) day 0 and 21
• Measure serum gonadotropins

Despite supraphysiologic doses of T, high levels of ITT are maintained with low-dose hCG

Concomitant Intramuscular Human Chorionic Gonadotropin Preserves Spermatogenesis in Men Undergoing Testosterone Replacement Therapy

26 hypogonadal men wishing to preserve fertility (mean age 36 years) followed serum T, semen parameters Mean of 6 months follow-up
CONCLUSIONS: hCG

- Low dose hCG maintains ITT production and spermatogenesis when given with exogenous T
- Low dose hCG may have a role for men in their reproductive years who do not want to stop TRT
- Need for injections and cost may be barriers to use
SELECTIVE ESTROGEN RECEPTOR MODULATORS: CLOMIPHENE CITRATE

- Competitively binds to estrogen receptors on the hypothalamus and pituitary
- The pituitary sees less estrogen, and makes more LH, increasing T production by the testis
- Off-label, 12.5-50 mg po daily
- Tamoxifen, toremifene

Clomiphene Citrate Effectively Raises Testosterone Levels

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


The effect of clomiphene citrate on serum hormone profiles

<table>
<thead>
<tr>
<th></th>
<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>
</tr>
<tr>
<td>Free testosterone pg/mL</td>
<td>22 (16)</td>
<td>95 (35)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Oestradiol pg/mL</td>
<td>26 (22)</td>
<td>39 (18)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>LH, IU/mL</td>
<td>2.6 (2.2)</td>
<td>6.8 (2.8)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>FSH, IU/mL</td>
<td>1.9 (1.7)</td>
<td>7.6 (1.9)</td>
<td>&lt; 0.01</td>
</tr>
</tbody>
</table>

Clomiphene was effective in raising free and total testosterone levels long-term.


THE EFFECT OF CLOMIPHENE CITRATE ON SERUM HORMONE PROFILES
Clomiphene improves serum T levels and symptoms

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Baseline %</th>
<th>Treatment %</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased libido</td>
<td>72</td>
<td>32</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Lack of energy</td>
<td>65</td>
<td>40</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Decreased strength / endurance</td>
<td>28</td>
<td>21</td>
<td>0.18</td>
</tr>
<tr>
<td>Lost height</td>
<td>4</td>
<td>5</td>
<td>0.45</td>
</tr>
<tr>
<td>Decreased life enjoyment</td>
<td>85</td>
<td>40</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sad / grumpy</td>
<td>60</td>
<td>30</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Erections weaker</td>
<td>12</td>
<td>8</td>
<td>0.29</td>
</tr>
<tr>
<td>Decreased sports performance</td>
<td>55</td>
<td>25</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Sleep after dinner</td>
<td>34</td>
<td>28</td>
<td>0.17</td>
</tr>
<tr>
<td>Decreased work performance</td>
<td>45</td>
<td>38</td>
<td>0.28</td>
</tr>
</tbody>
</table>

CLOMIPHENE CITRATE IS SAFE

“There were no major side effects recorded from CC during the course of follow-up and no patient ceased CC treatment because of adverse events.”

Clomiphene is safe with long-term use

Katz DJ et al. BJU Int. 2011; doi: 10.1111/j.1464-410X.2011.10702.x
• ADAM questionnaire and serum levels
• “No difference in overall hypogonadal symptoms exists between men on any TST.”
• “Despite lower serum total T levels, men taking CC and T gels report similar levels of satisfaction compared to men taking T injections.”

*J Urol. 2014 Sep;192(3):875-9.*
AROMATASE INHIBITORS (AI)

Aromatase inhibitors block the conversion of T→E₂
- ↓ The negative feedback of E₂
- ↑ GNRH, LH, FSH → ↑ intratesticular T

Estrogen-testosterone imbalance may be a cause of decreased spermatogenesis (desired T/E ratio<10-15:1)

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Selective Aromatase Inhibitors

<table>
<thead>
<tr>
<th>Drug</th>
<th>Aromatase Inhibition</th>
<th>Half Life</th>
<th>Dosing</th>
<th>Male Clinical Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anastrozole (Arimidex)</td>
<td>Non-steroidal, Competitive</td>
<td>47 h</td>
<td>0.5-1mg PO QD-QOD</td>
<td>Hypogonadism Gynecomastia</td>
</tr>
<tr>
<td>Letrozole (Femara)</td>
<td>Non-steroidal, Competitive</td>
<td>48 h</td>
<td>1.25-2.5mg PO QD-QOD</td>
<td>Hypogonadism Gynecomastia infertility</td>
</tr>
<tr>
<td>Exemestane (Aromasin)</td>
<td>Steroidal, Irreversible</td>
<td>24 h</td>
<td>12.5-25mg PO QD</td>
<td>Male breast cancer</td>
</tr>
<tr>
<td>Vorozole (Rivizor)</td>
<td>Non-steroidal, Competitive</td>
<td>8 h</td>
<td>2.5mg PO QD</td>
<td>None</td>
</tr>
<tr>
<td>Formestane (Lentaron)</td>
<td>Steroidal, Irreversible</td>
<td>96 h</td>
<td>250mg IM QOW 250mg PO QD</td>
<td>None</td>
</tr>
<tr>
<td>Fadrozole (Afema)</td>
<td>Non-steroidal, Competitive</td>
<td>11 h</td>
<td>2mg PO QD</td>
<td>None</td>
</tr>
</tbody>
</table>

*J Clin Endocrinol Metab. 2006; 91: 3324.*
*J Clin Endocrinol Metab. 2005; 90: 5717.*
Anastrozole and Hypogonadism

Testosterone + Anastrozole (Herzog et al.):
- Randomized, double-blind trial
- 40 men with epilepsy, hyposexuality, hypogonadism
- Mean age ~43 yo
- No studies evaluating hypogonadal symptoms directly
- T cypionate + anastrozole vs. placebo

<table>
<thead>
<tr>
<th></th>
<th>T + Anastrozole</th>
<th>P</th>
<th>T + Placebo</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/dL)</td>
<td>139.1±53.8</td>
<td>295.7±149.7</td>
<td>0.00</td>
<td>116.9±52.4</td>
</tr>
<tr>
<td>Estradiol (pg/mL)</td>
<td>22.5±17.5</td>
<td>7.6±6.0</td>
<td>0.002</td>
<td>29.1±18.3</td>
</tr>
<tr>
<td>BDI-II</td>
<td>16.7±12.4</td>
<td>11.3±8.2</td>
<td>0.008</td>
<td>15.3±10.7</td>
</tr>
<tr>
<td>Seizures / 3 mo</td>
<td>1.3±3.3</td>
<td>0.54±1.0</td>
<td>0.20</td>
<td>12.1±14.4</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>140.5±93.9</td>
<td>130.1±83.2</td>
<td>0.31</td>
<td>130.1±61.4</td>
</tr>
</tbody>
</table>

Anastrozole in Older Men

Burnett-Bowie et al.:
- Randomized, double-blind, 1 year
- 88 men ages 60+ years, T 150-300 ng/dL
- Anastrozole 1mg QD vs. Placebo
- Evaluate:
  - Hormones
  - Body composition
  - PSA
  - BPH symptoms
  - LIPIDS
- No change in:
  - Body composition / strength
  - PSA, BPH sx, lipids

Letrozole Lowers Estradiol and Raises Testosterone Levels in Obese Hypogondal Men

- Double blind, placebo-controlled 6 month trial
- 42 obese men (mean BMI 41 kg/m², age 45 yo)
- Hypogondal → T < 288 ng/dL
- Randomized to placebo vs. Letrozole 2.5mg/d
- Monthly dose escalation until T 577 ng/dL reached
- Primary Endpoints:
  - Psychological function (SCL-90, GIT, DPQ)
  - Body composition
  - Exercise capacity
  - Glucose levels
  - Lipid levels
  - Bone metabolism

Conclusions:
- No beneficial psychological or somatic effects from letrozole
- Letrozole raises testosterone and lowers estradiol levels
- Testosterone and estrogen signaling may need to be coupled for somatic effects

Letrozole in Males: Gynecomastia and Infertility

Large Cell Calcifying Sertoli Cell Tumors
- Express CYP19A1 → increased estradiol levels
- 6 boys with gynecomastia, testicular enlargement, advanced bone age
- Treated with anastrozole or letrozole for 6-60 months
- All had improvements in gynecomastia

Male Infertility
- 27 infertile men, mean age 35 yo, T <330 ng/dL
- Letrozole 2.5 mg/d for ≥6 months

Results:
- Increases in T, LH, decreases in E
- Increases in sperm count, motility, ejaculate volume

J Clin Endocrinol Metab. 2014; 99: E2673.
Aromatase Inhibitor Safety

Common Side Effects:
- Back pain
- Bone pain / fracture
- Hot flashes / night sweats
- Joint / Muscle pain
- Depression / Anxiety
- Pedal swelling
- Loss of desire

AI’s Summary
- AI’s (letrozole and anastrozole) increase testosterone levels and decrease estradiol levels.
- Minimal evidence for impact on hypogonadal symptoms.
- Neither has been well studied (in younger men).
- Side effects are not well established in men.
- Superiority of efficacy (letrozole vs. anastrozole) unknown.

WHO IS A CANDIDATE FOR AI THERAPY?
- Hypogonadal men on TTh with elevated estrogen levels / (gynecomastia?)
- Hypogonadal older men
- Hypogonadal men seeking fertility / not candidates for TTh
- Superiority of efficacy (letrozole vs. anastrozole) unknown
CONCLUSIONS

I. Testosterone therapy decreases intratesticular testosterone concentrations and thereby inhibits sperm production

II. Cessation of testosterone therapy usually results in restoration of sperm production

III. SERMs (clomiphene citrate) Aromatase Inhibitors and hCG-based treatments are potential effective strategies for HRT

THANK YOU