Testosterone Deficiency in Men

Ron Rothenberg MD
We age because our hormones decline, our hormones don’t decline because we age

- Testosterone replacement therapy is safe and can provide dramatic benefits
- Testosterone decreases inflammation
Testosterone Deficiency = Male Menopause = Andropause = Androgen Deficiency Aging Male = Hypogonadism

- Less sudden in onset than female menopause
- Just as severe in long term consequences
- The cause....
- Decreased bioavailable TESTOSTERONE +
Testosterone Deficiency

- Increased aging of heart and circulation
  - Increased MI’s and CVA’s
  - Decreased hemodynamic function
- Increased brain aging
  - Decreased memory
  - Decreased intelligence
  - Increased Dementia, Alzheimer's
Testosterone Deficiency

- Loss of drive and competitive edge
- Stiffness and pain in muscles and joints
- Falling level of fitness
- Decreased effectiveness of workouts
Testosterone Deficiency - Deteriorating body composition

- Sarcopenia
  - Less muscle, more fat
- Osteoporosis
- Anemia

Testosterone Deficiency
- Increased Cancer
Testosterone Deficiency

- Fatigue, Tiredness
- Depression, Mood changes
- Irritability
- Dysphoria
- Reduced libido and potency
  - decreased desire and fantasies
  - decreased morning erections
  - decreased erectile tension
  - longer recovery time between orgasms
  - decreased intensity of orgasms
Low Testosterone is a deficiency disease

- Half of healthy men between the ages of 50–70 yr will have a BT level below the lowest level seen in healthy men who are 20–40 yr of age

Testosterone Deficiency

- T decline:
- Begins early – 30 y/o
- 25-75 years old
  - 30% decrease in Total T
  - 50% decrease in bio-available T
- Severe T deficiency can start very early in 20’s
Testosterone getting lower every year

Phthalates and Decreased T

- Phthalates significantly reduced T in both sexes.
  - Women and men ages 40 – 60 years.
  - Boys 6 – 12 years old:
    - 29% reduction in T

- Meeker et al. Urinary Phthalate Metabolites Are Associated With decreased Serum Testosterone in Men, Women, and Children From NHANES. J Clin Endocrinol Metab. 2014 Aug 14
Testosterone Deficiency is a lethal disease

- Diabetes, Metabolic syndrome
- Brain
- Heart
- Frailty syndrome
- Bone
- Inflammation
- Cancer
High T = Low Mortality

- 10 year prospective study
- 11,606 men – 40-79 years old
- High Endogenous T = low mortality from CV disease and cancer
- Low T predicts CV disease
- High T = no increase in Prostate Cancer
- “Paradoxically” fear of Prostate Ca has keep men from T treatment

41% decrease in chance of dying in men with T >564 compared to 350
For each increase in T, chance of dying went down 14%
Extrapolating:
Comparing T 300 to 1000
57% decrease in chance of dying
This study was of endogenous T not treatment
Testosterone treatment and Mortality

- 1000 male veterans, > 40 years old, 4 years Rx
- Total test < 250
- 400 treated with testosterone
- Mortality treated 10% vs. 20% controls
  \[ p < .00001 \]

- Decreased risk of death
- Hazard ratio 0.61
- 95% confidence interval 0.42–0.88, \[ p = .008 \]

- Prostate CA treated 1.6%
- untreated 2.0

Shores MM et al. Testosterone Treatment and Mortality in Men with Low Testosterone Levels. *J Clin Endocrinol Metab*. 2012 Apr
Body Composition/Sexual Function


Findings
Some surprising, some not

- Higher testosterone, greater muscle size and strength
- Higher estrogen, less Fat
- Higher testosterone and higher estrogen, better libido and erection function
Analysis:

- Serum testing is effective and useful for transdermal testosterone.
- It takes 100 mg of testosterone transdermal to get significant results.
- E2 is beneficial in men up to 32 ng/dl but the study does not help us evaluate higher levels.
- Use anastrozole only if needed for symptoms or very high levels of E2.
Strength and muscle function

- T is major predictor of skeletal mass
- Synergistic with GH and IGF-1
- Improved strength even without exercise but marked improvement with exercise

Lower Free T T predictive of Frailty in Older Men

- Fatigue, stair climbing, walking more than 100 m, > 5 illnesses and weight loss >5 % measured in 3166 community dwelling men aged 70-93 over 8 years.
- Lower free T predicted frailty
TRT and erectile function

- Libido always increased
- Nitric Oxide receptors up regulated
- Usually improved erectile function
- May take up to 6 months
- Response to Sildenafil etc improved
T and cognitive function

- T correlated with cognitive function and TRT improves it


T and Alzheimer’s

- TRT prevents the production of beta amyloid precursor protein. (in men)

T Rx – Alzheimer’s

- Treated group improved over 1 year
- Control group deteriorated

T and mood (and erections)

- Effective when psych drugs do not work in pts with low T
- Cooper MA. Testosterone Replacement Therapy for Anxiety Am J Psychiatry 157:1884, November 2000
- TRT increases nocturnal and spontaneous erections and improves mood
High Free T was associated with better performance on tests of memory, executive function, and spatial ability, and with a reduced risk for Alzheimer's disease.

Improved cerebral blood flow

T and cardiovascular risk

- Lower T and free T the more likely coronary artery disease
- T improves exercise induced ST depression
- Dilates coronary arteries
- Effects on lipids variable, most current studies show no change or improvement
- Low T associated with dyslipidemia
- Decreased risk of CV death with higher endogenous T
“There is no convincing evidence of increased CV risks with T therapy.
On the contrary, there appears to be a strong beneficial relationship between normal T and CV health that has not yet been widely appreciated.”

ICD9 code study. No chart review or patient contact

Men who had angiography with many comorbidities including
- 20% hx of MI
- 18% CHF
- 55% Angiograms positive for coronary artery disease
- 55% Diabetes

Test < 300

“Treated” with test vs not treated

Reviewed ICD9 “events” Death, MI, CVA

Conclusions: No test 20%, Yes test 25% events
Problems with study

- Why were some patients started on test but others not? Sicker?
- Treatment group test 175, control group 200, was treatment group sicker
- Definition of treatment was at least 1 Rx
  - 20% only filled 1 Rx
  - 80% filled more than one
  - 60% had repeat test level, mean = 332
- Treatment group may or may not have had more than one Rx
- Started out deficient and ended up deficient
- No assessment of E2, DHT or Hg/Hct
Fuzzy math?

- Events
  - No testosterone: 7486 patients, 1587 events
    - = 21% events
  - Yes testosterone: 1223 patients, 122 events
    - = 10% events

- Deaths
  - No testosterone: 7486 patients, 681 deaths
    - = 9% deaths
  - Yes testosterone: 1223 patients, 67 deaths
    - = 5% deaths
Open Season on Testosterone

- Study claims risk of non-fatal MI greater in the 3 months after testosterone therapy Rx (TT) compared to the year before TT.
- Also compared TT to PDE5-I Rx in 3 months after and year before TT.

Finkle, W et al. Increased risk of non-fatal myocardial infarction following testosterone therapy Prescription in men. 2014 Plos One Volume 9 Issue 1
Ratio of non-fatal MI Post Rx/Pre Rx

- **Testosterone**
  - All ages: 1.36
  - Age > 65: 2.19
  - Age > 65 Heart hx: 2.16 but Not significant
  - Age > 65 No heart hx: 2.21
  - Age < 65 Not significant
  - Age < 65 No heart hx: Not significant
  - Age < 65 Yes heart hx: 2.9
- **PDE5-I** Not significant
Multiple Problems with study – Results useless

- ICD-9 study, patients not seen or interviewed
- No info on fatal MI or cardiovascular mortality or all cause mortality
- No information on testosterone serum levels before or after therapy
- No information on preparation, dose or interval of usage
  - Was dose adequate to significantly raise serum levels or did levels actually decrease?
  - Was IM testosterone used in long interval plan with resulting low levels in second week or beyond?
- Did the patients take the TT?
- No information on Estrogen levels or Hg/Hct
- No information on lifestyle management or lack thereof
- No information on clinical effects of treatment
- Why were the patients started on TT?
- Why were some given TT vs PDE5-I, TT group sicker?
- Pt’s on nitrates not Rx’d with PDE5-I
- PDE5-I’s are vasodilators and may have beneficial CV effects
Testosterone Treatments Linked to Health Problems

Results have included:
- Blood Clots
- Stroke
- Heart Attack

Don’t Wait to File your Lawsuit

Get Your FREE Consultation
4 major studies – low T assoc. with increased all cause mortality


MALE HYPOTESTOSTERONISM

- Hyperglycemia
- Hypertension
- Insulin Resistance
- ↑ Cytokines
- Metabolic Syndrome
- Atherosclerosis
- Dyslipidemia
- ↑ Vascular Stiffness
T and premature CAD

- TT and FT levels of men < 45 yo with coronary artery disease were significantly lower than those of controls.
- FT levels below of 17.3 pg/ml
- 3.3 x risk of premature CAD
BP and T: inverse relationship

Testosterone – CV classic studies

- Reduces angina – English, 2000
- IV T reduces ischemia – Rosano 1999
- Intracoronary T dilates – Webb 1999
- Improves exercise tolerance – Channer 2003
- Decreases inflammation, TNF, Malkin, 2004
- Decreases atherosclerosis, Hak 2002
- Improves CHF, Caminiti, 2009, Malkin 2005
The Progress of Atherosclerosis

Foam cells – beginning of fatty streak

Endothelial cell

Activated macrophage

T-cell

Monocyte

Adhesion molecules

LDL particle

IL-6

IL-1

TNF-α

Smooth muscle cells

Foam cells – beginning of fatty streak

Transdermal E2

Tissue Inhibitor of MMP (TIMP)

CRP

SAA

HDL

P-selectin

E-selectin

VCAM-1

ICAM-1

LDL

‘Oxidized’ LDL

Monocyte

E2

Test aromatase

IL-6

IL-1

TNF-α

Liver

MCP-1

P-selectin

E-selectin

VCAM-1

ICAM-1

Adhesion molecules

Stress

Epinephrine

E2

COMT

2-Methoxy E2

Melatonin

Tissue Inhibitor of MMP (TIMP)

Endothelial cell

MMP’s
Unified Theory of Wellness
Chronic Inflammation Is the Cause and the Effect of the Diseases of Aging

Inflammatory cytokines
NF Kappa Beta
Inflammatory Enzymes COX, LOX

Coxibs block Vioxx
PGI2 = prostacyclin
good eicosanoids

Acute phase proteins CRP, Fibrinogen
Control insulin, Less omega 6, Less Diet, Arachadonic acid

Adhesion molecules VCAM1, ICAM1, MCP1, MadCAM1

Anti-inflammatory cytokines

Anti-inflammation
Nutrition
Glucose and Insulin control

High Homocysteine

Stress
Infection
Depression
High Glucose and Insulin Hormone Decline
Lack of Exercise
Aging
High Homocysteine
Trans Fats

Vitamin D
CRP

Red inhibits
Yellow activates
Resveratrol
E PC’s

Pain
PGE2:
Cancer
Skin aging
ASCVD

Angiotensin II

PTE

B vits

Immune
Magnessium

Catecholamines

Good Eicosanoids

Wellness

ASCVD

Resveratrol

DHEA, Testosterone, Melatonin

P4

PGE2, LRC4 - CA
Pain

DHA

EPA

EPA, DHA

Good Eicosanoids

ASCVD

Chronic Illness

PGE2: Pain
Cancer
Skin aging

ASCVD

Atherosclerosis

Angiotensin II

RANKL

Parathyroid Hormone

Ca

IDH1

P53

Glutathione

Anti-Inflammatory Cytokines

Adipocytes

DHEA, Testosterone, Melatonin

Inflammatory Cytokines

Vitamin D

Red inhibits

Yellow activates

Resveratrol

E PC’s

Wellness

Chronic Inflammation Is the Cause and the Effect of the Diseases of Aging
T and BPH

“Multiple studies have failed to demonstrate exacerbation of voiding symptoms attributable to benign prostatic hyperplasia during testosterone supplementation”

Rhoden *NEJM* 2004
2014 European Study

- 1023 patients up to 17 years with TRT
- Cohort 1 261 Pca 54.4/10000 pt years
- Cohort 2 340 Pca 30.7/10000 pt years
- Cohort 3 422 Pca 0/10000 pt years
- Background prevalence 96.6/10000 pt yrs
- Conclusion- Testosterone therapy in hypogonadal men does not increase the risk of prostate cancer.

Prostate CA and Hormones

- 3886 men with prostate cancer, 6438 controls
- No associations were found between the risk of prostate cancer
- Testosterone, calculated free testosterone, dehydroepiandrosterone sulfate, androstenedione, androstanediol, estradiol, calculated free estradiol
- Endogenous Sex Hormones and Prostate Cancer: A Collaborative Analysis of 18 Prospective Studies
TRT and PC

- Review of 16 studies, some placebo controlled
- Various T formulations
- Up to 15 year studies
- No increased risk over the background prevalence

TRT and PC over 20 years

- 1365 men with TRT x 20 years
- Screened with PSA and DRE q 6 months
- Abnormal changes with US prostate and biopsy

Conclusion:
- No difference in PSA, free PSA and PCa as compared to background
- All cancer in treatment group localized and curative
- Testosterone treatment and monitoring may be safer than no treatment

History of “T causes PC” myth

- 1941: Huggins and Hodges reported that marked reductions in T by castration or estrogen treatment caused metastatic PC to regress.
- Administration of exogenous T caused PC to grow. This was based on only one patient.
- Based on increased acid phosphatase.
- Multiple subsequent reports revealed no PC progression with T administration.
- Some men even experienced subjective improvement, such as resolution of bone pain.

Recent data have shown no apparent increase in PC rates in clinical trials of T supplementation in normal men or men at increased risk for PC.

No relationship of PC risk with serum T levels in multiple longitudinal studies.

No reduced risk of PC with low T.

The paradox in which castration causes PC to regress yet higher T fails to cause PC to grow.

Resolved by a saturation model, in which maximal stimulation of PC is reached at relatively low levels of T.
Morgentaler conclusion

“There is not now-nor has there ever been a scientific basis for the belief that T causes PC to grow”
Pomegranate Juice and PC

- Rising PSA after surgery or radiotherapy
- 8 ounces of pomegranate juice daily until disease progression
- Mean PSA doubling time significantly increased with treatment from 15 months to 54 months (P < 0.001).
- 12% decrease in cell proliferation
- 17% increase in apoptosis
- Significant reductions in oxidative state
Treating with T after Radical Prostatectomy for PC

- Organ confined PC
- Radical Prostatectomy
- PSA <0.1 after 1 year
- Treated with T
- No recurrences or increase in PSA

TRT. Prostate Ca, Brachytherapy

- TRT 0.5 – 8.5 years after brachytherapy
- Follow up 1.5- 9 years
- 1 patient with transient rise of PSA <1.0
- No patient stopped TRT due to cancer recurrence or disease progression
Active Prostate CA and Testosterone Therapy

- 13 testosterone deficient men with untreated prostate CA
- Testosterone increased 238 to 664, PSA, prostate volume – unchanged
- After 2.5 years - No cancer found in 54% of prostate biopsies.
- No local progression or metastases

Morgantaler et al. Testosterone Therapy in Men with untreated Prostate CA. *J Urol* 2011 Apr, (185:4) 1256-60

Testosterone Supplementation Augments Overnight Growth Hormone Secretion

- 100 mg T IM q 2 weeks x 26 weeks
- Total T increased 33%
- E2 increased 31%
- SHBG decreased 17%
- GH secretion increased 1.9 x
- IGF-1 increased 22%
- IGFBP-3 no change

Testosterone Treatment and Diabetes and Metabolic Syndrome

- Can have dramatic effect on insulin resistance, visceral fat, blood pressure
Mechanisms Testosterone vs. Diabetes

- Modulator of body composition - promoting myogenesis and inhibiting adipogenesis
- Enhances transport of glucose into cells
- Improved Endothelial function may be the basis for the reduction of BP and HR and ED
- One-year TU is able to improve arterial stiffness and endothelial function
- Improved Vitamin D status may be - up regulated 1 alpha hydroxylase / decreased adipose

Testosterone (cont)

- Induces normal pulsatile GH secretion
- Regulates lineage of mesenchymal pluripotent cells by promoting the myogenic lineage and inhibiting the adipogenic lineage
- Mobilizes lipids from the visceral fat depot which improves CV risks
- Increases motivation, enhancement of mood, and promotion of more energy expenditure
Treatment with Testosterone in Diabetes and Metabolic Syndrome
T and Diabetes and Insulin Resistance

- Replacement doses decrease insulin resistance
- Supraphysiologic doses increase insulin resistance
- Men with T2DM have 2 X rate of T deficiency
- Low levels of T contribute to type 2 diabetes
- Hyperinsulinemia decreases T
- TRT decreases hyperinsulinemia
- Low T associated with Metabolic Syndrome, hypertension, type 2 diabetes, fibromyalgia, CAD

Diabetes and Testosterone Treatment

- Oral Testosterone Undecanote treatment of type 2 diabetic men with T deficiency
- Improves glucose homeostasis and body composition – visceral fat
  - Hg A1c decreased 17.3%
  - Decrease in visceral obesity
- Improves sx of T deficiency including ED

TRT and Diabetes - Improved

- 24 hypogonadal men with T2DM, double blind, placebo controlled
- Test 200 mg IM 2 q 2 weeks x 3 months vis placebo then crossover
- Improved Insulin Sensitivity, A1C, Fasting glucose, visceral adiposity

Testosterone Treatment with Metabolic Syndrome

- Testosterone = 241 (mean)
- Metabolic syndrome
- All had nutrition and exercise counseling
- T undecanoate 1000 mg q 6 weeks x 2 then q 12 weeks x 60 months

TRT but not control group

- BMI $-2.9 \pm 1.4$  P < 0.0001
- Waist circumference $-9.6 \pm 3.8$ cm  P < 0.0001
- Weight $-15 \pm 2.8$ Kg  P < 0.0001
- HgA1C $-1.6 \pm 0.5\%$  P < 0.001
- Insulin Sensitivity $-2.8 \pm 0.6$  P < 0.0001
- Total/HDL-cholesterol: $-2.9 \pm 1.5$  P < 0.0001
- Triglycerides: $-41 \pm 25$  P < 0.0001

### TRT but not control group - continued

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td>$-23 \pm 10$ mmHg</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Diastolic</td>
<td>$-16 \pm 8$ mmHg</td>
<td>$&lt; 0.001$</td>
</tr>
<tr>
<td>Neck and lumbar T-scores</td>
<td>$.5 \pm 0.15$ gr/cm$^3$</td>
<td>$&lt; 0.0001$</td>
</tr>
<tr>
<td>Serum vitamin D</td>
<td>$+14.0 \pm 1.3$ ng/mL</td>
<td>$&lt; 0.01$</td>
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<tr>
<td>TSH</td>
<td>$-0.9 \pm 0.3$ mUI/mL</td>
<td>$&lt; 0.01$</td>
</tr>
<tr>
<td>IGF1</td>
<td>$+105 \pm 11$</td>
<td>$&lt; 0.01$</td>
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<tr>
<td>Hematocrit</td>
<td>$+2.8 \pm 0.9$%</td>
<td>$&lt; 0.001$</td>
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<tr>
<td>PSA levels</td>
<td>$+0.37 \pm 0.29$ ng/mL</td>
<td>$&lt; 0.01$</td>
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</table>

Francomano D et al. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol.* 2014 Feb 12
“The present study also provides first evidence that remarkable reduction of blood pressure and heart rate, as well as amelioration of vitamin D, GH/IGF1, and TSH plasma levels, are also attained. This may in turn yield to different overall CVD estimated risk and overall survival rates as well as to different pharmacological management of T2DM, hypertension, and dyslipidemia in men with MS and obesity.”

# Testosterone Lab Testing

<table>
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<th>Test</th>
<th>Sex</th>
<th>Reference</th>
<th>Optimal</th>
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<tbody>
<tr>
<td>Total ng/dl</td>
<td>Male</td>
<td>350-1030</td>
<td>790-1100</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10-55</td>
<td>50-80</td>
</tr>
<tr>
<td>Free* ng/dl (Equilibrium dialysis)</td>
<td>Male</td>
<td>8-30</td>
<td>20-35</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1.1-6.3</td>
<td>3-8</td>
</tr>
<tr>
<td>Bioavailable pg/ml</td>
<td>Male</td>
<td>120-600</td>
<td>400-640</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>2-20</td>
<td>10-25</td>
</tr>
</tbody>
</table>

* Free testosterone results vary with methodology – direct analog (RIA) in pg/ml – same ref range
FREE TESTOSTERONE

SEX HORMONE BINDING GLOBULIN

ALBUMIN
BIOAVAILABLE TESTOSTERONE

SEX HORMONE BINDING GLOBULIN

ALBUMIN
SHBG binds T > E

- 20-60 nmol/l male
- 40-120 nmol/l female
- Low SHBG assoc with Insulin Resistance in men
- And women
• Increases SHBG
  – Thyroid
  – Estrogens
  – Progesterone
  – Aging
  – Low Insulin
  – Coffee (not decaf). Green tea, soy

• Decreases SHBG
  – Testosterone
  – DHEA
  – Glucocorticoids
  – GH
  – High Insulin
“Free” Free T calculator

http://www.issam.ch/freetesto.htm
T Metabolites - Estradiol

- E2 usually increases with increasing T
- Do not let E2 get too low
  - Optimal? 25-50 pg/ml
  - NEJM 9/2013 Finkelstein study
  - Need E2 for fat control, libido and erectile function

Aromatase Inhibition
- Chrysin 250 mg BID PO
- Topical 50 mg/gm
- Zinc 50 mg per day
- Progesterone 5-10 mg transdermal
Anastrozole

- Anastrozole 0.5 mg 1-3 x per week
  - Can precisely control E2
  - Do not let levels fall too low, take it easy with E2 control
  - E2 is necessary for brain, heart, bone, fat control, sexual function
  - Use with clinical symptoms only?


DHT can increase with increasing T, especially with transdermal T.
DHT does not aromatize to E2.
Is DHT evil twin of T or “good” androgen?
DHT needed for erectile function and anabolic effects.
Not associated with Prostate CA in serum levels.
Possibly associated with BPH and hair loss.
5-alpha reductase inhibition

- 5- alpha reductase and dutasteride and finasteride
- PCa risk reduction?
- Higher grade Pca?
- Major drug intervention
5-alpha reductase inhibition

- Neuroactive steroids - 5-allo-pregnenolone needed for neuronal repair and memory
- Inhibition of 5-alpha-reductase by finasteride inhibits hippocampal neurogenesis
- Contributes to the pathophysiology of depression and memory loss
- Neurosteroids are potent endogenous modulators of the GABA receptor

Reported side effects of finasteride and dutasteride

- Impair sexual function, including sexual desire, erectile and orgasmic function
- Impair NO function and can produce ED and this can be long lasting and irreversible
- Depression
- Do not reduce incidence of aggressive and high grade prostate cancer
Mild 5-alpha reductase inhibition

- Saw palmetto  320 mg/day
- Progesterone transdermal  5-10 mg/day
Progestosterone men

- Similar levels present in men and women in follicular phase 0.5 ng/ml
- GABA receptor binding
- Improves hot flashes in men treated with leuprolide

Potential Adverse effects

- Major side effect
  - Increased RBC’s - Erythocytosis
  - More likely with injections
  - Phlebotomy if needed every 3 – 12 months
  - Donate or discard 1 unit when hemoglobin > 17.5
Thromboembolic Events?

“No testosterone-associated thromboembolic events have been reported to date.” Rhoden *NEJM, 2004*

Thrombophilia in patients with hypercoag genetic disorders - *Glueck 2013*


Glueck, C et al. Testosterone, Thrombophilia, and Thrombosis *Clin Appl Thromb Hemost.* 23 April 2013
Potential Adverse effects

- Gynecomastia or nipple tingling or irritation—decrease E2 if elevated
- Should you treat asymptomatic patients with elevated E2?
Potential Adverse effects

- Acne
- Fluid retention (rare)
- Does TRT accelerate male pattern hair loss? Possibly.
- Possible decrease in testicular size.
- Decreased sperm count
Transdermal

- Well absorbed in most men -
- Saliva levels may reflect intracellular effects
- More DHT since hair follicles contain 5 alpha reductase
- Steady state after 24 hours
Pellets

- Subcutaneous pellets
  - Minor surgical procedure
  - Last 3 + months
  - 75 mg pellets x 7-14
HCG injections

- Human chorionic gonadotropin (HCG)
- Polypeptide hormone produced by the human placenta
- Alpha and beta sub-unit.
- Alpha sub-unit is essentially identical to the alpha sub-units of LH and FSH
HCG

- If there is no Leydig cell failure can treat hypogonadism with HCG injections
- 2000-5000 units per week sub-q - divided
- No decrease in testicular size or sperm count
- Can use as TRT (measure free T to confirm success) or cycle with TRT every 6 months
HCG

- If FSH and LH already relatively high, probably will not work
- Avoids the TRT side effects of loss of testicle volume and decreased sperm count
- More aromatization?
Oral

Oral – Methyltestosterone
  - Hepatotoxic, contraindicated

Oral – T undecanoate
  - Lymphatic absorption, no hepatic toxicity reported
  - Must use TID
  - No available in US
  - No great levels produced

- IM T undecanoate can be given 1000 mg q 12 weeks with stable T levels, but in the US available as 750 mg every 10 weeks
T Dose Men

• Cream  50-200 mg/day
• Cypionante  50-150 mg IM or SQ/ week
• Pellets  75 mg x 5-15  q 3 months
• HCG  1000-5000 units per week
  – Possible dosing:
  – 250 units per day
  – 1000 units twice a week
  – T cypionate 100 mg IM on day 1
  – HCG 250 units SC days 5 and 6
Testosterone and satellite cells (stem cells)

- Older men treated with T: dose-dependent increase in muscle fiber CSA and satellite cell number.
- Testosterone-induced skeletal muscle hypertrophy in older men is associated with increased satellite cell replication and activation.
T Rx Increases EPC’s

- Hypogonadism – low EPC
- T gel 50 mg/day x 6 months
  - Normalized EPC’s
  - Androgen receptor expressed on EPC’s
- May be mechanism of T benefit in CV disease

Foresta C et al. Reduced Number of Circulating Endothelial Progenitor Cells in Hypogonadal Men. *Journal of Clinical Endocrinology & Metabolism* 91(11):4599–4602
T and ED and EPC (Stem cells)

- T improves ED and can resolve ED with PDE5 inhibitors when PDE5 inhibitors do not work.
- T increases circulating Endothelial Progenitor Cells from Bone Marrow which cause vascular repair.