Testosterone Deficiency
Testosterone and Diabetes

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
Testosterone Treatment – 56% less mortality

- 83,000 VA men > 50 y/o low testosterone
- Normalized-TRT– treated and test normalized
- Non-normalized-TRT– treated and test not normalized
- No TRT – not treated

Normalized-TRT vs. No TRT Hazard Ratios

- All cause mortality  \(0.44\) CI \(.42-.46\) p<.00001
- Risk of MI  \(0.76\) CI \(.63-.93\) p<.00001
- Risk of Stroke  \(0.64\) CI \(.43-.96\) p<.00001
- Significant but higher hazard ratios
  - Normalized-TRT vs. Non-normalized-TRT
- No difference
  - Non-normalized-TRT vs. No TRT

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
4 major studies – low T assoc. with increased all cause mortality


MALE HYPOTESTOSTERONISM

- Hyperglycemia
- Hypertension
- Insulin Resistance
- ↑ Cytokines
- Metabolic Syndrome
- Atherosclerosis
- Dyslipidemia
- ↑ Vascular Stiffness
Testosterone –CV classic studies

- T and BP inverse relationship - Khaw 1988
- 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
- Low T premature CVD, Turhan 2006
- Improves CHF, Caminiti, 2009, Malkin 2005
The Progress of Atherosclerosis

- Foam cells – beginning of fatty streak
- Endothelial cell
- Activated macrophage
- T-cell
- IL-6
- IL-1
- TNF-α
- Smooth muscle cells
- 'Oxidized' LDL
- MCP-1
- Liver
- CRP
- SAA
- HDL
- P-selectin
- E-selectin
- VCAM-1
- ICAM-1
- IL-6
- IL-1
- TNF-α
- Tissue Inhibitor of MMP (TIMP)
- Transdermal E2
- Oral E2
- Test aromatase
- E2
- E2
- 2-Methoxy E2
- COMT
- Epinephrine
- Stress
- Melatonin
- Melatonin
- Foam cells – beginning of fatty streak
- MMP’s
- E2
- Oral E2
- 2-Methoxy E2
- COMT
Inflammatory cytokines

NF Kappa Beta

Inflammatory enzymes

COX, LOX

Arachidonic acid

Bad eicosanoids

TXA2, ASCVD

PGE2, LRC4 - CA

Pain

PGE2:

Cancer

Skin aging

ASCVD

Chronic Illness

Wellness

TXA2

Atherosclerosis

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Vitamin D

CRP

Red inhibits

Yellow activates

Resveratrol

EPC’s

Unified Theory of Wellness

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

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 Rx – Alzheimer’s

- Treated group improved over 1 year
- Control group deteriorated
- TRT prevents the production of beta amyloid precursor protein. (in men)

T and mood (and erections)

- Effective when psych drugs do not work in pts with low T

- 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

Hypogonadism-TRT 2002-2012- LUTS

Conclusion: TRT does not worsen lower urinary tract symptoms and many patients reported improvement.


European Study T and PCa

- 1023 patients up to 17 years with TRT
- Cohort 1 261 Pca 54.4/10,000 pt years
- Cohort 2 340 Pca 30.7/10,000 pt years
- Cohort 3 422 Pca 0/10,000 pt years
- Background prevalence 96.6/10,000 pt yrs

Conclusion- Testosterone therapy in hypogonadal men does not increase the risk of prostate cancer.

Morgentaler conclusion

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

PSA or Tumor Growth

Androgen-dependent growth

Androgen-indifferent growth

Saturation point

Serum Testosterone Concentration

100  200  1000
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
Conclusions: Testosterone therapy in men following radiation therapy for PCa was associated with a minor increase in serum PSA and a low rate of BCR.

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
Active Surveillance, Prostate CA, Testosterone Treatment

- 28 men on AS with Gleason 3+3, 3+4 x 3 years treated with testosterone, 96 controls untreated
- Biopsy progression in men on AS appears unaffected by T therapy over 3 years

Does Testosterone Reverse Diabetes in Cats?

By Steve Dale, Wednesday at 8:05 am

Q: Two of my medical patients have taken the liberty of successfully using their own testosterone injectables on their cats to reverse diabetes. I thought you might want to pass this information along. -- E.L., via cyberspace
Bi-directional relationship between visceral fat and testosterone: a self-perpetuating cycle promoting insulin resistance.

Type 2 diabetes/metabolic syndrome

Insulin resistance

Muscle

Decreased myocyte differentiation/mitochondrial function

CNS

Liver

Bone

Symptoms/end organ deficits

Age comorbidities

Testosterone

Visceral adipose tissue

Stimulation of adipocyte differentiation and triglyceride uptake

SHBG

Cytokines

Cytokines

Insulin

Leptin

Ghrelin

HPT axis

Kisspeptin

Cytokines

Visceral adipose tissue

CNS
Testosterone Treatment and Diabetes and Metabolic Syndrome

- Can have dramatic effect on insulin resistance, visceral fat, blood pressure
- Testosterone Replacement therapy can “cure” type 2 diabetes
Diabetes and Testosterone Treatment

- Oral Testosterone Undecanote treatment of type 2 diabetic men with androgen deficiency
- Improves glucose homeostasis and body composition – visceral fat
  - Hg A1c decreased 17.3%
  - Decrease in visceral obesity
- Improves symptoms of androgen deficiency including erectile dysfunction
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 $-9.6 \pm 3.8 \text{ cm}$ P $< 0.0001$
- Weight $-15 \pm 2.8 \text{ Kg}$ 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 $< 0.0001$

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.* 2014Feb 12
TRT but not control group- continued

- Systolic: $-23 \pm 10$ mmHg, $P < 0.0001$
- Diastolic: $-16 \pm 8$ mmHg, $P < 0.001$
- Neck and lumbar T-scores: $.5 \pm 0.15$ gr/cm$^3$, $P < 0.0001$
- Serum vitamin D: $+14.0 \pm 1.3$ ng/mL, $P < 0.01$
- TSH: $-0.9 \pm 0.3$ mUI/mL, $P < 0.01$
- IGF1: $+105 \pm 11$, $P < 0.01$
- Hematocrit: $+2.8 \pm 0.9\%$, $P < 0.001$
- PSA levels: $+0.37 \pm 0.29$ ng/mL, $P < 0.01$

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 TX Diabetes

- Randomized, placebo controlled
- Treated with 250 mg T q 2 weeks
- TT decreased free fatty acids, C-reactive protein, interleukin-1β, tumor necrosis factor-α, and leptin (P < 0.05 for all).
- TT decreased SQ fat mass (−3.3 kg) and increased lean mass (3.4 kg) (P < 0.01)

Sandeep Dhindsa et al. Insulin Resistance and Inflammation in Hypogonadotropic Hypogonadism and Their Reduction After Testosterone Replacement in Men With Type 2 Diabetes. *Diabetes Care*. 2016 Jan;39(1):82-91
Testosterone Deficiency and Metabolic Syndrome

N= 255 tx with Testosterone undecanoate 1000 mg at baseline, 6 weeks and q12 weeks thereafter up to 60 months.

CONCLUSIONS:

Long-term T therapy, at physiological levels, ameliorates metabolic syndrome components.

T therapy in hypogonadal men is reduces the risk of cardiometabolic diseases

# Testosterone Lab Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Sex</th>
<th>Reference</th>
<th>Optimal</th>
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</thead>
<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>
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<td></td>
<td>Female</td>
<td>1.1-6.3</td>
<td>3-8</td>
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<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
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?


T Metabolites - DHT

- 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
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
VTE Risk on TRT

- 30,572 men 40 years and older
- No increased risk of VTE


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

- Major side effect
  - Increased RBC’s - Erythrocytosis
  - More likely with injections
  - Phlebotomy if needed every 3 – 12 months
  - Donate or discard 1 unit when hemoglobin > 17.5
Potential Adverse effects

- Gynecomastia - rare
- Acne
- Fluid retention (rare)
- Does TRT accelerate male pattern hair loss? Possibly.
- Possible decrease in testicular size.
- Decreased sperm count
CONCLUSION: Therapy with weekly subcutaneous testosterone produced serum levels that were within the normal range in 100% of patients for both peak and trough levels.

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

- If there is no Leydig cell failure can use 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
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   2000-5000 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.

“Because of excessive reliance on laboratory measures of androgens and undue safety concerns, many men who could benefit from symptom relief, improvement in related clinical conditions and given preventive medical benefits remain untreated.”