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
Male Menopause = Andropause = ADAM

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

- 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
Male Menopause

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

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

Male Menopause – Increased Cancer
Male Menopause

- 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
Andropause 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

T decline:

- Begins early – 30 y/o
- 25-75 years old
- 30% decrease in Total T
- 50% decrease in bio-available T
Testosterone getting lower every year

Andropause 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 173, 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
Low T and mortality

- Low T group had 88% increased mortality
- Excluding first year 68% increased mortality
- Equivocal group had 38% increased mortality

Adjusted for age reference levels

- “Age adjusted T reference values should be eliminated”
- “Long term standing fear of stimulating prostate cancer with T is without scientific basis”
Adverse effects of Testosterone treatment on older men

- In older men with decreased mobility and chronic disease, testosterone gel treatment was associated with increased adverse cardiovascular events.
- Improvement in mobility and strength noted
- Estradiol not reported or optimized
- Limited small study

Basaria S et al. Adverse events associated with Testosterone Administration. NEJM June 2010
BIOAVAILABLE TESTOSTERONE

T T T T T
T T T T
T

ALBUMIN

T T T T T T T
T T T T
T

SEX HORMONE BINDING GLOBULIN
Total T

350-1030 ng/dl  male
10-55    ng/dl   female

10.4 nMol/L= 300 ng/dl

nMol/L x 28.8 = ng/dl
pMol/L x 0.0288 = ng/dl

“Reference ranges” are not “Optimal ranges”

Optimal  750-1100 male
50-80    female
SHBG binds T > E

- 20-60 nmol/l male
- 40-120 nmol/l female
- Increases SHBG
  - Thyroid
  - Estrogens
  - Progesterone
  - Aging
  - Low Insulin
- Decreases SHBG
  - Testosterone
  - DHEA
  - Glucocorticoids
  - GH
  - High Insulin
Free T

- 8-30 ng/dl = 80-300 pg/ml  male
- 1.1-6.3 pg/ml  female

- Fraction of T that is unbound to albumin and SHBG

- Optimal  20-35 pg/ml  male
  5-8  pg/ml  female
Free T

- Lab methods differ in accuracy
- Does not include “useable” loosely bound to albumin
Bioavailable T

120-600 ng/dl  male
2-20 ng/dl  female

- Free T + Loosely bound to albumin T
- Calculated
- Probably most useful “number”
  400-640 ng/dl Optimal male
  10-30 ng/dl  Optimal female
“Free” Free T calculator

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

- E2 can increase with increasing T
- Do not let E2 go to 0
  - Optimal? 25 pg/ml

- 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
  - E2 is necessary for brain, heart, bone
  - Can use as only agent to increase T in men with high E2 levels


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
- 5α-reductase and dutasteride and finasteride
- Prostate cancer risk reduction?
- Major drug intervention
5-alpha reductase inhibition

- Saw palmetto 320 mg/day
- Progesterone transdermal 5-10 mg/day
P4 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

Testosterone Cypionate IM or SC

- Weekly dose - 100 mg
  - Physiologic stable levels
  - Easy self injection
  - Less DHT than transdermal
  - Potentially more E2
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

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

- **Commercial brands**
  - 1% transdermal gel
  - Commercially available
  - 50, 75 or 100 mg packages

- **Compounding pharmacies**
  - Can custom produce transdermal gel
  - Less expensive than commercial
  - Can titrate to serum levels by varying percentage 1-10, and dose
  - Preferred to commercial in most men
Compounded T gel dose

- 1gm = ¼ tsp
- 1gm 10% = 100 mg
- 100 mg per day
- Titrate follow up dose to
  - Clinical results
  - Serum Total, Bioavailable or Free
  - Salivary or 24 hour Urine
- Does lower dose (10-20 mg per day) produce = results and less E?
T gel precautions

- Avoid scrotum (increased DHT)
- Avoid getting gel on females and kids
- Rub in well over large surface area
- Can increase hair growth in area of application but (unfortunately) not on head
- Total, Free and Bioavailable T can actually decrease with gel. Total androgen may increase if add T + 3 x DHT
- Some men do not absorb gel well
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

Can use 250 units sc on days 5 and 6 of T cypionate weekly cycle

Can use low dose of 250 units sc daily
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?
HCG

- 3000 Units q 2 weeks
- Total, Free and Bio-available T increased about 25% and PADAM sx improved

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

Bioavailable T and Alzheimers

- 153 older community living Chinese men with mean age 72.7
- Significant for serum Bio T, systolic blood pressure and APO E genotype
- Relative risk for Bio T 0.22 such that higher the Bio T, lower the risk for developing Alzheimer’s

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.

TBI and Sex steroids

- T suppression 100% men
- E suppression > 40% women
- IGF-1 suppression 77%
- GH non-measurable 38%

The lower the 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
Testosterone reduces angina

- Exercise induced myocardial ischemia reduced
- Significant Improvements in pain perception and role limitation from physical problems
- No change in lipids, coagulation, hemoglobin
- 5 mg patch used, androgen levels doubled

T and cardiac ischemia

- Anti-Anginal treatment withdrawn
- Placebo controlled
- IV T 2.5 mg
- Bruce protocol stress tests
- Increased time to ST depression
- Less chest pain
“Short-term administration of testosterone induces a beneficial effect on exercise-induced myocardial ischemia in men with coronary artery disease. This effect may be related to a direct coronary-relaxing effect.”

T and coronary blood flow

- Intracoronary injection of T at physiological concentrations in men with established CAD
- Coronary artery dilation
- Increased coronary blood flow

T improves cardiac function

- Low testosterone in the older man may have adverse effects on atherosclerosis
- Explains the higher incidence of coronary heart disease in the male
- Vasodilates
- Improves exercise tolerance
- Improves angina threshold

T replacement and inflammation

- Less inflammatory cytokines TNF, IL-1beta
- More anti-inflammatory cytokines IL-10
- Lower total cholesterol
*p = 0.05 (by analysis of the difference)

- Placebo effect
- Testosterone effect

- Total cholesterol (mmol/l)
- LDL (mmol/l)
- HDL (mmol/l)
- Triglyceride (mmol/l)
- Haemoglobin (g/l)
- Haematocrit (1/litre)
- TNFα (pg/ml)
CHF treated with Testosterone Undecanoate

- Improved exercise capacity
- Improved muscle performance
- Improved insulin resistance

T and severe heart failure

- CHF
- Maladaptive and prolonged neurohormonal and pro-inflammatory cytokine activation
- Metabolic shift favoring catabolism, vasodilator incapacity, and loss of skeletal muscle bulk and function

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

Rhoden *NEJM* 2004
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
Estrone and Prostate Cancer

- Only Estrone associated with PC
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

Prospective, 15 years 2200 men

2100 man-years of TRT

0.48% cases per annum

European background prevalence 0.55% cases per annum

Feneley MR et al. PSA monitoring during Testosterone replacement therapy: low long-term risk of prostate cancer with improved opportunity for cure. Andrologia 2004; 36:212
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 alkaline 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”
No adverse effects of T on prostate

- Men 44-78 yo with T < 300
- Rx: T enanthate 150 mg q 2 weeks x 6 months
- Prostate Bx before and after
- T increased from 282 to 640
- No change prostate tissue levels of T and DHT
- No change in prostate cancer incidence or severity
TRT and PSA

- Pts with ED and hypogonadism
- T 250 mg IM q 2 weeks
- No significant change PSA after 1 year

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
Prostate Cancer with T therapy

- 84 y/o Gleason 6 PC, total T 400 and free T 7.4, PSA 8.5
- T gel for 21 months, PSA down to 6.2
- Dutasteride added PSA 3.8 at 24 month

5-ARI and Prostate Cancer

“Presently, there is no evidence that 5-ARIs or any other approach to prostate cancer risk reduction will reduce the risk of lethal prostate cancers.”

Dutasteride and PC

- Less positive biopsies, more high grade (Gleason 8-10) biopsies

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

Change in fat free mass


Change in Quad area


Change in squat strength

Decline in T may be responsible for Frailty syndrome

- Accelerated osteoporosis
- Decreased muscle mass
- Anemia


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
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

T and diabetes and insulin resistance

- Replacement doses decrease insulin resistance
- Supraphysiologic doses can increase insulin resistance
- Low levels of T play some role in the development of type 2 diabetes (Stellato)
- Hyperinsulinemia decreases T and TRT decreases hyperinsulinemia
- Low T associated with Syndrome X, hypertension, type 2 diabetes, fibromyalgia, CAD
**T and metabolic syndrome**

- Low levels of T have several common features with the metabolic syndrome.
- T levels were inversely associated with central obesity
- T was inversely associated with systolic BP
- Men with diabetes had lower T levels
- Inverse association between T and Hg A1C
- T may have a protective role in the development of metabolic syndrome and subsequent diabetes mellitus and cardiovascular disease in aging men
T and diabetes

- Oral TU treatment of type 2 diabetic men with androgen deficiency
- Improves glucose homeostasis and body composition – visceral fat
  - Hg Ac decreased 17.3%
  - decrease in visceral obesity
- Improves symptoms of androgen deficiency including erectile dysfunction

Potential Adverse effects

- Major side effect
  - Increased RBC’s - Erythocytosis
  - More likely with injections
  - Phlebotomy at Hct 55+
- “No testosterone-associated thromboembolic events have been reported to date.” Rhoden *NEJM*
- Gynecomastia – watch for elevated E2
- Block aromatase before E2 rises
Potential Adverse effects

- Fluid retention (rare)
- Does TRT accelerate male pattern hair loss? No info.
- Possible decrease in testicular size.
- Decreased sperm count
Management TRT

- Prior to TRT
- Comprehensive evaluation
  - Physical exam, Lab including T, Free T, SHBG, FSH, LH, Cardiac risk factors, all hormone levels, fitness evaluation, bone density, body composition, cognitive function
- Every 3-6 months for first several years:
  - T and Free or Bioavailable T, CBC, PSA, E2
  - Titrate T and E2 to stay in physiological range plus clinical optimization
- Yearly DRE
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.

If symptomatic or suboptimal on labs, does sperm count and/or testicular volume need to be maintained?

- **NO**
  - Proceed with testosterone replacement, as per algorithm.
  - Consider combination of testosterone IM and HCG 250-500 IU SQ on day 6 & 7.
  - Consider HCG treatment at 250-500 IU SQ daily. May use 5000 IU weekly if desires.

- **YES**
  - Is the FSH and/or LH elevated?
    - **YES**
      - Monitor lab values and symptoms as per algorithm
    - **NO**
      - Proceed with testosterone replacement, as per algorithm
      - Consider combination of testosterone IM and HCG 250-500 IU SQ on day 6 & 7.
      - Consider HCG treatment at 250-500 IU SQ daily. May use 5000 IU weekly if desires.
Testosterone Replacement Men -3-

Treatment
T Cream 100 mg /day
T Cypionate 100 mg/week
Other options: Pellets, HCG

Follow up in 3 months:
Testosterone, E2, H&H, DHT?

H&H > 17.5/54

NO
Continue

YES
Donate/discard 1 unit blood

E2 > 50

NO
Continue

YES
Chrysin, P4, lose fat

DHT > 100
Side effects?

NO
Continue

YES
Saw Palmetto, Progesterone

NO
Chrysin, P4, lose fat

YES
Anastrozole 0.5 mg 1-3 x per week

Dutasteride?
Treatment
- T Cream 100-200 mg/day
- T Cypionate 100-150 mg/week,
  Other options: Pellets, HCG

Follow up at 6 months:
Testosterone E2, H&H, PSA

Too high > 1000 or too low < 600?
- Titrate dose

How does patient feel on TRT?
- Libido too high? Too Aggressive? Feels worse not better? (unlikely)
  - Titrate dose

PSA velocity > 1.0/yr
- Repeat PSA Urology Consult

TRT Men -4-
Symptoms of Relative Androgen Deficiency (RAD) or testosterone deficiency?

- NO: No TRT

Is Testosterone Optimal?

- YES: Consider just DHEA RX
  - NO: RAD SX despite optimal T
    - YES: Testosterone Crea 0.5-1% 1.25 to 10 mg/day
      - NO: Consider T treatment monitoring for androgenic side effects
        - Levels optimal? or a little high? Side effects?
          - YES: Titrate dose
          - NO: Clinical response without side effects most important

Testosterone Deficiency
- Fatigue
- Low sense of well being
- Low libido
- Forgetful/memory loss
- Abdominal Fat
- Weight gain

Testosterone Excess
- Acne/Oily Skin
- Excessive Sweating
- Facial Hair
- Excess body hair growth
- Increased Libido
- Scalp hair loss
- Violent/Aggressive Behavior