

# Testosterone Replacement Therapy Male Menopause

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# Testosterone shirt

- 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

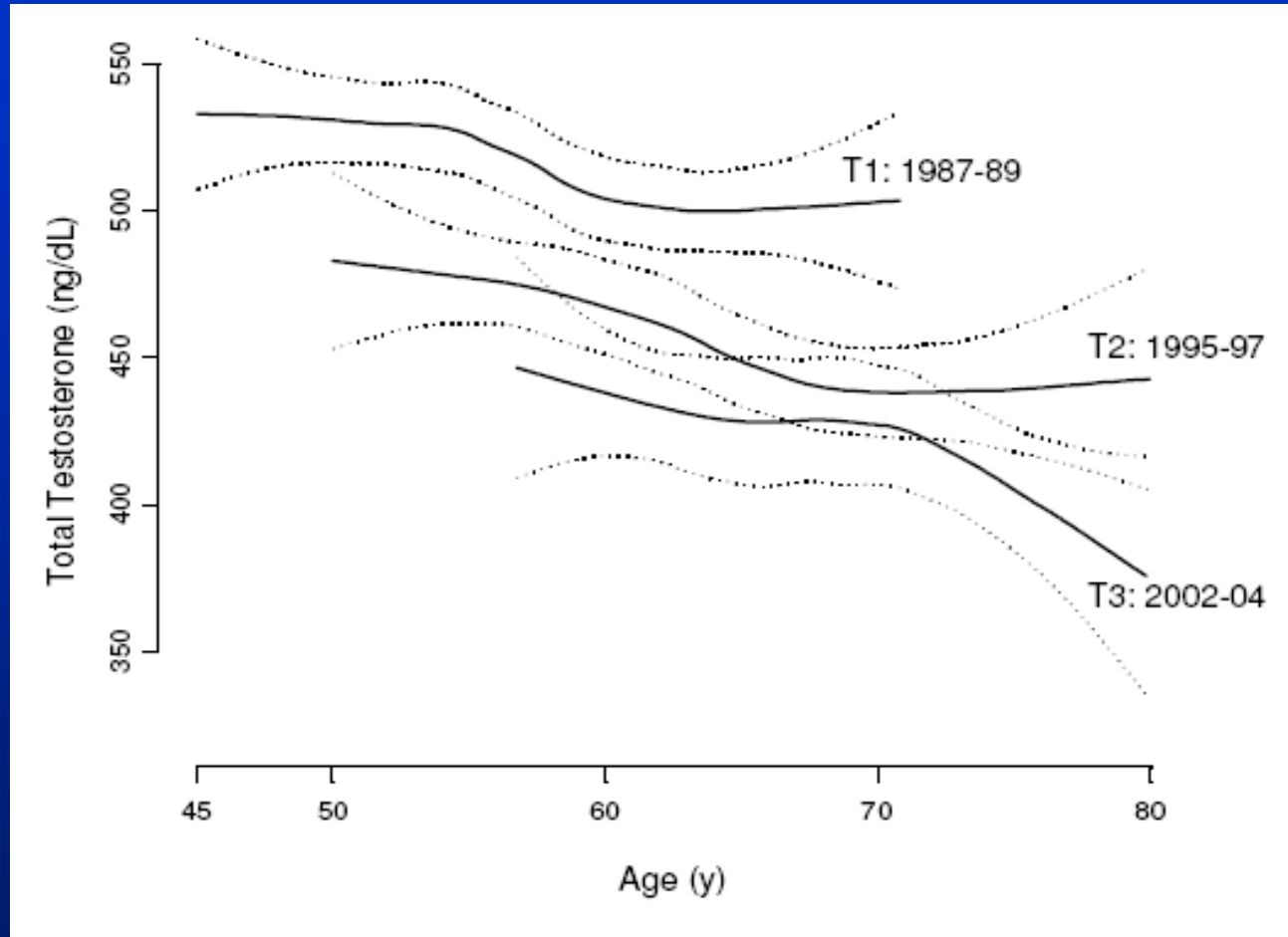


# Andropause is a deficiency disease

- 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
- Korenman SG, Morley JE, Mooradian AD, et al. 1990 Secondary hypogonadism in older men: its relationship to impotence. *J Clin Endocrinol Metab.* 71:963–969.

- 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



- Trivison TG et al. A population-level decline in serum testosterone levels in American men. *J Clin Endocrinol Metab.* 2006 Oct 24

# 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
- Khaw KT. et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men. *Circulation*. 2007;116:2694-2701

- 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
  
- Shores MM et al. Low serum testosterone and mortality in male veterans. *Arch Intern Med.* 2006 Aug 14;166(15):1660-5.

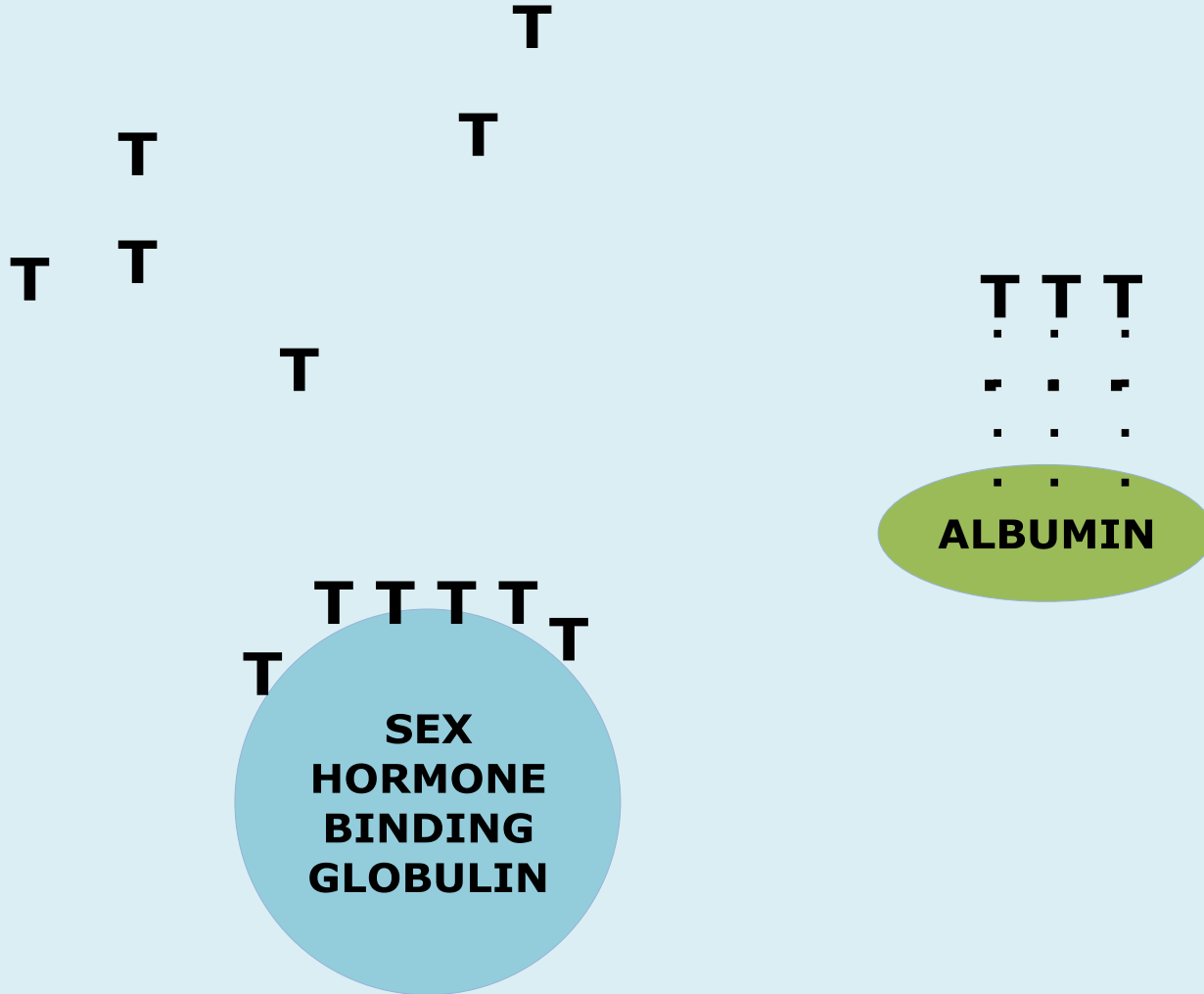
# Adjusted for age reference levels

- “Age adjusted T reference values should be eliminated”
- “Long term standing fear of stimulating prostate cancer with T is without scientific basis”
- Morgentaler, M. Guideline for Male Testosterone therapy. A clinician’s perspective. *J. Clin Endo Metab.* 92 (2) 416-417, 2007

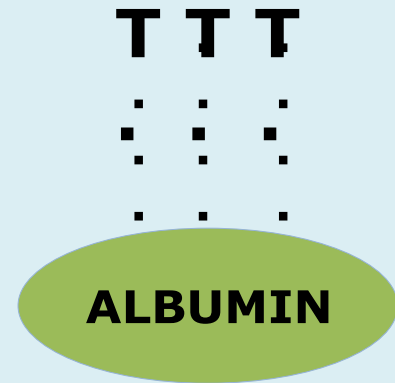
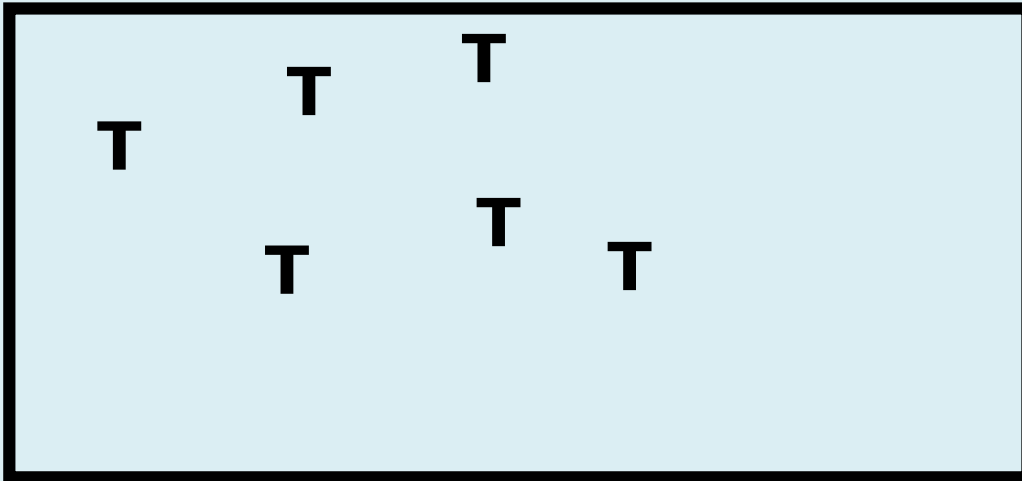
# Adverse effects of Testosterone treatment on older men

- 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

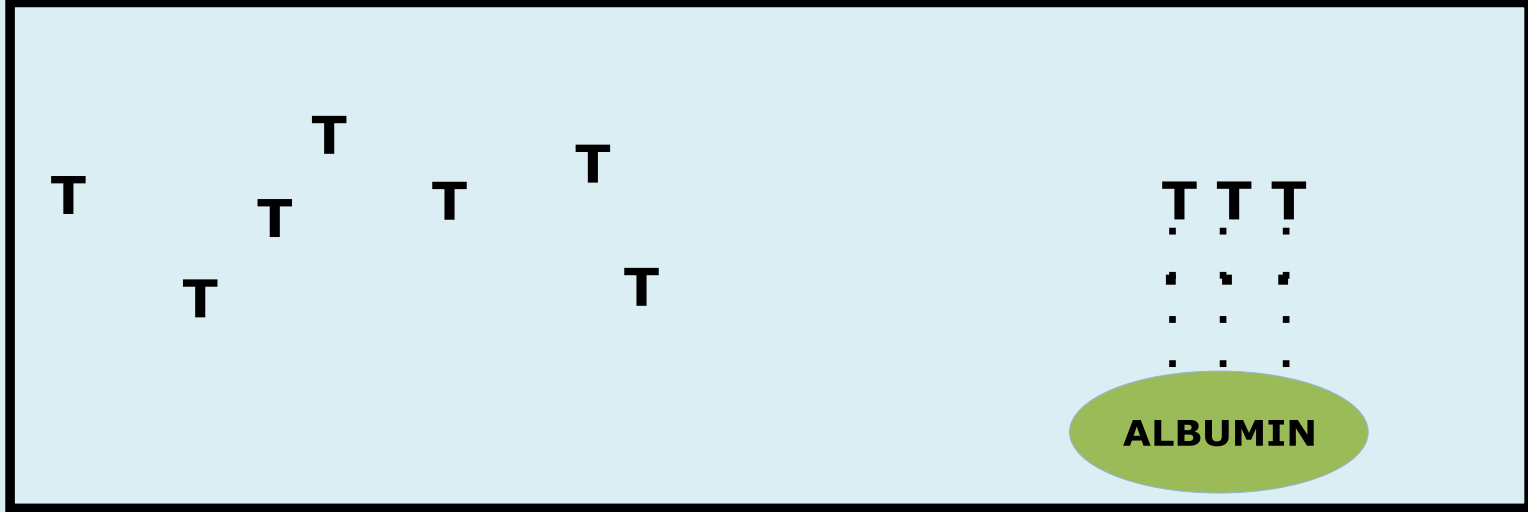
# TOTAL TESTOSTERONE



# FREE TESTOSTERONE



# BIOAVAILABLE TESTOSTERONE



# 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

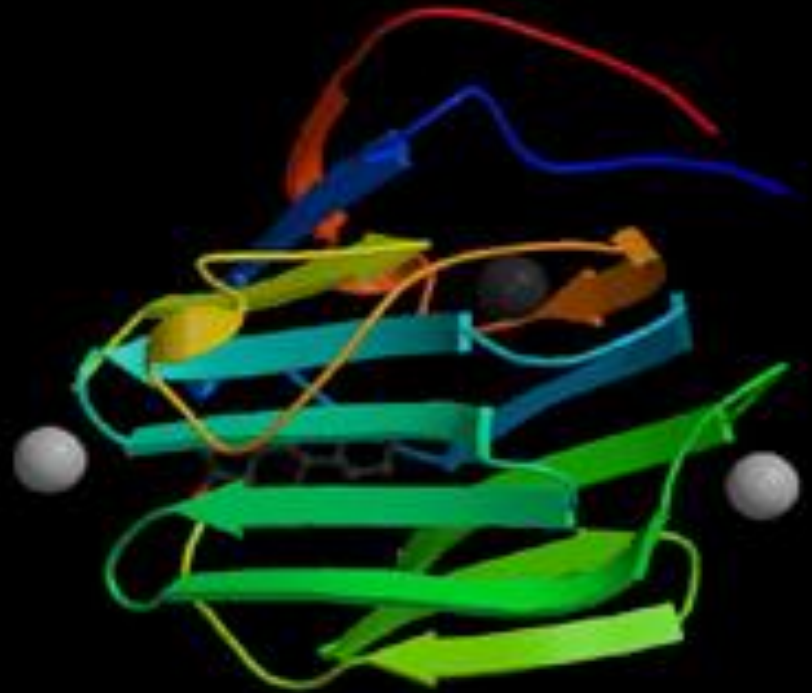
pMol/L x 0.0288 = ng/dl

“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

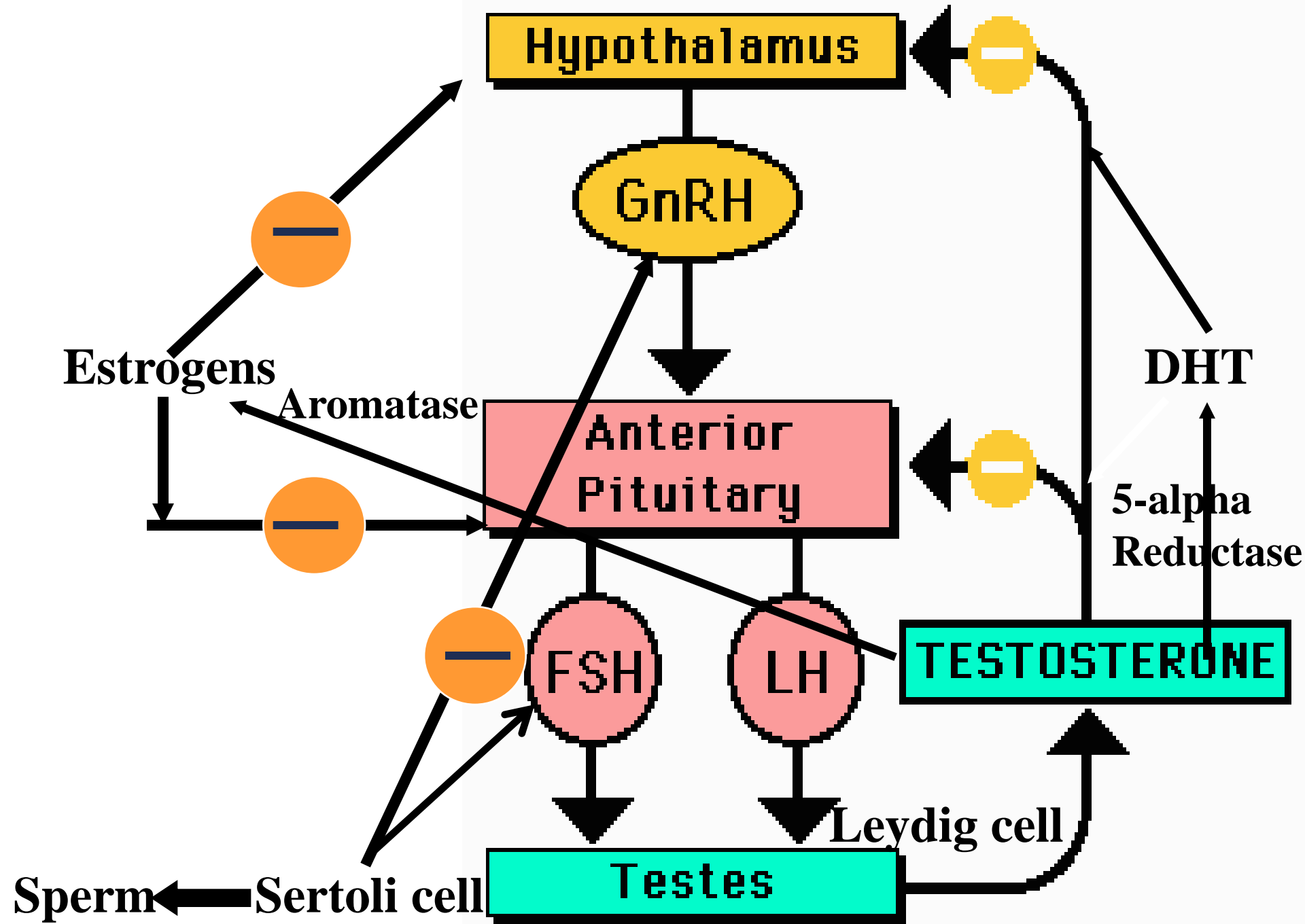
120-600 ng/dl      male

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

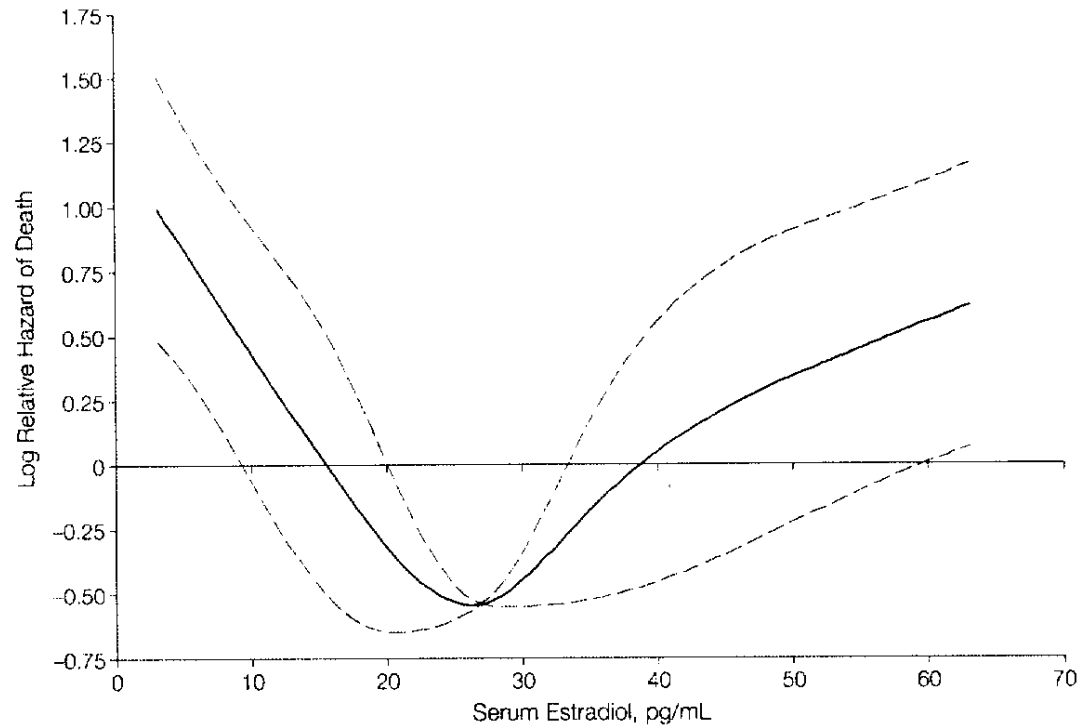
- E2 can increase with increasing T
- Do not let E2 go to 0
  - Optimal? 25 pg/ml
- Aromatase Inhibition
  - Chrysin 250 mg BID PO
  - Topical 50 mg/gm
  - Zinc 50 mg per day
  - Progesterone 5-10 mg transdermal

# 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

- Schmidt M, Renner C, Loffler G. **Progesterone inhibits glucocorticoid-dependent aromatase** induction in human adipose fibroblasts. *J Endocrinol*. 1998 Sep;158(3):401-7.
- Leder BZ et al. Effects of aromatase inhibition in elderly men with low or borderline-low serum testosterone levels. *J Clin Endocrinol Metab*. 2004 Mar;89(3):1174-80.
- Jeong, HJ et al. Inhibition of aromatase activity by **flavonoids**. *Arch Pharm Res*. 1999 Jun;22(3):309-12

**Figure 1.** Serum Estradiol by Log Relative Hazard of Death Using Cubic Splines With 5 Knots During 3-Year Follow-up in Men With Chronic Heart Failure and Reduced Left Ventricular Ejection Fraction



- Jankowska EA. Circulating estradiol and mortality in men with systolic chronic heart failure. *JAMA*. 2009 May 13;301(18):1892-901.

# T Metabolites

- 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 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
- Oettel M et al. Progesterone: the forgotten hormone in men?  
*Aging Male*. 2004 Sep;7(3):236-57

# 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
- Schubert M et al. Intramuscular testosterone undecanoate: pharmacokinetic aspects of a novel testosterone formulation during long-term treatment of men with hypogonadism. *J Clin Endocrinol Metab.* 2004 Nov;89(11):5429-34.

- 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 =  $\frac{1}{4}$  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

# 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
- Zitzmann M Hormone substitution in male hypogonadism *Mol Cell Endocrinol* 2000 Mar 30;161(1-2):73-88

- 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
- Tsujimura A et al. Treatment with human chorionic gonadotropin for PADAM: a preliminary report. *Aging Male*. 2005 Sep-Dec;8(3-4):175-9.

# 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
- Alexander GM, Swerdloff RS, Wang C, et al. Androgen-behavior correlations in hypogonadal men and eugonadal men. II. Cognitive abilities. *Hormones and Behavior* 1998; 33(2):85-94.
- Barrett-Connor E et al. Endogenous sex hormones and cognitive function in older men. *J Clin Endocrinol Metab* 1999 Oct;84(10):3681-5

# T and Alzheimer's

- TRT prevents the production of beta amyloid precursor protein. (in men)
- Gouras GK et al. Testosterone reduces neuronal secretion of Alzheimer's beta-amyloid peptides. *Proc Natl Acad Sci U S A* 2000 Feb 1;97(3):1202-5

# T Rx – Alzheimer's

- Treated group improved over 1 year
- Control group deteriorated
  
- Tan RS A pilot study on the effects of testosterone in hypogonadal aging male patients with Alzheimer's disease. *Aging Male*. 2003 Mar;6 (1):13-7.

# 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
- Chu LW et al. Bioavailable Testosterone Predicts a Lower Risk of Alzheimer's Disease in Older Men. *J Alzheimers Dis* 2010 Aug 6

# 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
- Burris A et al. A long-term, prospective study of the physiologic and behavioral effects of hormone replacement in untreated hypogonadal men. *J Androl* 1992 Jul-Aug;13(4):297-304

# T and cognitive – cerebral blood flow

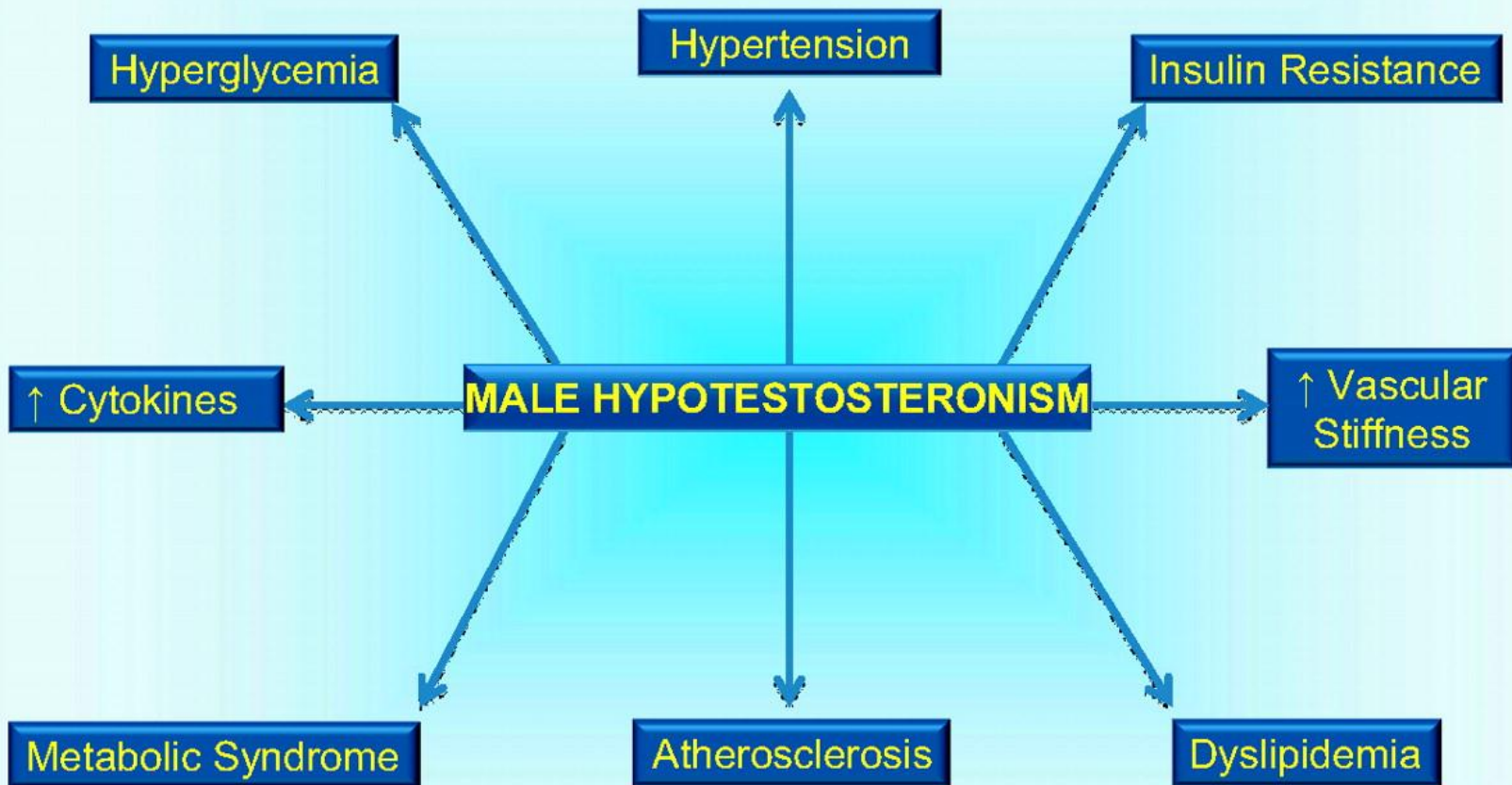
- High Free T was associated with better performance on tests of memory, executive function, and spatial ability, and with a reduced risk for Alzheimer's disease.
- Improved cerebral blood flow
- Moffat SD, Resnick SM. Long-term measures of free testosterone predict regional cerebral blood flow patterns in elderly men.  
*Neurobiol Aging*. 2006 May 11

# TBI and Sex steroids

- T suppression 100% men
  - E suppression > 40% women
  - IGF-1 suppression 77%
  - GH non-measurable 38%
- 
- Wagner J et al. Acute Gonadotroph and Somatotroph Hormonal Suppression after Traumatic Brain Injury. *J Neurotrauma*. 2010 Mar 9.

# T and cardiovascular risk

- 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
- English KM et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina : A randomized, double-blind, placebo-controlled study. *Circulation* 2000 Oct 17;102(16):1906-11

# 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.”
- Rosano GM et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation* 1999 Apr 6;99(13): 1666-70

# T and coronary blood flow

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

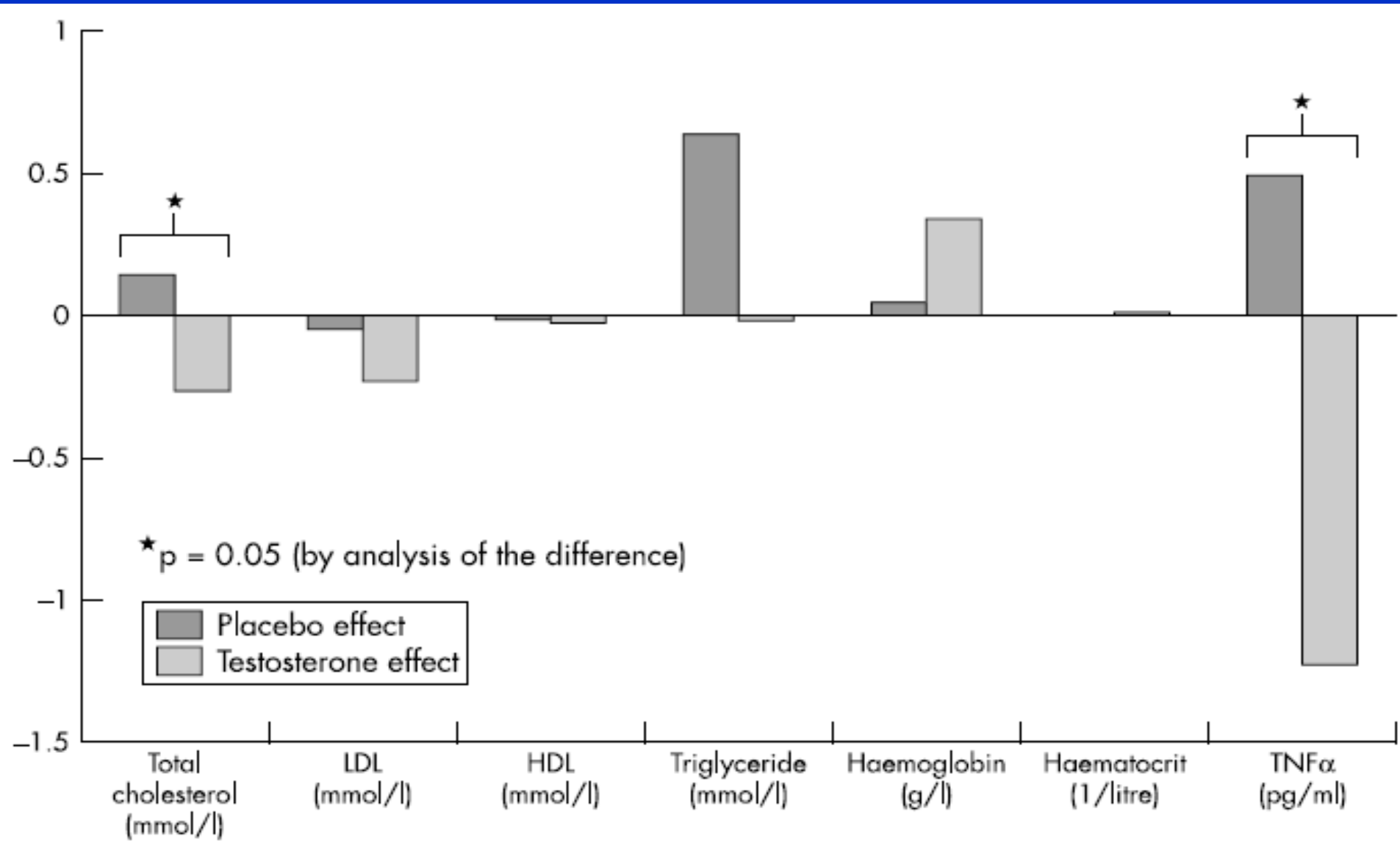
- Webb CM et al. Effects of testosterone on coronary vasomotor regulation in men with coronary heart disease. *Circulation*. 1999 Oct 19;100(16):1690-6.

# T improves cardiac function

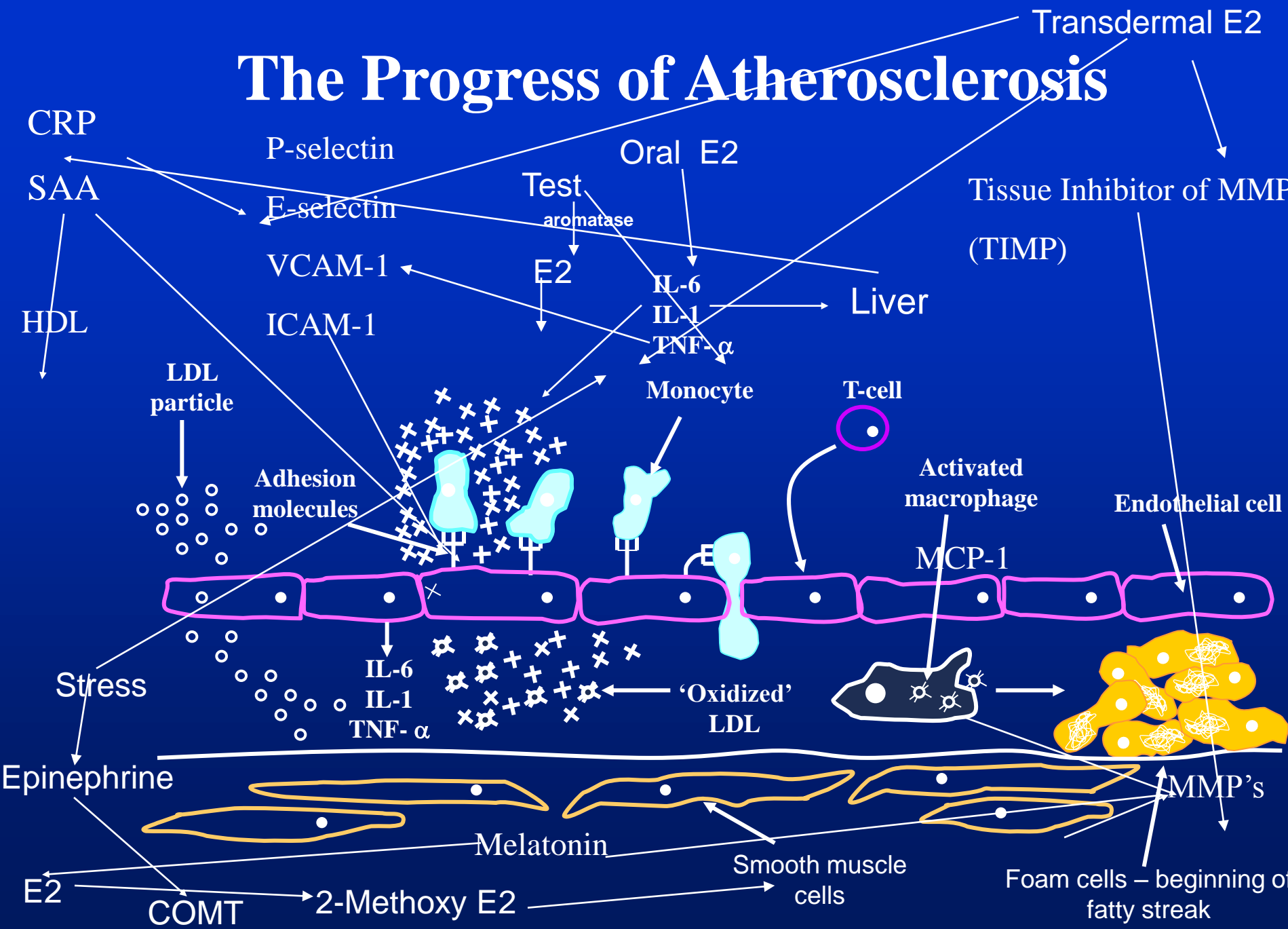
- Low testosterone in the older man may have adverse effects on atherosclerosis
- Explains the higher incidence of coronary heart disease in the male
- Vasodilates
- Improves exercise tolerance
- Improves angina threshold
  
- Channer KS, Jones TH Cardiovascular effects of testosterone: implications of the "male menopause"? *Heart*. 2003 Feb;89(2):121-2.

# T replacement and inflammation

- Less inflammatory cytokines TNF, IL-1beta
- More anti-inflammatory cytokines IL-10
- Lower total cholesterol
- Malkin CJ et al. The effect of testosterone replacement on endogenous inflammatory cytokines and lipid profiles in hypogonadal men *J Clin Endocrinol Metab.* 2004 Jul;89(7):3313-8.
- Malkin CJ et al. Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart.* 2004 Aug;90(8):871-6.



# The Progress of Atherosclerosis



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



p53

Angio-tensin II

EPA, DHA from Fish OIL

Pain

PGE2:  
Pain  
Cancer  
Skin aging

TXA2  
Athero-sclerosis

# CHF treated with Testosterone Undecanoate

- Improved exercise capacity
- Improved muscle performance
- Improved insulin resistance
- Caminiti G et al. Effect of long-acting testosterone treatment on functional exercise capacity, skeletal muscle performance, insulin resistance, and baroreflex sensitivity in elderly patients with chronic heart failure a double-blind, placebo-controlled, randomized study. *J Am Coll Cardiol.* 2009 Sep 1;54(10):919-27.

# 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
- Malkin CJ et al. Testosterone therapy in men with moderate severity heart failure: a double-blind randomized placebo controlled trial. *Eur Heart J*. 2005 Aug 10

# 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
- Turhan S et al. The association between androgen levels and premature coronary artery disease in men. *Coron Artery Dis.* 2007 May;18(3):159-62.

# BP and T: inverse relationship

- Khaw KT, Barrett-Connor EJ. Blood pressure and endogenous testosterone in men: an inverse relationship. *Hypertens.* 1988 Apr;6(4):329-32.

# T and BPH

- “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  
Endogenous Hormones and Prostate Cancer Collaborative Group . *J Natl Cancer Inst* 2008 100: 170-183

# Estrone and Prostate Cancer

- Only Estrone associated with PC
- Daniels N et al. Sex Hormones and the Risk of Incident Prostate Cancer *Urology*. 2010 May 6.

# 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
  
- Gould DC, Kirby RS. Testosterone replacement therapy for late onset hypogonadism: what is the risk of inducing prostate cancer? *Prostate Cancer Prostatic Dis.* 2006;9(1):14-8.

# TRT and PC over 15 years

- 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
- Morgantaler A. Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth. *Eur Urol.* 2006 Jul 26;

- 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
- Marks LS et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial *JAMA*. 2006 Nov 15;296(19):2369-71.

# TRT and PSA

- Pts with ED and hypogonadism
- T 250 mg IM q 2 weeks
- No significant change PSA after 1 year
  
- El-Sakka AI et al. Prostatic specific antigen in patients with hypogonadism: effect of testosterone replacement. *J Sex Med.* 2005 Mar;2(2):235-40.

# 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
- Pantuck AJ et al. Phase II Study of Pomegranate Juice for Men with Rising Prostate-Specific Antigen following Surgery or Radiation for Prostate Cancer. *Clin Cancer Res.* 2006 Jul 1;12(13):4018-4026.

# 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
  
- Agarwal PK et al. Testosterone replacement therapy after primary treatment for prostate cancer. *J Urol.* 2005 Feb;173(2):533-6.

# 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
- Sarosdy MF. Testosterone replacement for hypogonadism after treatment of early prostate cancer with brachytherapy. *Cancer*. 2007 Feb 1;109(3):536-41.

# 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

Morgentaler A. et al Two years of testosterone therapy associated with decline in prostate-specific antigen in a man with untreated prostate cancer. *J Sex Med.* 2009 Feb;6(2):574-7.

# 5-ARI and Prostate Cancer

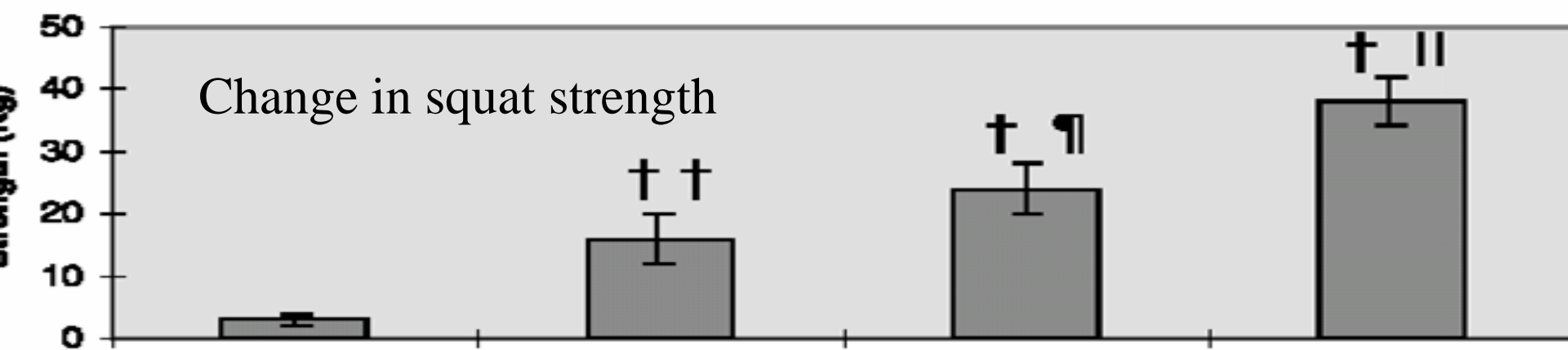
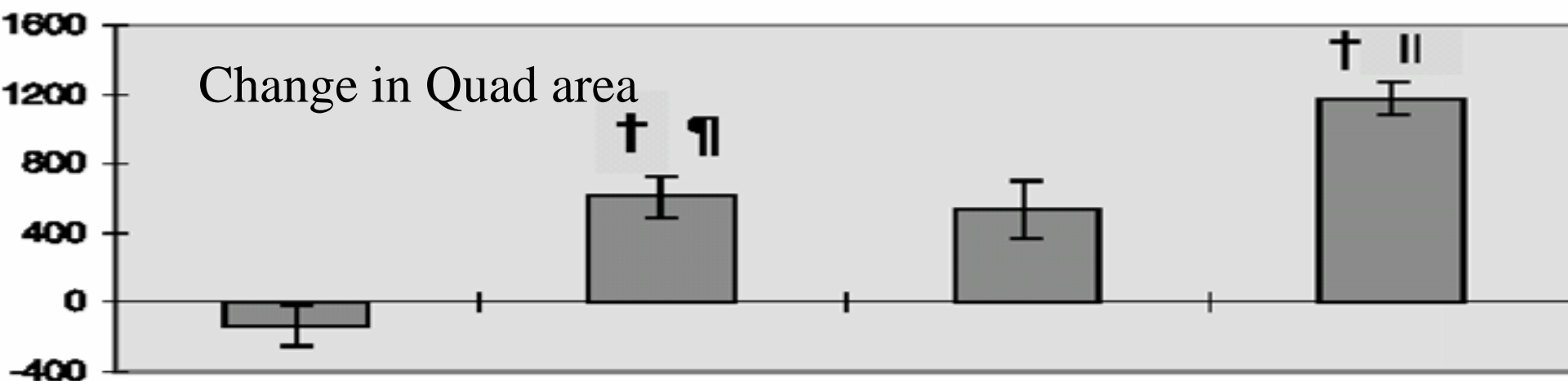
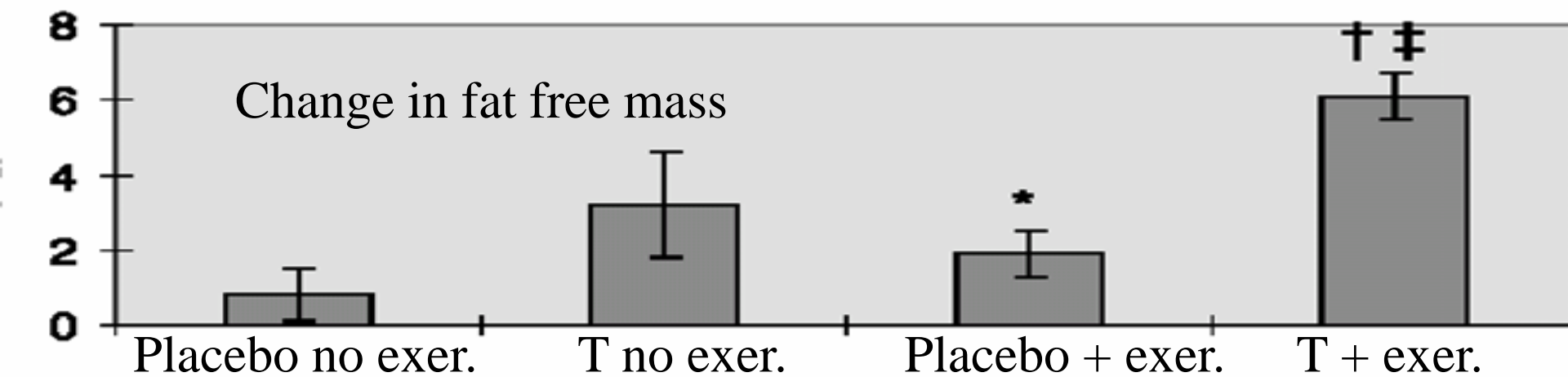
- “Presently, there is no evidence that 5-ARIs or any other approach to prostate cancer risk reduction will reduce the risk of lethal prostate cancers.”
- Rittmaster RS et al. Pharmacological approaches to reducing the risk of prostate cancer. *Eur Urol.* 2009 May;55(5):1064-73.

# Dutasteride and PC

- Less positive biopsies, more high grade (Gleason 8-10) biopsies
- Andriole GL et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med*. 2010 Apr 1;362(13):1192-202.

# 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
  
- Bhasin S. The dose-dependent effects of testosterone on sexual function and on muscle mass and function. *Mayo Clin Proc.* 2000 Jan;75 Suppl:S70-5



# Decline in T may be responsible for Frailty syndrome

- Accelerated osteoporosis
- Decreased muscle mass
- Anemia

Morley JE, Solomon DH. 1990 The new geriatrics.  
*J Am Geriatr Soc.* 38:1373–1378.

Nunez AA. 1982 Dose dependent effects of  
testosterone on feeding and body weight in  
male rats. *Behav Neurol Biol.* 34:445–449.

Vermeulen A. 1991 Androgens in the aging male.  
*J Clin Endocrinol Metab.* 73:221–224.

# Lower Free 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
- Hyde, Zoe et al. Low Free Testosterone Predicts Frailty in Older Men: The Health in Men Study. *JCEM* Vol 95, No 7.p 3165-3172.

# 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
- Muniyappa R et al. Long-Term Testosterone Supplementation Augments Overnight Growth Hormone Secretion in Healthy Older Men. *Am J Physiol Endocrinol Metab.* 2007

# 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
- Svartberg J. Epidemiology: testosterone and the metabolic syndrome. *Int J Impot Res.* 2006 Jul 20

# 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
- Boyanov MA et al. Testosterone supplementation in men with type 2 diabetes, visceral obesity and partial androgen deficiency. *Aging Male*. 2003 Mar;6(1):1-7.

# Potential Adverse effects

- Major side effect
  - Increased RBC's - Erythrocytosis
  - 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.
- Sinha-Hikim I et al. Effects of testosterone supplementation on skeletal muscle fiber hypertrophy and satellite cells in community-dwelling older men. *J Clin Endocrinol Metab.* 2006 Aug;91(8):3024-33.

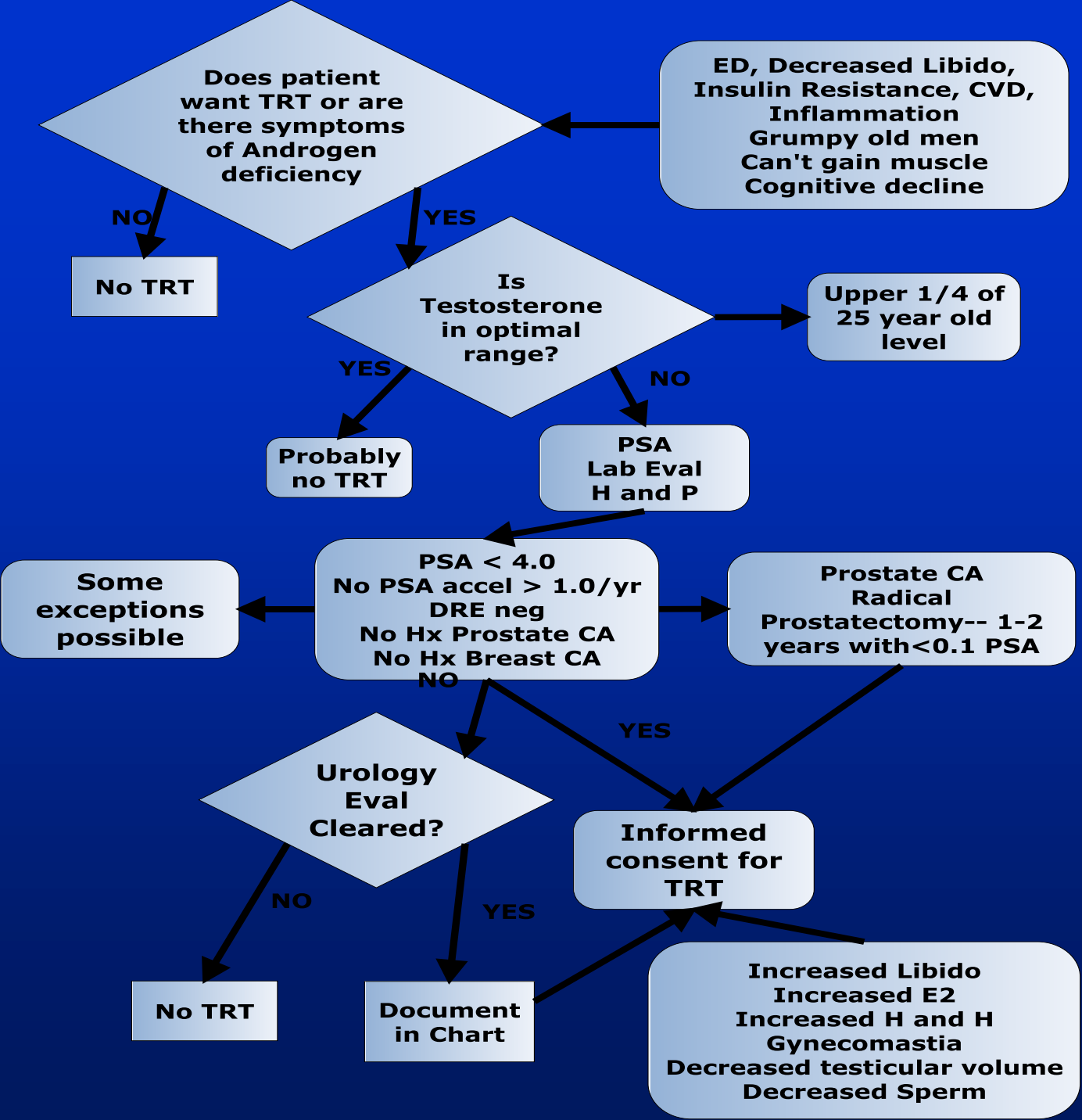
# T Rx Increases EPC's

- 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

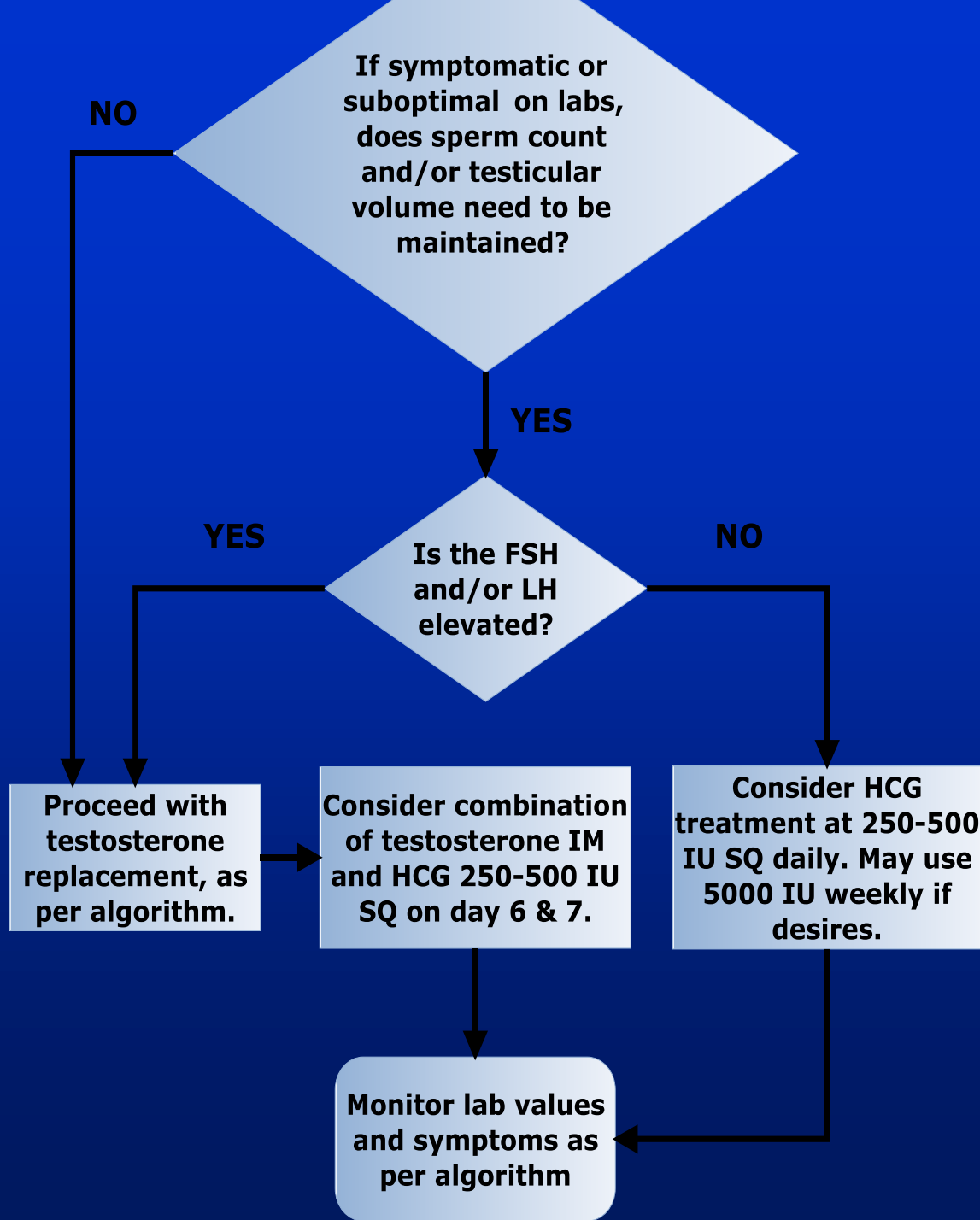
# T and ED and EPC (Stem cells)

- 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.
  
- Caretta N et al. Erectile dysfunction in aging men: testosterone role in therapeutic protocols. *J Endocrinol Invest.* 2005;28 (11 Suppl Proceedings):108-11

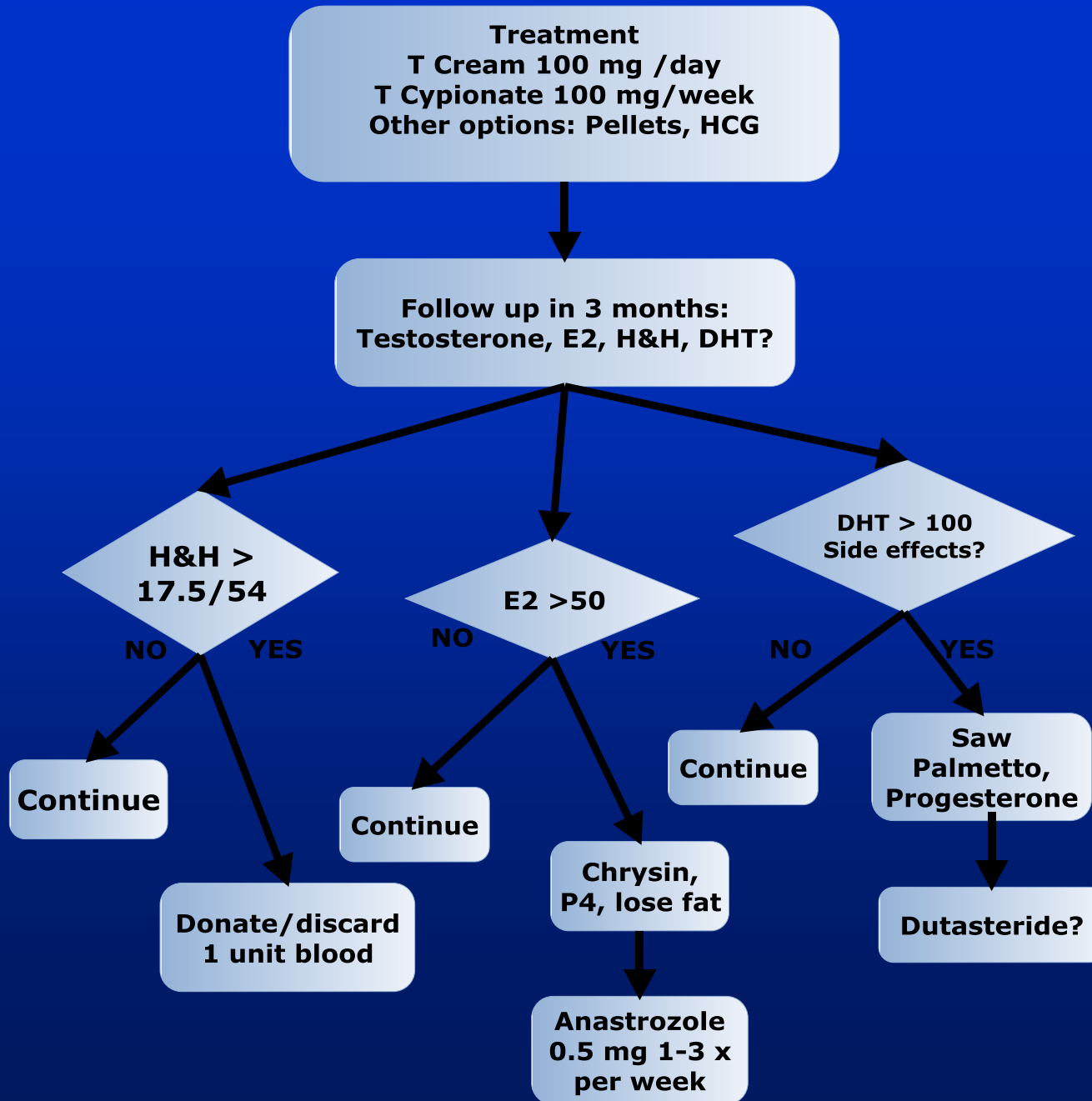
# TRT MEN



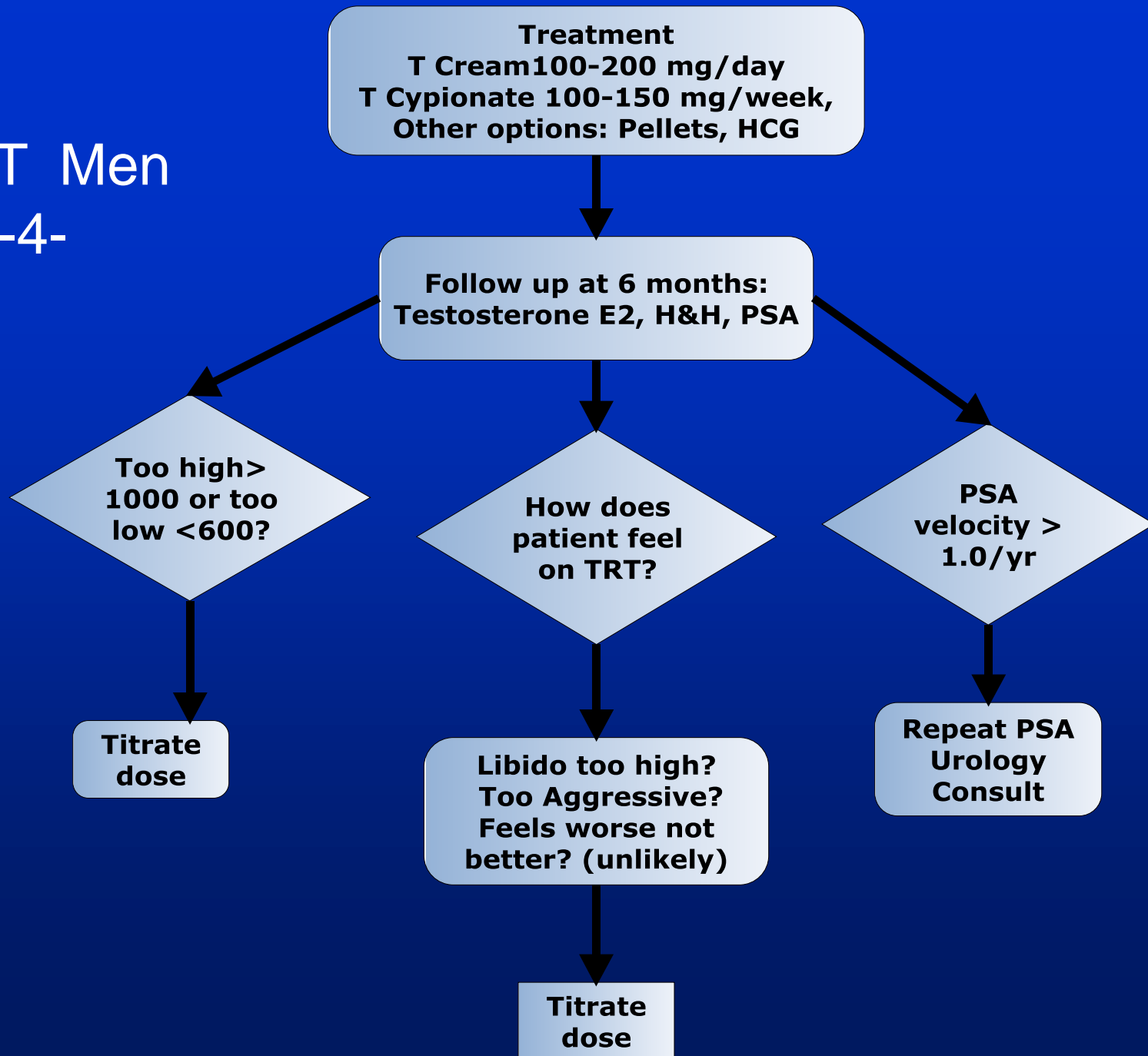
**TRT  
MEN-2**



# Testosterone Replacement Men -3-



TRT Men  
-4-



**6-12 Month  
TRT check**

**DRE  
Abnormal?**

**Failure to  
increase Free T  
on cream?**

**Urology  
consult**

**DHT not T  
increase? Use  
another method  
of treatment**

**Clinical  
Response?**

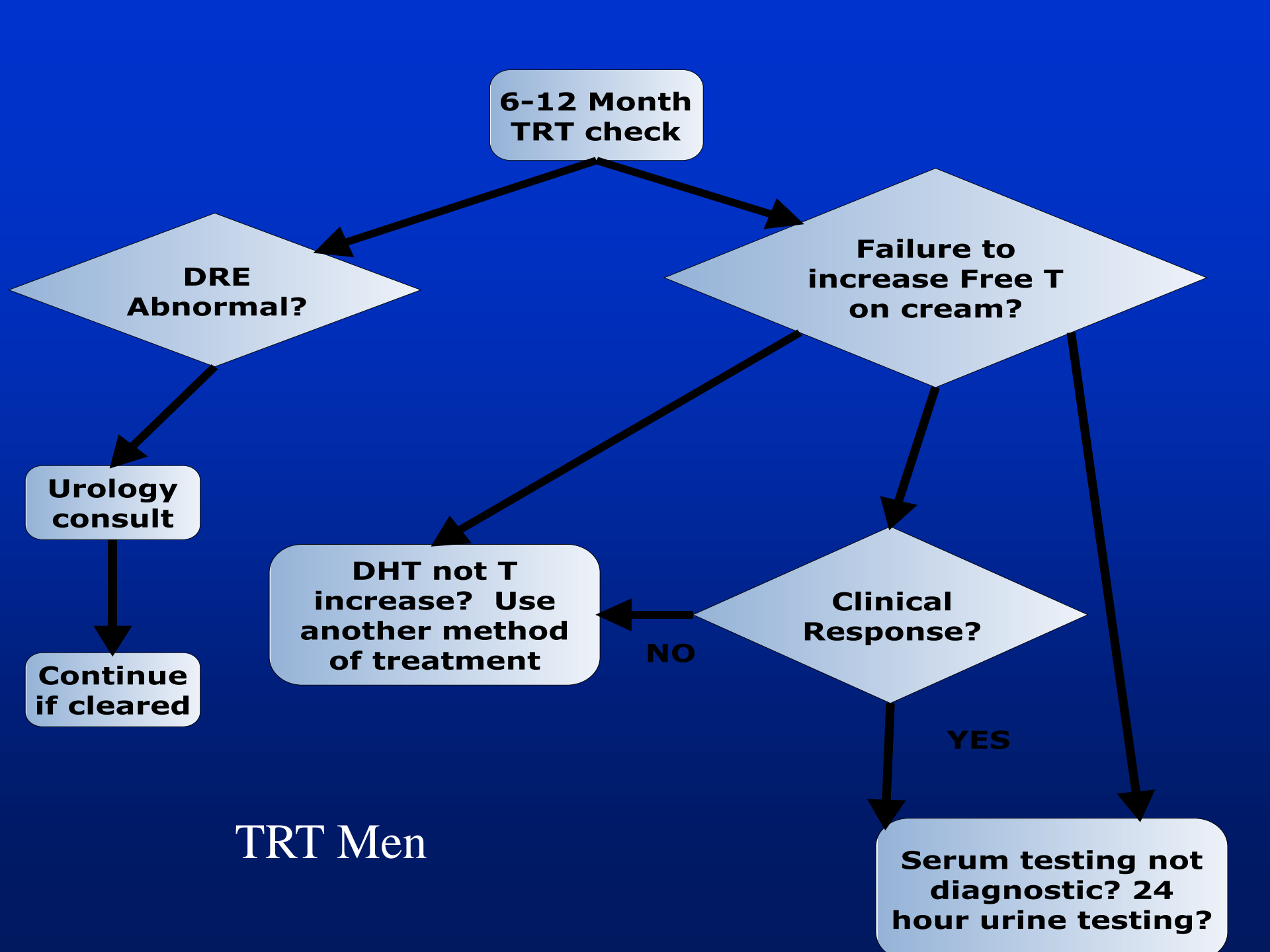
**Continue  
if cleared**

**NO**

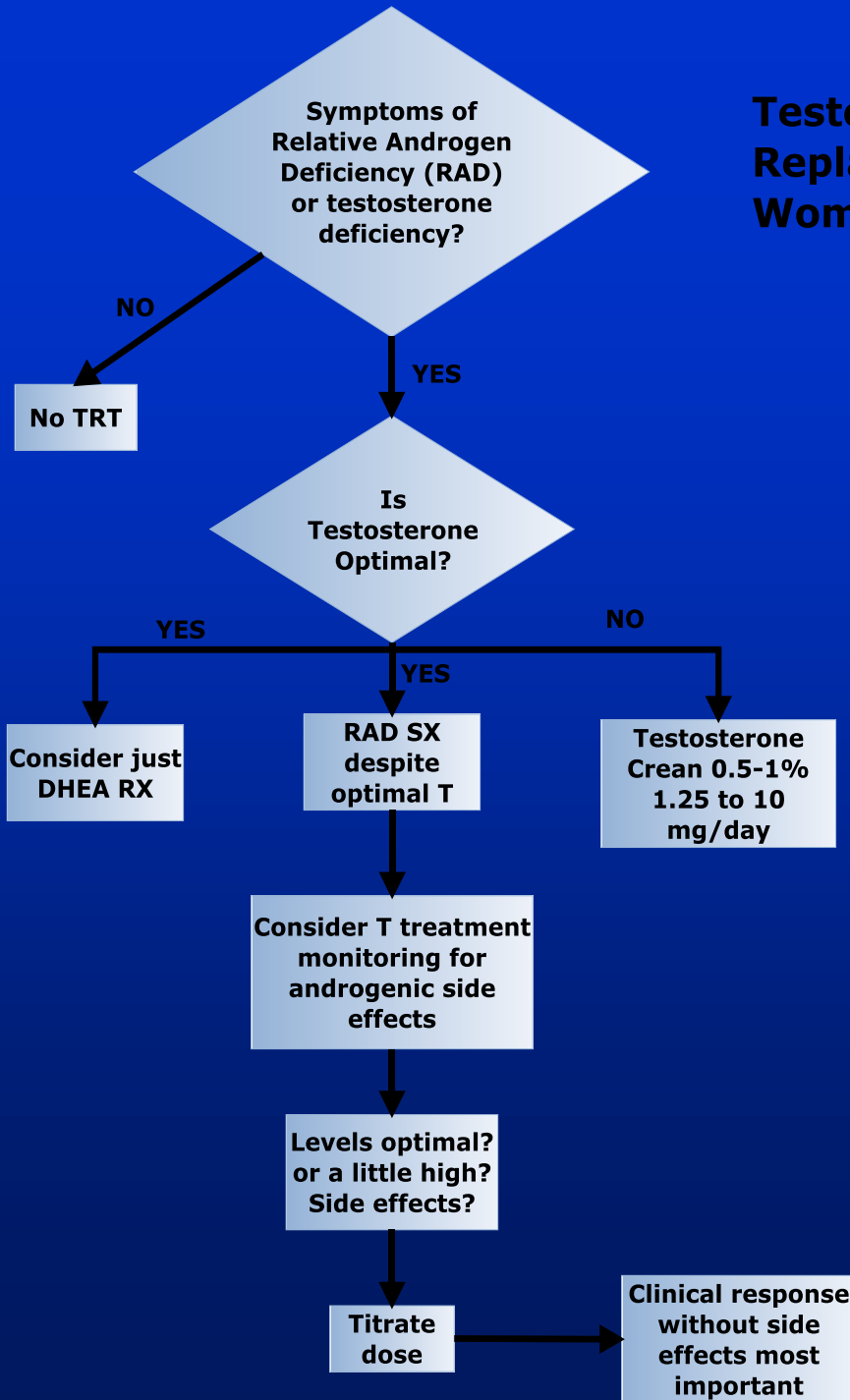
**YES**

**Serum testing not  
diagnostic? 24  
hour urine testing?**

**TRT Men**



# Testosterone Replacement Women



**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