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

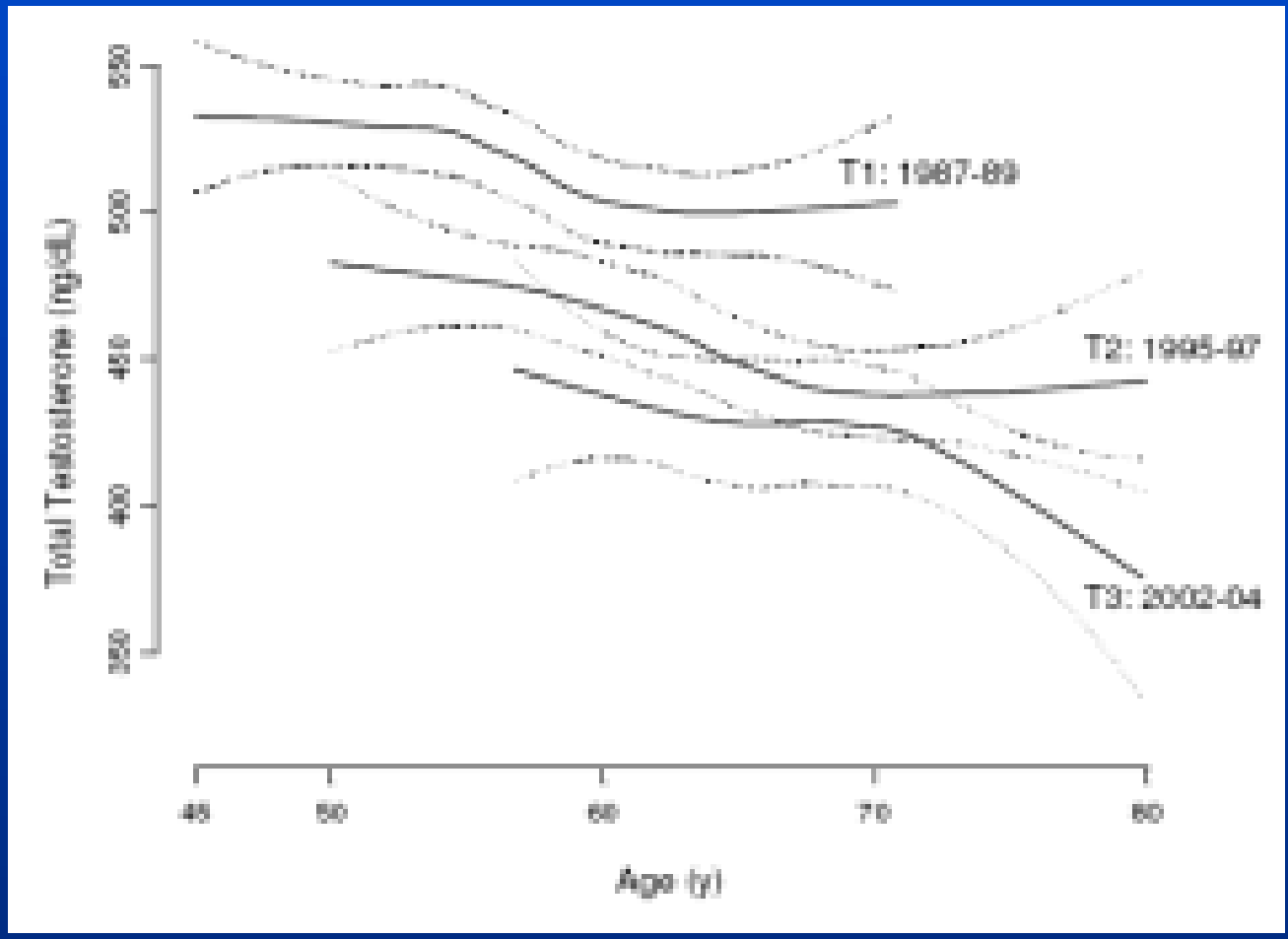
- Half of healthy men between the ages of 50–70 yr will have a BT level below the lowest level seen in healthy men who are 20–40 yr of age

- 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.

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



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

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
- 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

Testosterone treatment and Mortality

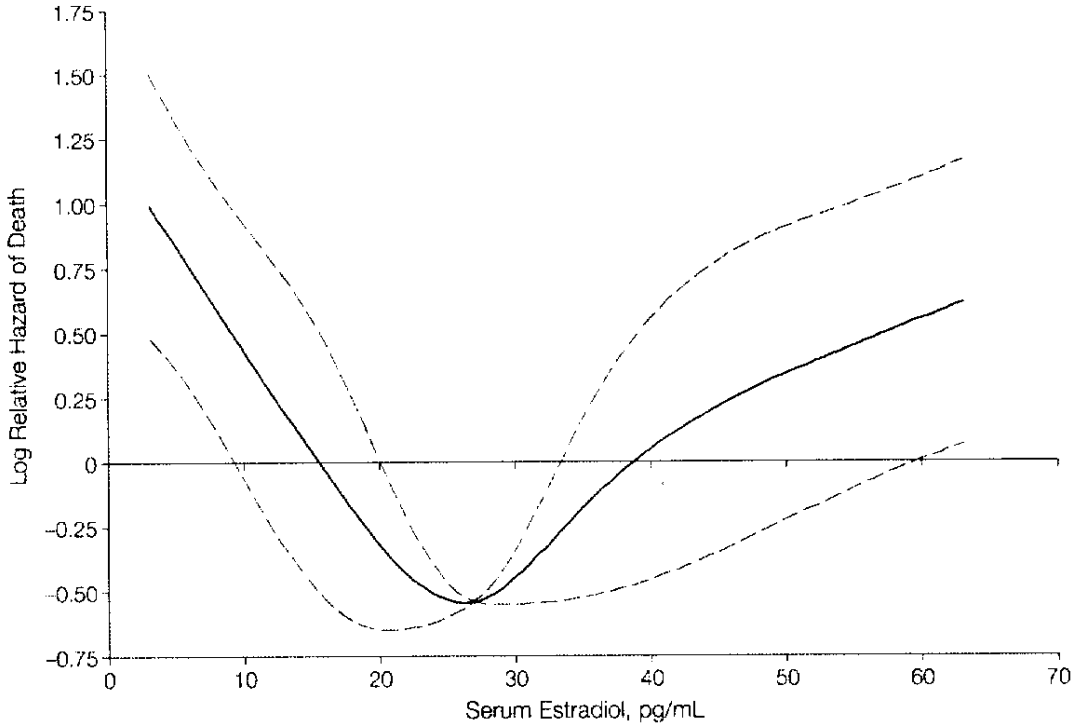
- 1000 male veterans , > 40 years old, 4 years Rx
- Total test < 250
- 400 treated with testosterone
- Mortality treated 10% vs. 20% controls
- p < .00001

- 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

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._

Body Composition/Sexual Function

- Finkelstein JS et al. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013 Sep 12;369(11):1011-22
- Handelsman D. Mechanisms of action of testosterone--unraveling a Gordian knot. *N Engl J Med.* 2013 Sep 12; 369(11):1058-9.

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

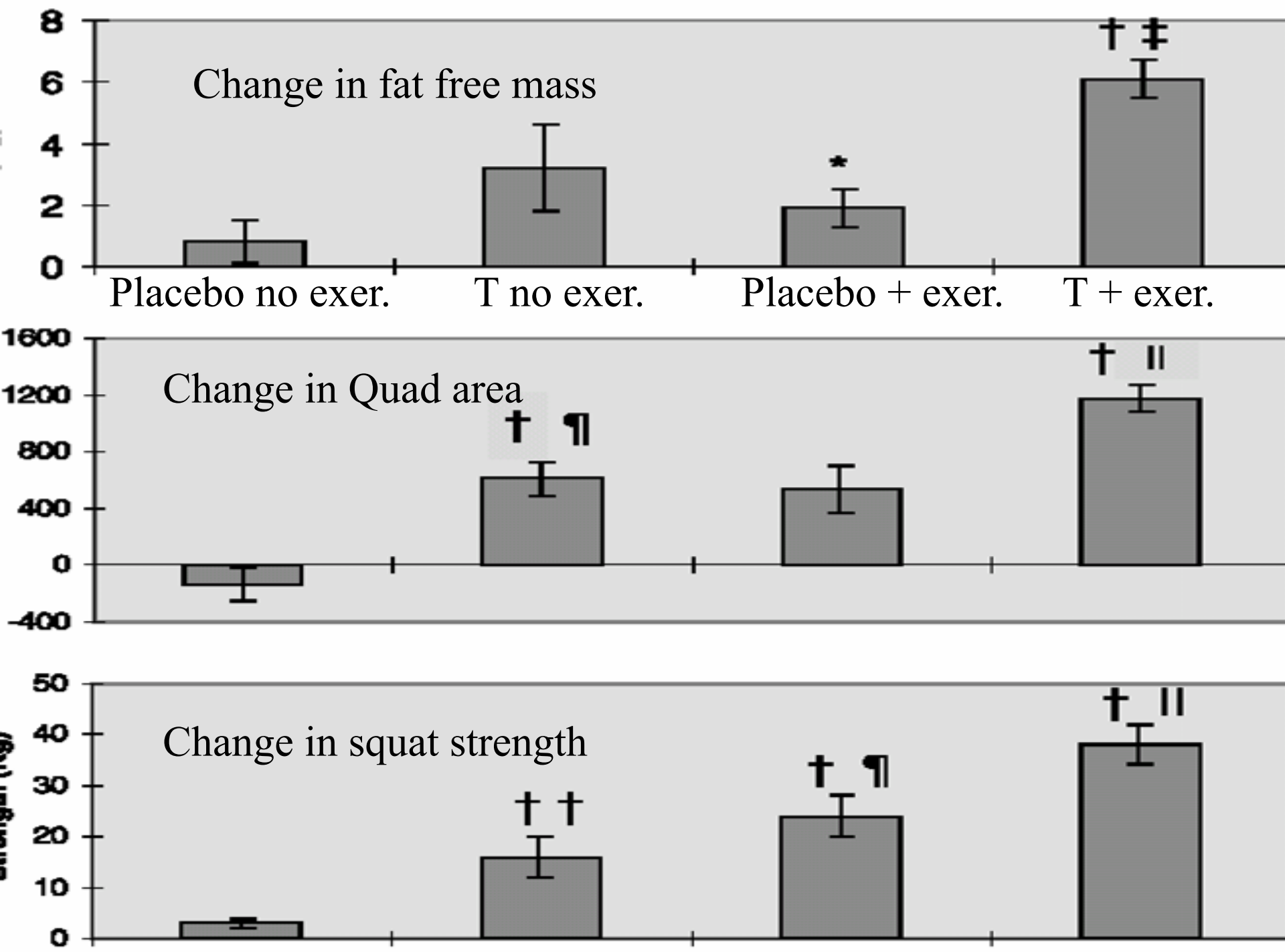
Analysis:

- 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

- 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


Change in fat free mass
8
6
4
2
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*
Placebo no exer.
T no exer.
Placebo + exer.
T + exer.
Change in Quad area
1600
1200
800
400
0
-400
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Change in squat strength
50
40
30
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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.

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.

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

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

T Therapy and CV risk

- "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."

- Morgantaler, A et al. Testosterone Therapy and Cardiovascular Risk:Advances and Controversies. *Mayo Clin Proc*. February 2015;90(2):224-251

JAMA Testosterone study 2013

- Vigen R et al. Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels. *JAMA*. 2013 Nov 6;310(17):1829-36.

JAMA Testosterone 2013

- 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

- 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

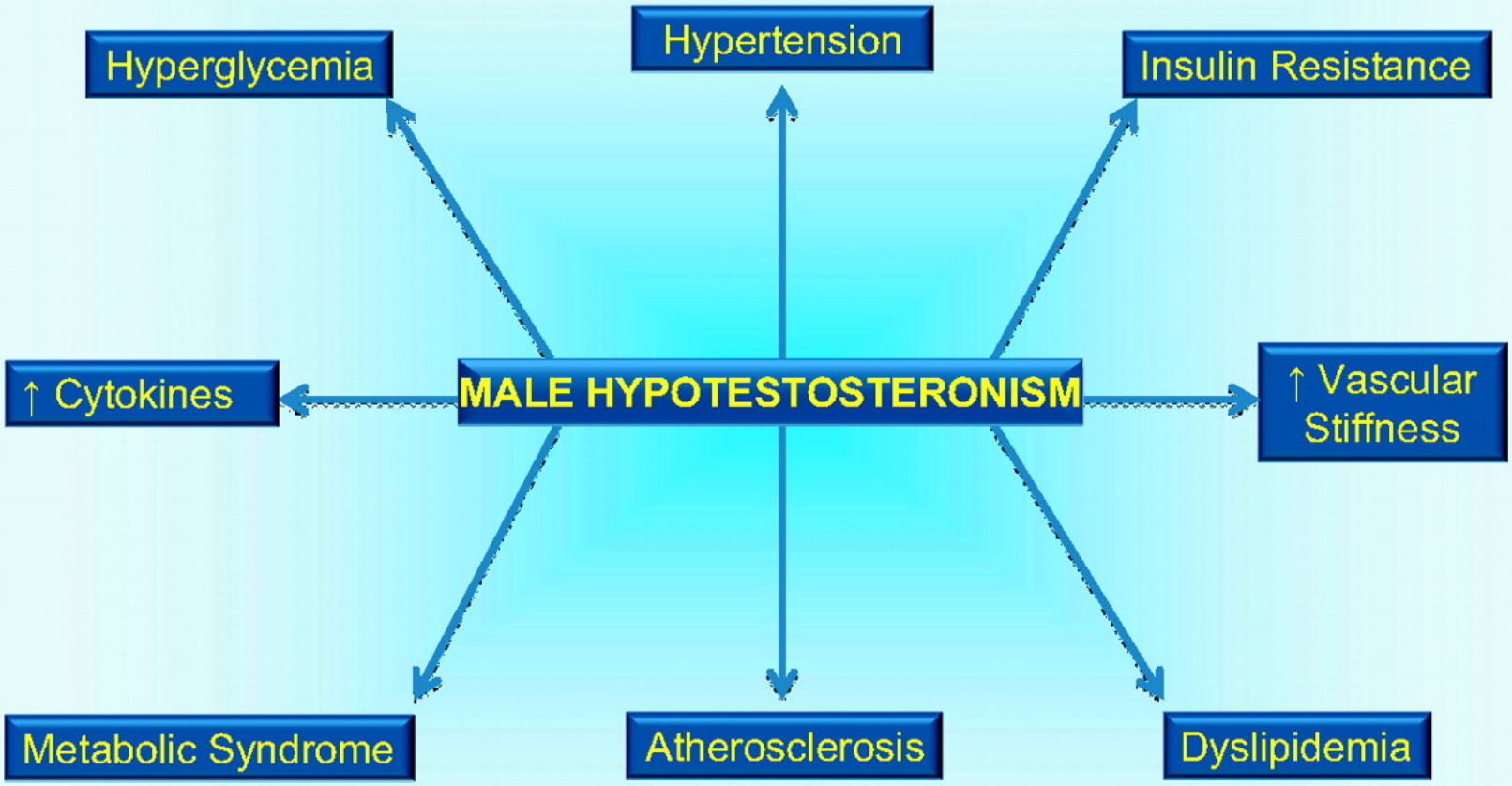
- ICD-9 study, patients not seen or interviewed
- No info on fatal MI or cardiovascular mortality or all cause mortality
- No information on testosterone serum levels before or after therapy

- 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 there of

- 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

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

- Shores MM, Moceri VM, Gruenewald DA, et al. Low testosterone is associated with decreased function and increased mortality risk: a preliminary study of men ina geriatric rehabilitation unit. J Am Geriatr Soc 2004;52:2077e81.
- Khaw KT, Dowsett M, Folkerd E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. Circulation 2007;116:2694e701.
- Shores MM, Matsumoto AM, Sloan KL, et al. Low serum testosterone and mortality in male veterans. Arch Intern Med 2006;166:1660e5.
- Laughlin GA, Barrett-Connor E, Bergstrom J. Low serum testosterone and mortality in older men. J Clin Endocrinol Metab 2008;93:68e75


Hyperglycemia
Hypertension
Insulin Resistance
↑ Cytokines
MALE HYPOTESTOSTERONISM
↑ Vascular Stiffness
Metabolic Syndrome
Atherosclerosis
Dyslipidemia

T and premature CAD

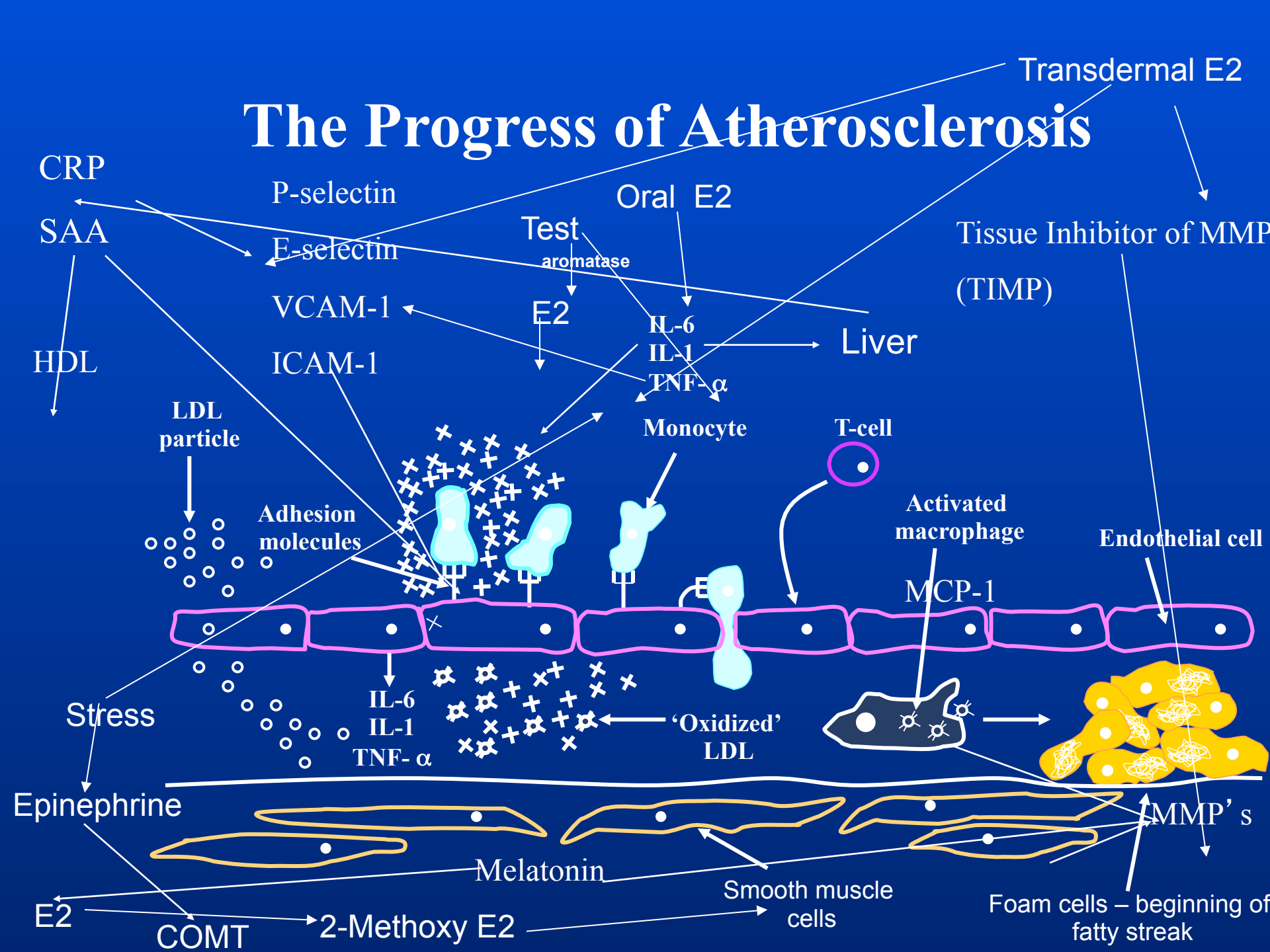
- TT and FT levels of men < 45 yo with coronary artery disease were significantly lower than those of controls
- FT levels below of 17.3 pg/ml
- 3.3 x risk of premature CAD
- Turhan S et al. The association between androgen levels and premature coronary artery disease in men. *Coron Artery Dis*. 2007 May; 18(3):159-62.

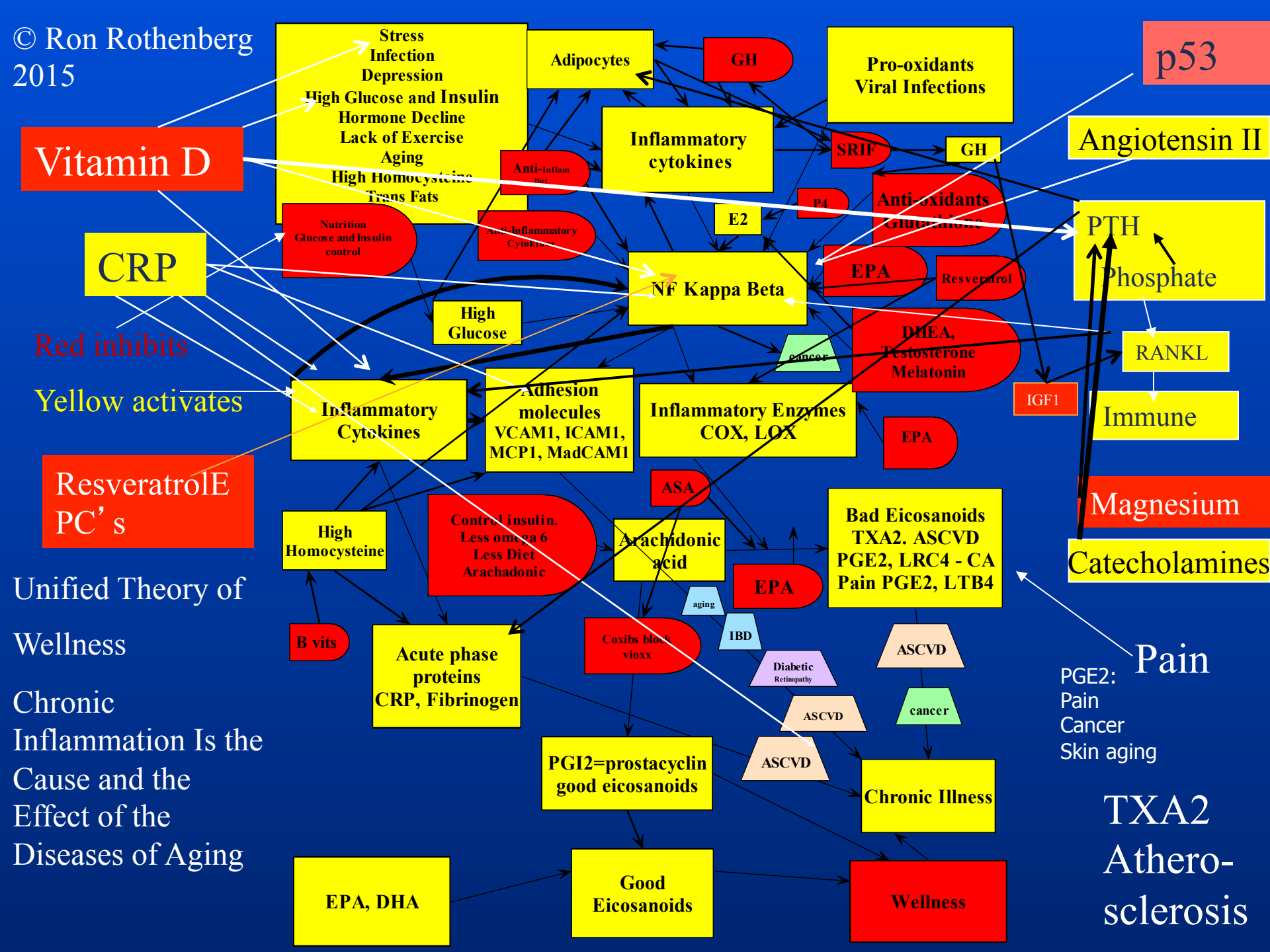
BP and T: inverse relationship

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

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


Transdermal E2
The Progress of Atherosclerosis
CRP
SAA
HDL
P-selectin
E-selectin
VCAM-1
ICAM-1
Test
aromatase
E2
Oral E2
IL-6
IL-1
TNF- α
Liver
Tissue Inhibitor of MMP
(TIMP)
LDL particle
Adhesion molecules
Monocyte
T-cell
Activated macrophage
MCP-1
Endothelial cell
Stress
IL-6
IL-1
TNF- α
'Oxidized' LDL
Epinephrine
MMP' s
Melatonin
E2
COMT
2-Methoxy E2
Smooth muscle cells
Foam cells – beginning of fatty streak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Vitamin D
CRP
Red inhibits
Yellow activates
ResveratrolE PC's
Unified Theory of Wellness
Chronic Inflammation Is the Cause and the Effect of the Diseases of Aging
Stress
Infection
Depression
High Glucose and Insulin
Hormone Decline
Lack of Exercise
Aging
High Homocysteine
Trans Fats
Adipocytes
GH
Pro-oxidants
Viral Infections
p53
Angiotensin II
Inflammatory cytokines
SRIF
GH
Anti-Inflam Diet
Nutrition Glucose and Insulin control
Anti-Inflammatory Cytokines
P4
E2
Anti-oxidants Glutathione
PTH
Phosphate
EPA
Resveratrol
NF Kappa Beta
High Glucose
DHEA, Testosterone Melatonin
RANKL
cancer
IGF1
Immune
Inflammatory Cytokines
Adhesion molecules VCAM1, ICAM1, MCP1, MadCAM1
Inflammatory Enzymes COX, LOX
EPA
ASA
Magnesium
Catecholamines
High Homocysteine
Control insulin. Less omega 6 Less Diet Arachadonic
Arachidonic acid
Bad Eicosanoids TXA2. ASCVD PGE2, LRC4 - CA Pain PGE2, LTB4
EPA
aging
IBD
B vits
Coxibs block vioxx
Acute phase proteins CRP, Fibrinogen
Diabetic Retinopathy
ASCVD
cancer
ASCVD
ASCVD
PGI2=prostacyclin good eicosanoids
Chronic Illness
Pain
PGE2:
Pain
Cancer
Skin aging
EPA, DHA
Good Eicosanoids
Wellness
TXA2
Athero-
sclerosis

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.
- Ahmad Haider et al. Incidence of Prostate Cancer in Hypogonadal Men Receiving Testosterone Therapy: Observations from Five Year-median Follow-up of Three Registries. *The Journal of Urology*, Volume 193/Issue 1 (January 2015)

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

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 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
- Feneley MR et al. Is testosterone treatment good for the Prostate? Study of safety during long term treatment. *Journal of Sex Med* 2012; June 6

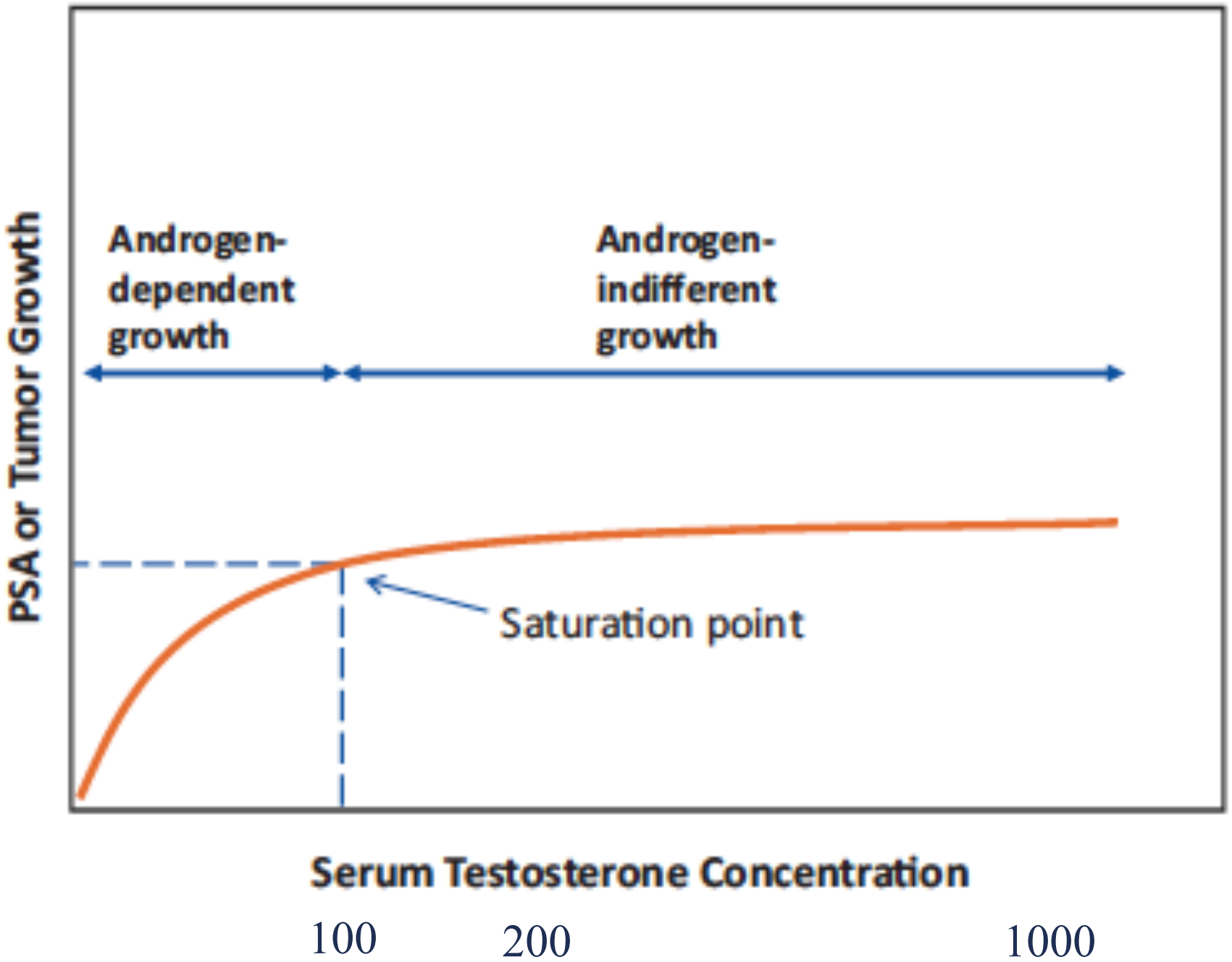
History of “T causes PC” myth

- 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
- 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”


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
- 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.

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

- Morgentaler A et al. A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications. *Eur Urol.* 2013 Aug 16.

- Morgentaler A. Testosterone therapy in men with prostate cancer: scientific and ethical considerations. *J Urol.* 2013 Jan; 189(1 Suppl):S26-33.

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

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
- Mathis Grossmann. Testosterone and glucose metabolism in men: current concepts and controversies. *Journal of Endocrinology*. 2014 Jan 27;220(3):R37-55.

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

- Stellato, R et al. Testosterone, Sex Hormone Binding Globulin, and the Development of Type 2 Diabetes in Middle-Aged Men Prospective results from the Massachusetts Male Aging Study. *Diabetes Care.* 23:490–494, 2000

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

- 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.

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

- Kapoor D. Testosterone replacement therapy improves insulin resistance, glycaemic control, visceral adiposity and hypercholesterolaemia in hypogonadal men with type 2 diabetes. *Eur J Endocrinol*. 2006 Jun;154(6):899-906.

Testosterone Treatment with Metabolic Syndrome

- Testosterone = 241 (mean)
- Metabolic syndrome
- All had nutrition and exercise counseling
- T undecanoate 1000 mg q 6 weeks x2 then q 12 weeks x 60 months

- Francomano D, Lenzi A, Aversa A. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol*. 2014;2014:527470.

TRT but not control group

- BMI −2.9 ± 1.4 P < 0.0001
- Waist circumference −9.6 ± 3.8 cm P < 0.0001
- Weight −15 ± 2.8 Kg P < 0.0001
- HgA1C −1.6 ± 0.5% P < 0.001
- Insulin Sensitivity −2.8 ± 0.6 P < 0.0001
- Total/HDL-cholesterol: −2.9 ± 1.5 P < 0.0001
- Triglycerides: −41 ± 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 ± 10mmHg	P < 0.0001
Diastolic	−16 ± 8mmHg	P < 0.001
Neck and lumbar T-scores	.5 ± 0.15gr/cm3	P < 0.0001
Serum vitamin D	+14.0 ± 1.3ng/mL	P < 0.01
TSH	−0.9 ± 0.3 mUI/mL	P < 0.01
IGF1	+105 ± 11	P < 0.01
Hematocrit	+2.8 ± 0.9%	P < 0.001
PSA levels	+0.37 ± 0.29ng/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

Conclusion

- "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."

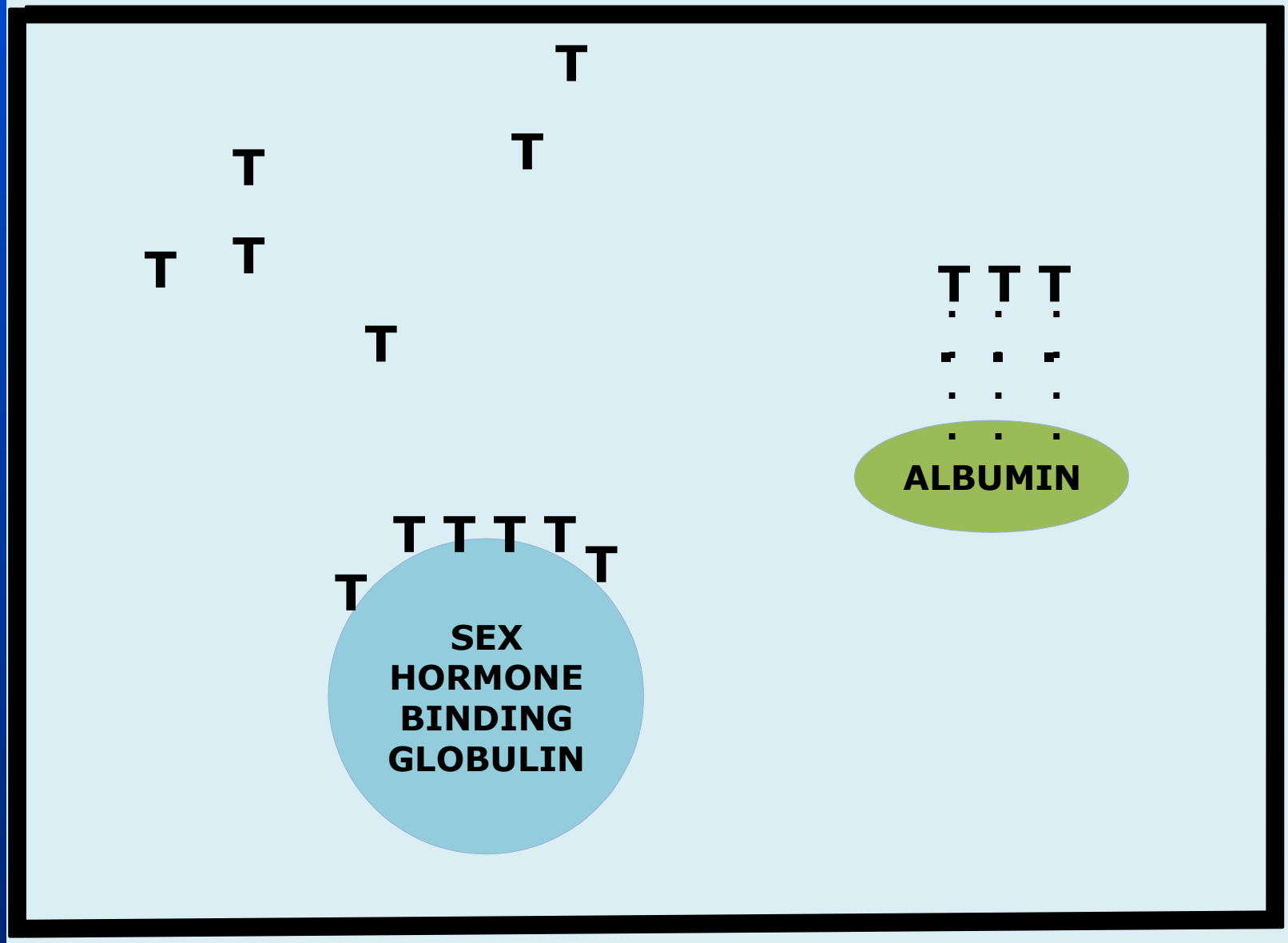
- Francomano D et al. Effects of five-year treatment with testosterone undecanoate on metabolic and hormonal parameters in ageing men with metabolic syndrome. *Int J Endocrinol*. 2014 Feb 12

Testosterone Lab Testing

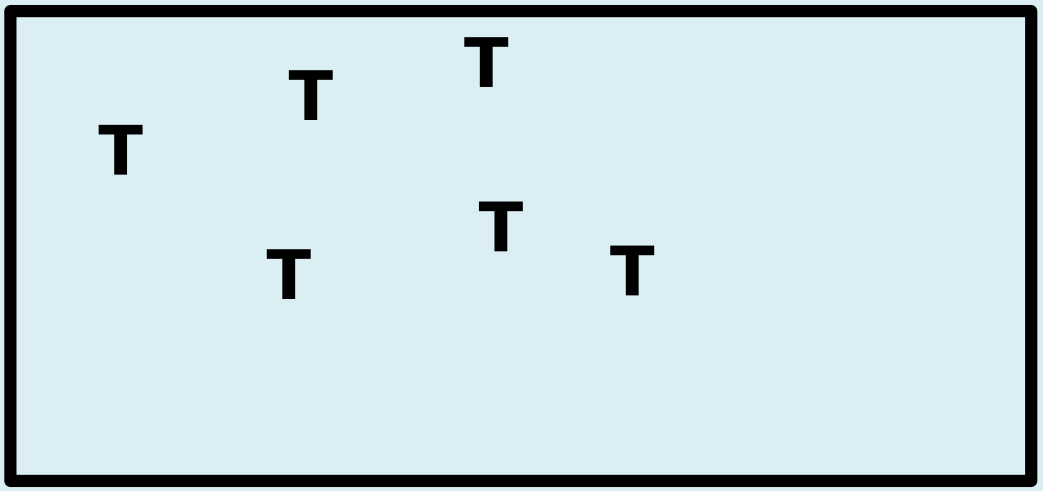
Test	Sex	Reference	Optimal
Total ng/dl	Male	350-1030	790-1100
	Female	10-55	50-80
Free* ng/dl (Equilibrium dialysis)	Male	8-30	20-35
	Female	1.1-6.3	3-8
Bioavailable	Male	120-600	400-640
pg/ml	Female	2-20	10-25

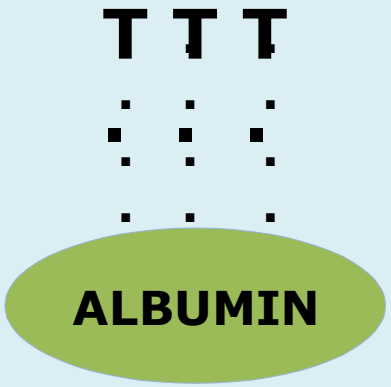
* Free testosterone results vary with methodology – direct analog (RIA) in pg/ml – same ref range

TOTAL TESTOSTERONE

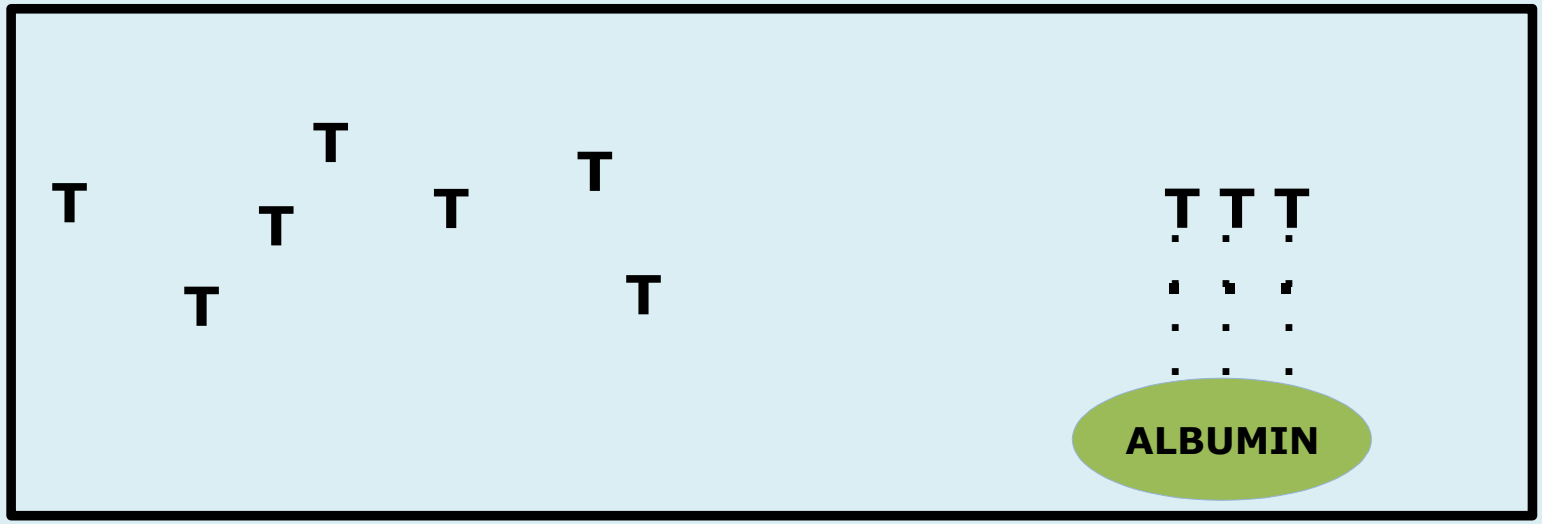


FREE TESTOSTERONE





BIOAVAILABLE TESTOSTERONE



SHBG binds T > E

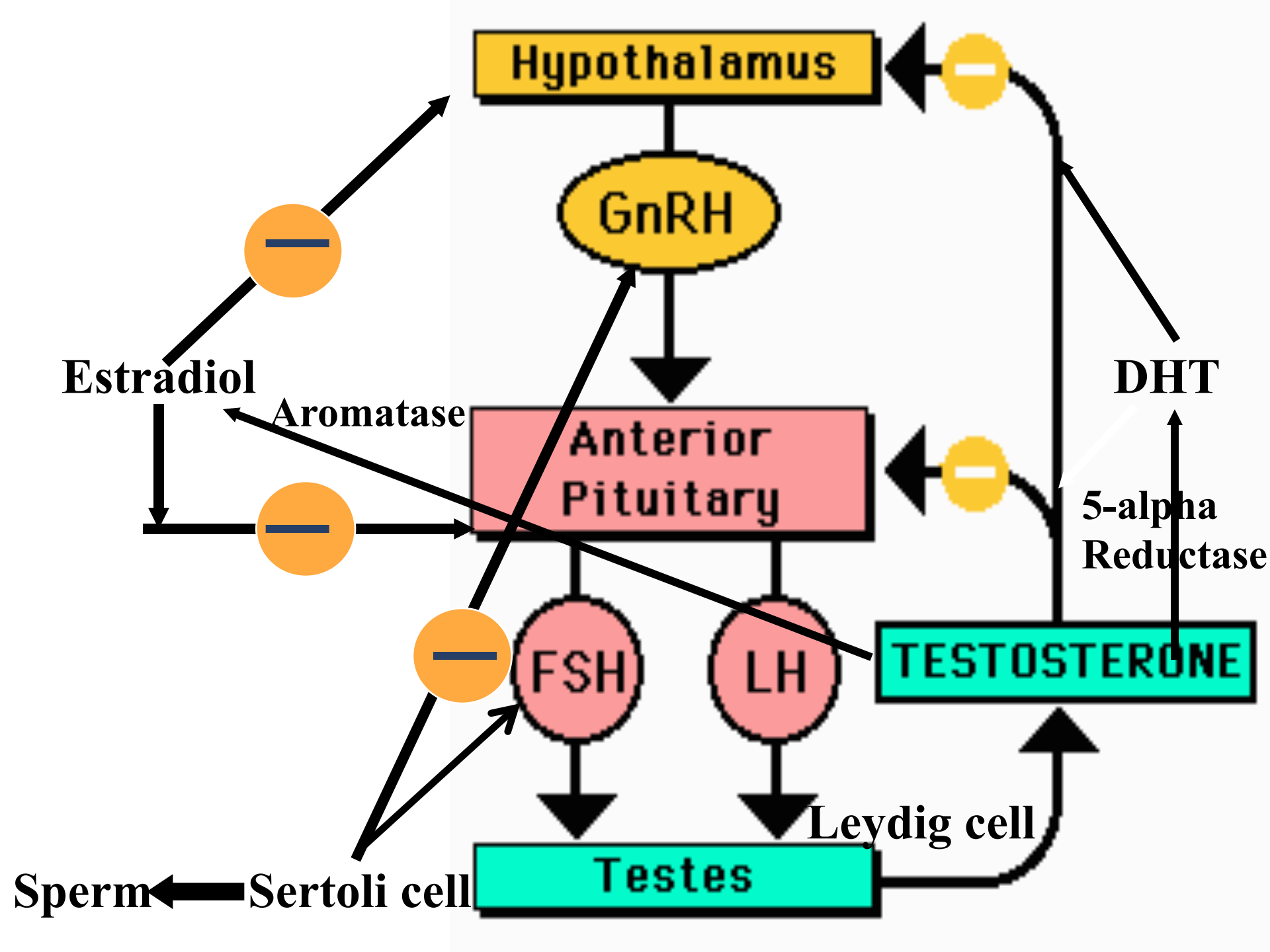
- 20-60 nmol/l male
- 40-120 nmol/l female

- 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


Hypothalamus
GnRH
Estradiol
Aromatase
Anterior Pituitary
DHT
5-alpha Reductase
FSH
LH
TESTOSTERONE
Leydig cell
Testes
Sperm
Sertoli cell

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?

- 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 flavinoids. *Arch Pharm Res*. 1999 Jun;22(3):309-12

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

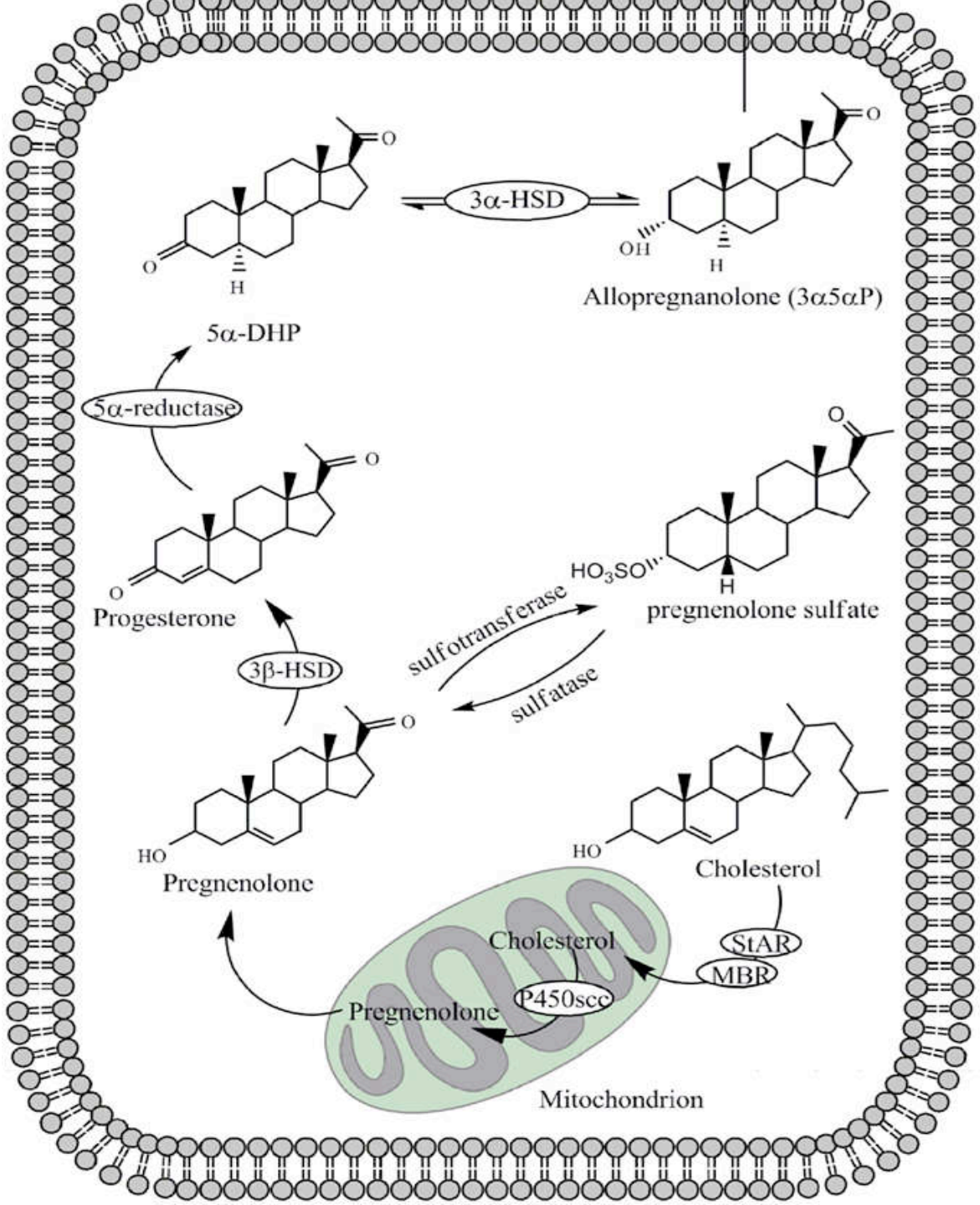
5-alpha reductase inhibition

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

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

- Traish AM et al. 5- alpha-reductases in human physiology: an unfolding story. *Endocr Pract*. 2012 Nov-Dec;18(6):965-75.


3α-HSD
Allopregnanolone (3α5αP)
5α-DHP
5α-reductase
Progesterone
3β-HSD
sulfotransferase
sulfatase
pregnenolone sulfate
Pregnenolone
Cholesterol
StAR
MBR
Cholesterol
P450scc
Pregnenolone
Mitochondrion

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
- Scaglione F et al. Comparioson of the potency of 10 different brands of Serenoa repens extracts. *Eur Rev Med Pharmacol Sol*. 2012 May16(5)569-74

Progesterone 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

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.Thrombosis in three postmenopausal women receiving testosterone therapy for low libido. *Women's Health.* (2013) 9(4), 405–410
- Glueck, C et al. Thrombosis-Pulmonary Embolus: An Exploratory, Hypothesis-Generating Study -Testosterone Therapy, Thrombophilia-Hypofibrinolysis, and Hospitalization for Deep Venous. *Clin Appl thromb Hemost*. 7 August 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
- Zitzmann M Hormone substitution in male hypogonadism *Mol Cell Endocrinol* 2000 Mar 30;161(1-2):73-88

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
- 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.

T Dose Men

- Cream 50-200 mg/day
- Cypionate 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.
- 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