MALE HORMONES, THE LATEST GUIDELINES

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Disclosures

- National Medical Director and Chief Medical Advisor, Vault Health – Salary

Outline

- Clinical Problem of low T (TD)
- Male hormones in general
- TD Symptoms, Impacts, Causes
- TRT and impact on Health & Symptoms
- TRT Nuts & Bolts
  - Testing
  - Formulations
  - Clomiphene & HCG
  - Monitoring
- Other treatments
- Conclusion

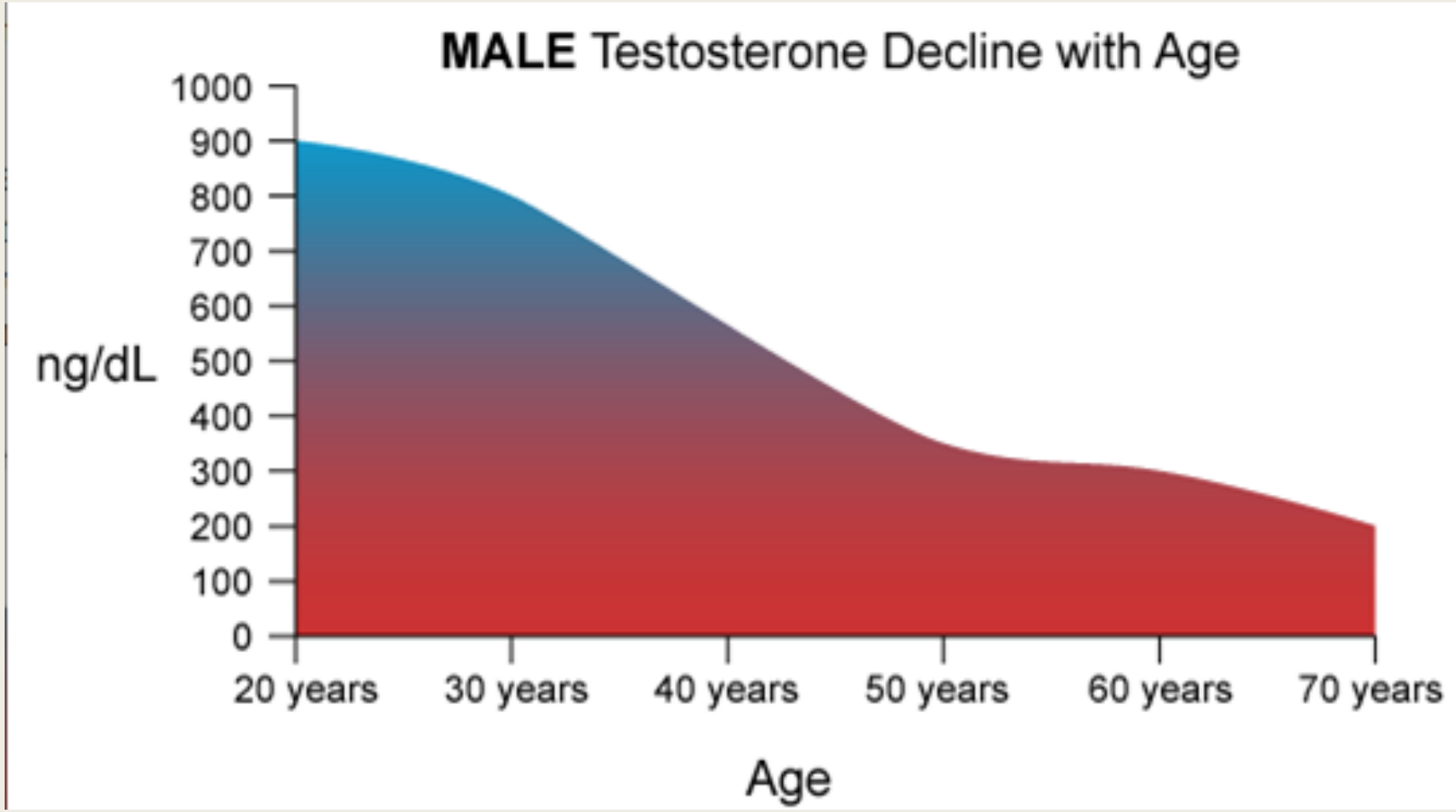
Low T: The Clinical Problem

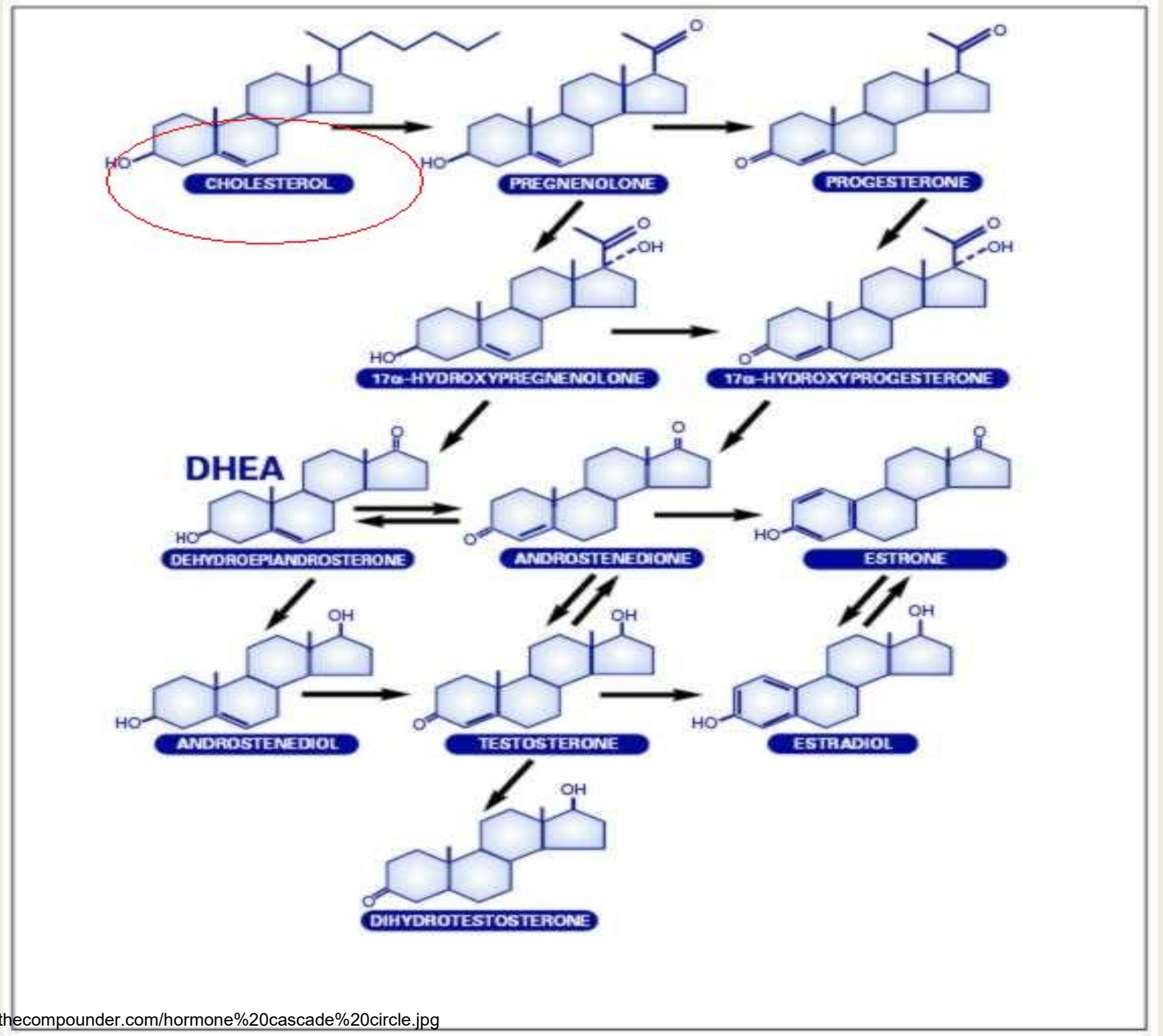
- Hypogonadism affects 30% men age 40-79
  - A gradual, age-associated decline in serum total testosterone levels begins in men in their mid-30s and continues at an average rate of 1.6% per year

- Symptoms
  - *Fatigue / Cognitive function decline*
  - *Decreased libido*
  - *ED*
  - *Depression, irritability, decreased sense of well-being*
  - *Decreased muscle mass / increased body fat*
  - *Decreased bone mineral density*

Feldman et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts male aging study. J Clin Endocrinol Metab. 2002;87:589-98
Tajar A et al. Characteristics of secondary, primary, and compensated hypogonadism in aging men: evidence from the European Male Ageing Study. J Clin Endocrinol Metab.2010;95:1810-8
Harman et al. Baltimore Longitudinal Study of Aging
Longitudinal effects of aging on serum total and free testosterone levels in healthy men. Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab.2001;86:724-31.

Men - Testosterone Decline





http://www.thecompounder.com/hormone%20cascade%20circle.jpg

Male Hormones

- Pregnenolone
- Progesterone
- DHEA
- Androstenedione
- Estradiol/Estrone
- Testosterone
- Dihydrotestosterone (DHT)

Pregnenolone

- Synthesized directly from cholesterol
  - *Precursor to all other sex hormones*
- Levels start to decline around age 30
- Functions to:
  - *Enhance nerve transmission and memory*
  - *Improve energy and sleep*
  - *Increase stress resistance*
  - *Mood elevation*
  - *Reduce pain and inflammation*
- Deficiency associated with:
  - *Depression*
  - *Fatigue*
  - *Inability to deal with stress*
  - *Insomnia*
  - *Lack of focus*
  - *Memory decline*

Pregnenolone Dosing

- Pregnenolone SR to start at 10mg per day and titrate up slowly until you reach a blood level of 100 which is optimal
- SR form more physiological
- Can cause agitation and anxiety if titrate to fast or if the dose is high for patient

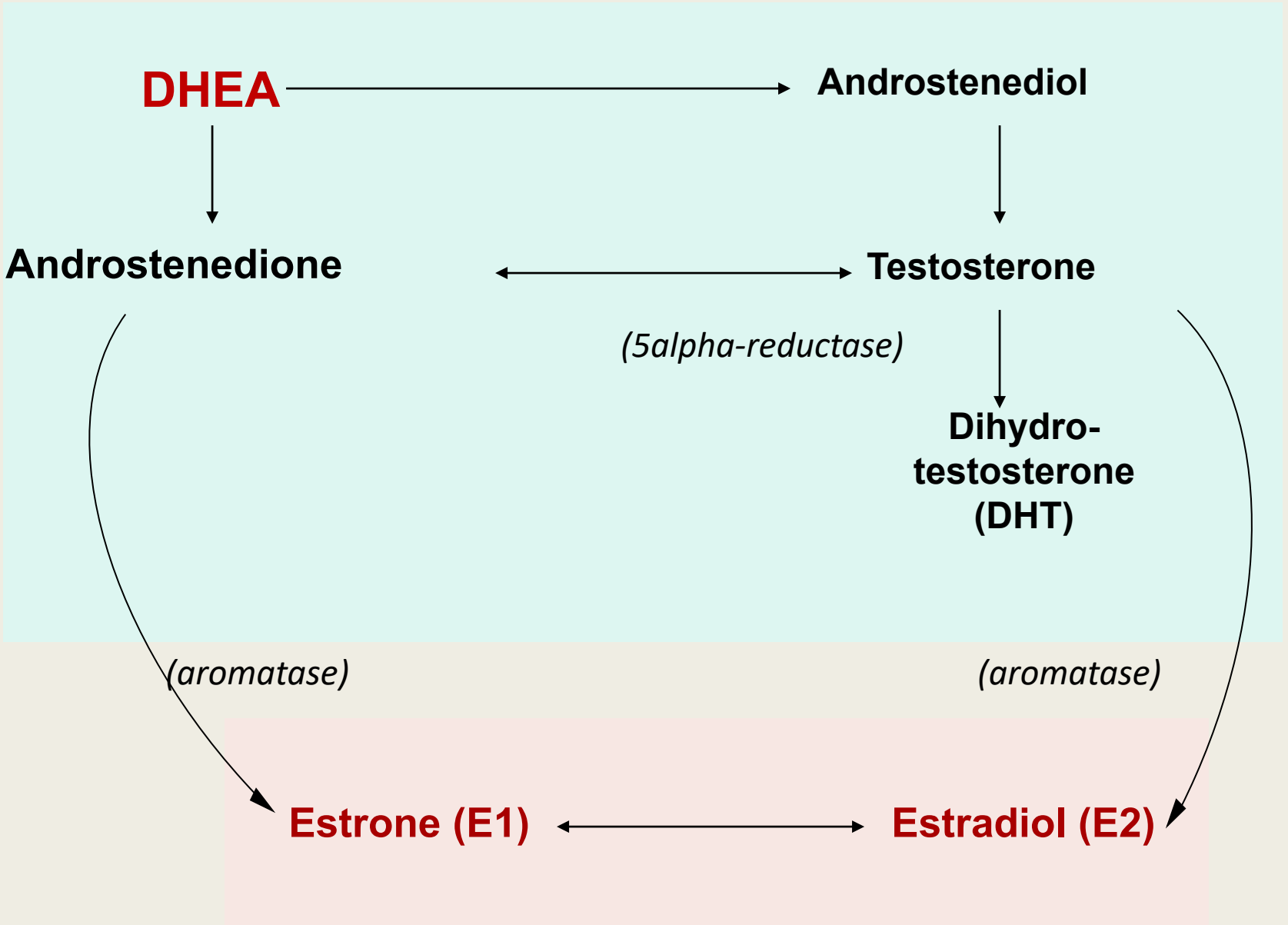
Progesterone

- Made by the adrenal glands
- Precursor to androstenedione
- Levels start to decline in men around age 60
- Functions to balance estrogen
  - *Inhibits aromatase and 5-alpha reductase*
  - *Antagonizes stimulatory effects of estrogen on the prostate gland and lowers PSA*
  - *Stimulates anti-tumor antigen, p53, to prevent prostate cancer*

Progesterone Dosing

- In men, you start with 3-5mg topically daily
- Usually added to testosterone/Chrysin cream topically
- Can use capsule form if the patient has sleep issues. Dose range 5-15mg oral

Androgens


DHEA
Androstenediol
Androstenedione
Testosterone
(5alpha-reductase)
Dihydro-
testosterone
(DHT)
(aromatase)
(aromatase)
Estrone (E1)
Estradiol (E2)

DHEA

- Made by the adrenal glands
- Precursor to estrogen and testosterone
- Production declines with age
- Protective effect against:
  - *Cancer, diabetes, obesity, high cholesterol, heart disease, and autoimmune diseases*
- Symptoms of deficiency:
  - *Decreased energy & muscle strength, difficulty dealing with stress, increase risk of infection, irritabilty, joint soreness, and weight gain*

Enomoto M, Adachi H, Fukami A, et al. Serum dehydroepiandrosterone sulfate levels predict longevity in men: 27-year follow-up study in a community-based cohort (Tanushimaru study). J Am Geriatr Soc. 2008 Jun;56(6):994-8.

Actions of DHEA

- Prohormone for sex steroids
- Anti-glucocorticoid
- Immune supporting
- Anti-atherogenic, lowers serum triglycerides
- Enhances insulin sensitivity; anti-obesity effect
- Maintains tissue strength and repair, supports bone density
- Neuroprotective; enhances memory
- Promotes sense of well-being
- Libido enhancing

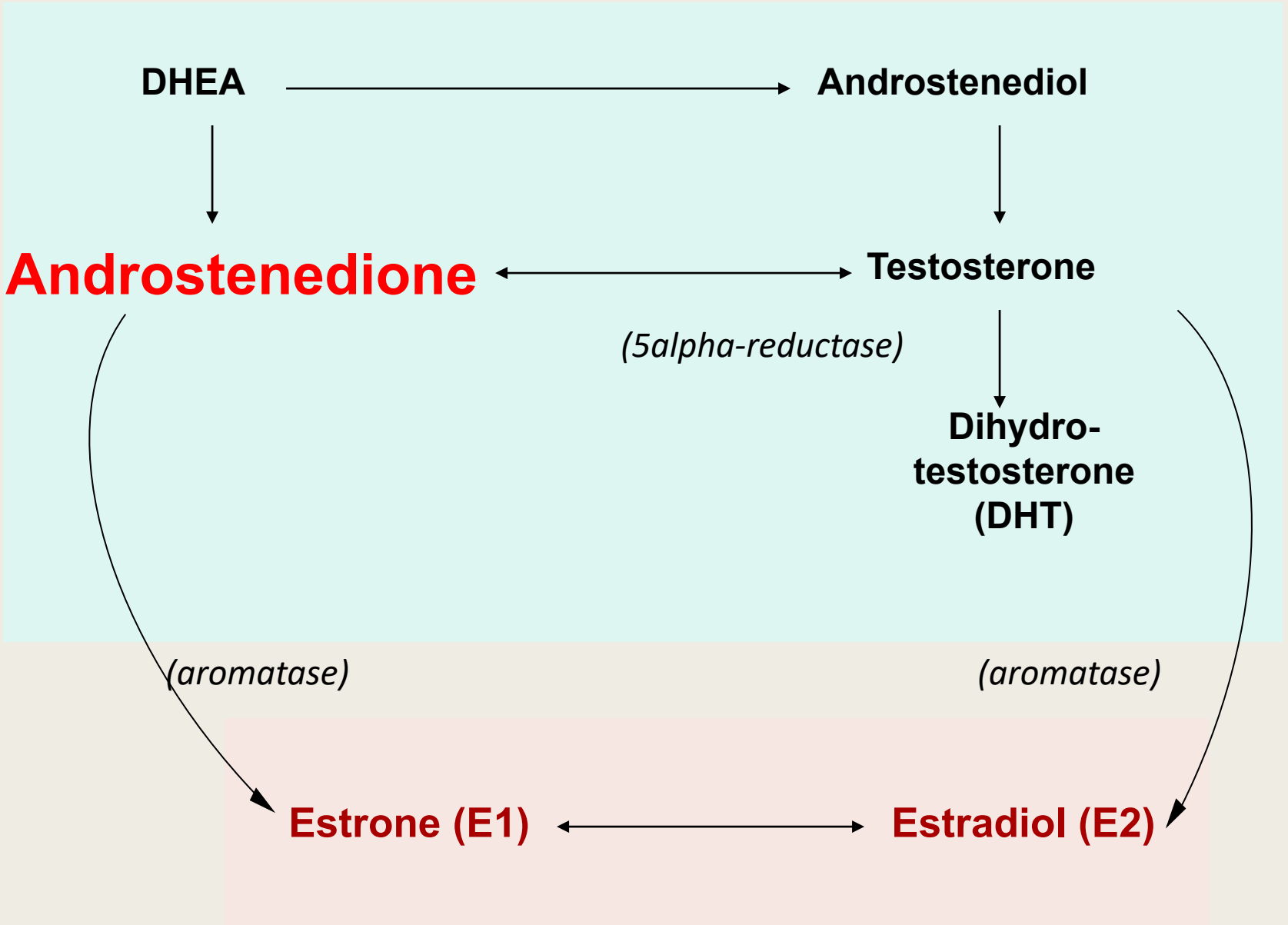
DHEA Dosing

Replacement linked with improved libido, mood, erectile function

- Improves neural protection especially when Cortisol is high
- Men need 25-50mg per day
- SR form is more physiological
- DHEA is a large molecule and therefore, it is not well absorbed topically
- Side effects include oily skin, hirsuitism, acne
- K-DHEA form can be used if concern for cancer and want to bypass hormonal byproducts

Jin RO, Mason S, Mellon SH, et al. Cortisol/DHEA ratio and hippocampal volume: A pilot study in major depression and healthy controls. Psychoneuroendocrinology. 2016;72:139–146. doi:10.1016/j.psyneuen.2016.06.017

Androgens


DHEA
Androstenediol
Androstenedione
Testosterone
(5alpha-reductase)
Dihydro-
testosterone
(DHT)
(aromatase)
(aromatase)
Estrone (E1)
Estradiol (E2)

Androstenedione

- Common precursor of male and female sex hormones
  - *Converted to testosterone through 17β-hydroxysteroid dehydrogenase*
  - *Converted to estrogen through aromatase*
- Found in testes and adrenal glands
- Short half-life
- No reliable studies on benefits

Dihydrotestosterone (DHT)

- Most potent naturally occurring androgen
  - *3 times more potent than testosterone*
- Synthesized from the conversion of testosterone through 5-alpha reductase
- Responsible for formation of male sex-specific characteristics and development of male genitalia and prostate
  - *Low levels can affect sexual function and libido, muscle tone*
- Elevated levels can cause:
  - *Hirsuitism*
  - *Male pattern baldness*
  - *BPH*
  - *Prostate cancer*

Dihydrotestosterone (DHT)

- ~25% secreted by testes, 75% from bioconversion from T in liver, kidney, muscle, prostate, and skin
- Blood concentration of DHT is 10% that of T, but at least twice as potent due to increased affinity for androgen receptor; cannot be aromatized to estrogen
- Produced *in utero*, is responsible for devlopment of male sex characteristics
- Primary contributing factor in androgenic alopecia, benign prostatic hypertrophy, hirsutism in women

5 Alpha-Reductase Inhibitors

- Finasteride
- Dutasteride
- Zinc
  - *Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. **J Nutr**. 1996 Apr;126(4):842-8*
- Progesterone
  - ***Mini Rev Med Chem**. 2003 May;3(3):225-37.*
- Other Natural Inhibitors:
  - *Saw palmetto*
  - *Beta sitosterol*
  - *L-lysine*
  - *Epigallocatechin gallate (EGCG)*
  - *Linolenic acid*

*Rushton DH. Nutritional factors and hair loss. **Clin Exp Dermatol**. 2002 Jul;27(5):396-404*

Estradiol/Estrone

- Made in muscle, skin, and adipose tissue
- Adequate levels protect against bone fractures, and maintain cognitive function
- Excess associated with:
  - *Gynecomastia*
  - *Decreased sex drive/erectile dysfunction*
  - *Doubled risk of stroke*
  - *Higher rates of heart attack, peripheral artery disease, and coronary atherosclerosis*
  - *Insulin resistance*
  - *Rheumatoid arthritis*
  - *BPH*
  - *Prostate cancer*

Aromatase Inhibitors

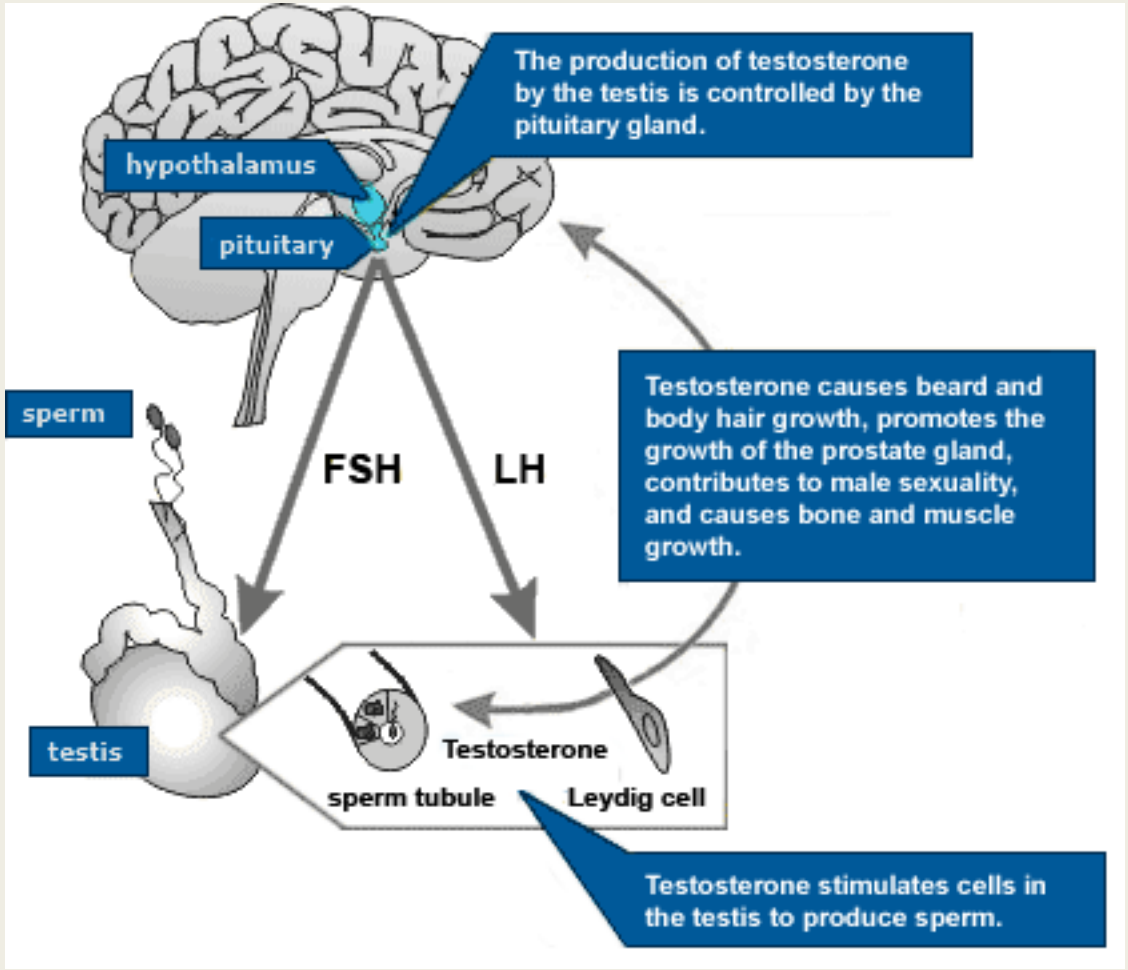
- Anastrozole
- Letrozole
- Natural - bioflavinoids
  - *Quercetin*
  - *Chrysin*
  - *Resveratrol*
  - *Zinc*
    - Om AS, Chung KW. Dietary zinc deficiency alters 5 alpha-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. **J Nutr**. 1996 Apr;126(4):842-8
  - *Progesterone*
    - Schmidt M, Renner C, Loffler G. Progesterone inhibits glucocorticoid-dependent aromatase induction in human adipose fibroblasts. **J Endocrinol**. 1998 Sep;158(3):401-7

Testosterone

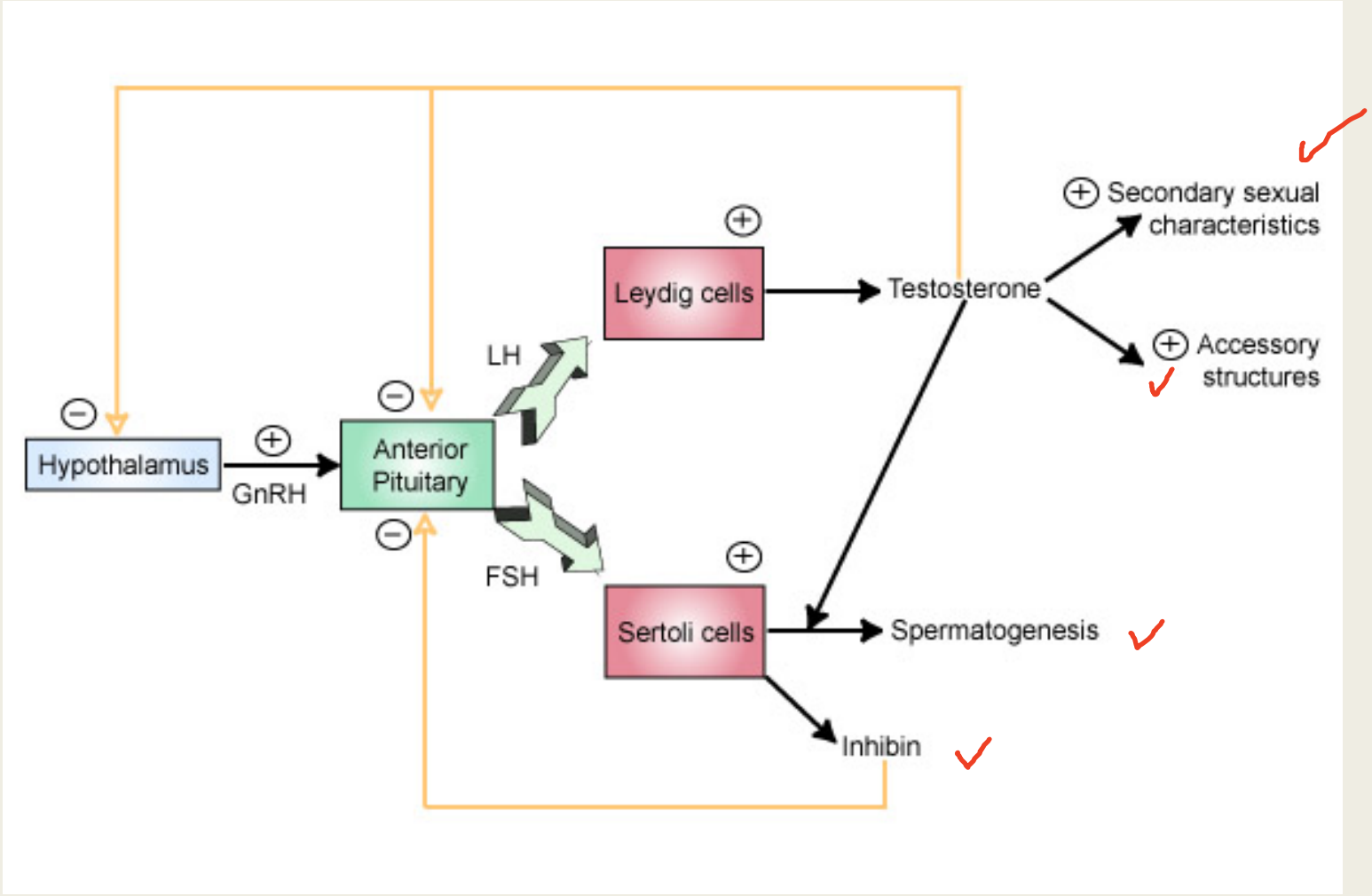
- Principal male hormone
- Anabolic steroid produced from cholesterol
- Primarily secreted in the testes and small amounts secreted from the adrenal glands
- Functions:
  - *Anabolic effects: increased muscle mass, bone density, and bone maturation*
  - *Androgenic effects: development of sex organs, deepening of voice, hair growth*

Testosterone: Target Organs

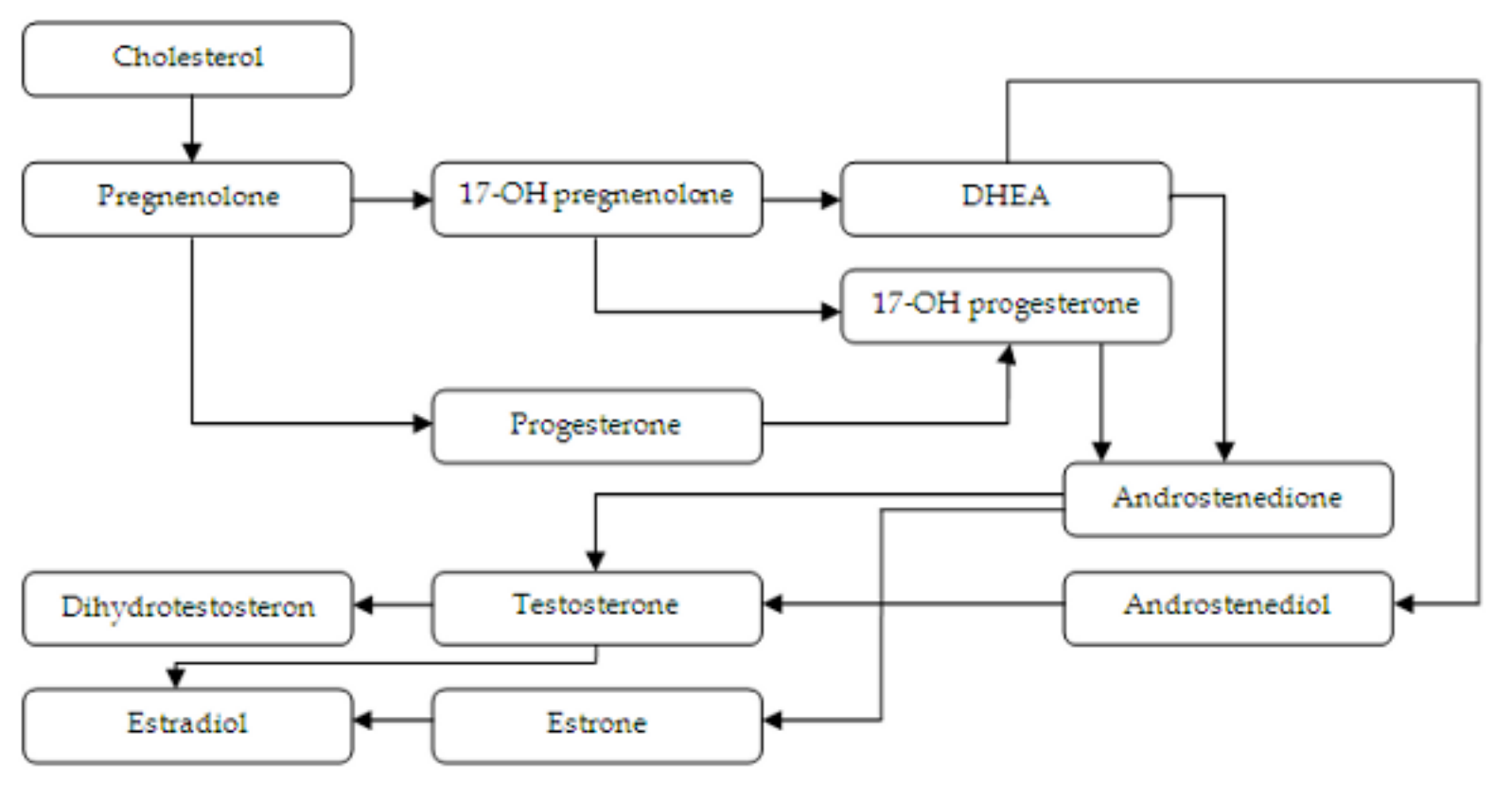
Feedback Mechanism



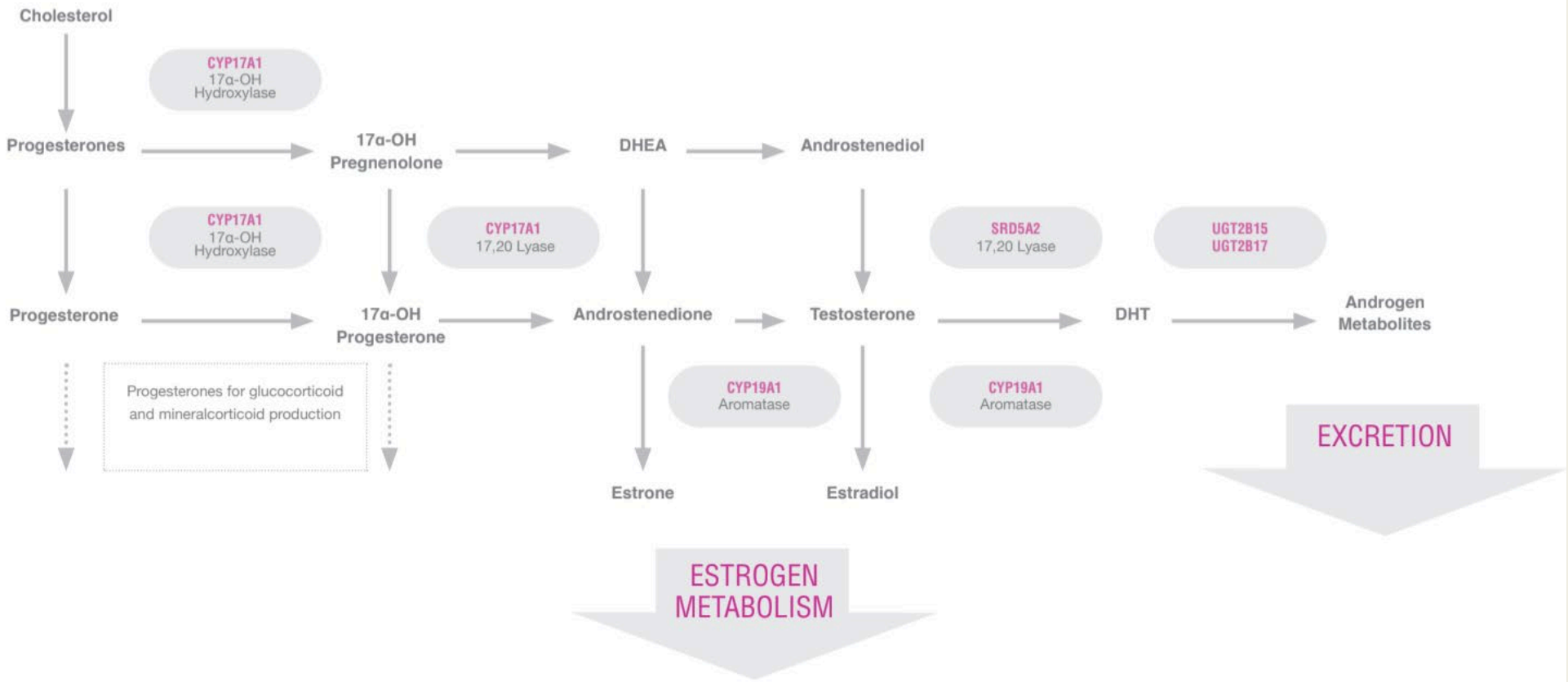
Feedback mechanism



Androgen synthesis



Androgen metabolism

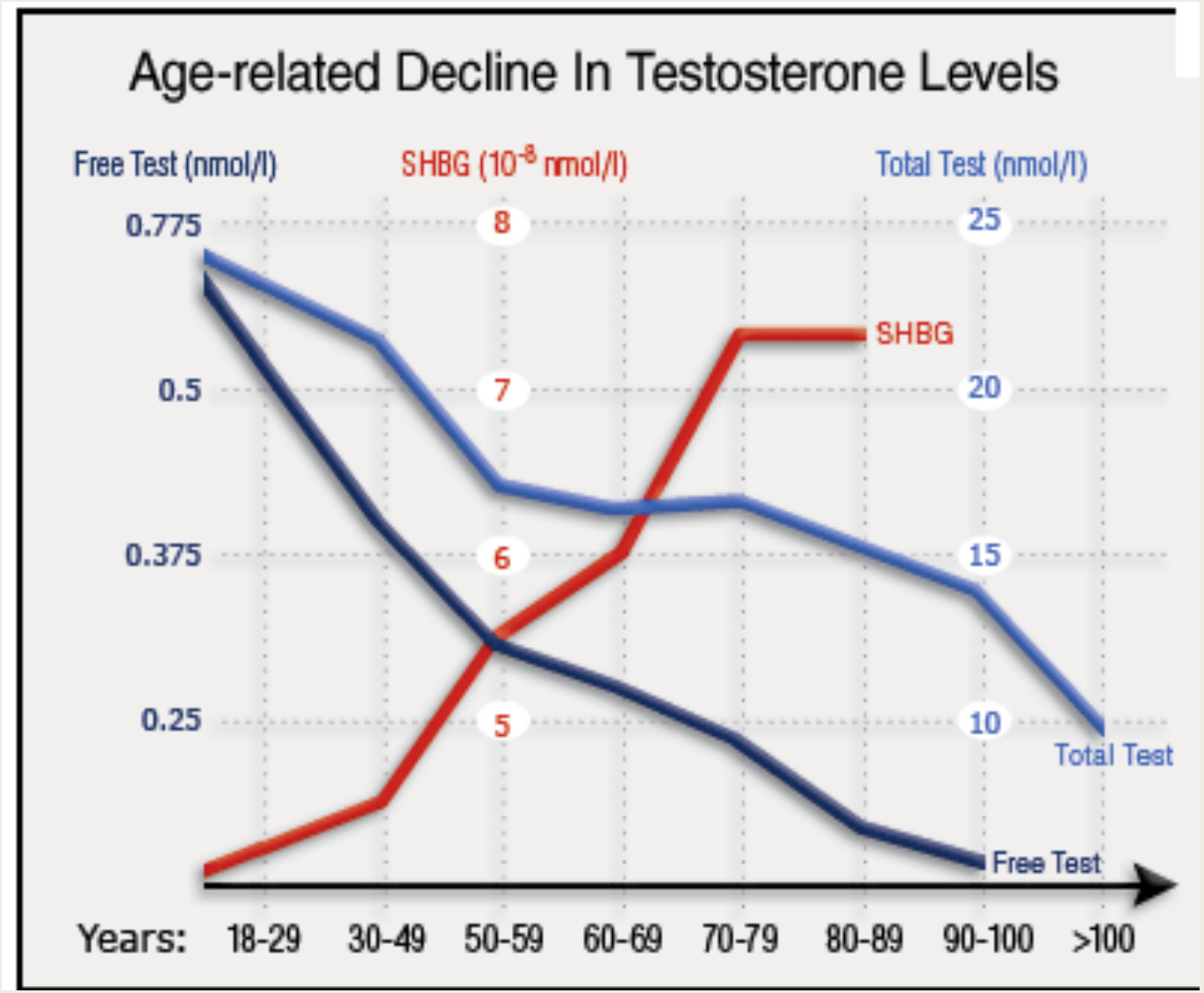


TESTOSTERONE DEFICIENCY (TD)

Factors Contributing to Testosterone Decline

- AGE
- AGE
- AGE
- Diet and insulin resistance
- Stress levels/cortisol demand
- Toxin exposure

Free Testosterone vs. SHBG



Effects of Aging on the Male Body

Vigor	Vitality	Virility
Loss of sense of well being	Decrease in hair density	Decline in sexual function and interest
Difficulty concentrating	Reduction in masculinity	Diminished libido
Depression	Decrease in muscle mass and strength	Erectile dysfunction
Irritability and nervousness		Decrease in bone mass (osteoporosis)
Altered behavior		
Change in sleep habits/insomnia		

Male Diminished Libido

- *Low Bioavailable Testosterone*
  - Age-Related Testosterone Decline
    - *(Leydig Cell Dies Every 4 Seconds)*
  - Obesity – Lowers Testosterone
  - Beta-Blockers, Statins, NSAIDS, SSRIs
  - High SHBG
- *Excess Prolactin*
  - Inhibits Dopamine Release
  - Responsible for the Refractory Period

Andropause Contributes to Many Diseases

- Diabetes/Metabolic Syndrome
- Brain (Dementia, Alzheimer's)
- Heart (MI's)
- Frailty Syndrome/Sarcopenia
- Bone (Osteoporosis)
- Inflammation

Bain. 2010; "Testosterone and the aging male: To treat or not to treat?" **Maturitas.** 2010 May;66(1):16-22. Epub 2010 Feb 13

Testosterone Decline

- Testosterone declines with age beginning in the early 30's
- By age 40, levels naturally decline by >1% per year
- Testosterone production declines due to
  - *Increasing SHBG*
  - *Decreasing LH*
  - *Decreased Leydig cell activity*
- During the time between 25 to 75 years old:
  - *30% decrease in Total Testosterone*
  - *50% decrease in Bioavailable Testosterone*

Testosterone Decline

- “Half of healthy men between the ages of 50-70 years will have a bioavailable testosterone level below the lowest level seen in healthy men who are 20-40 years of age.”

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

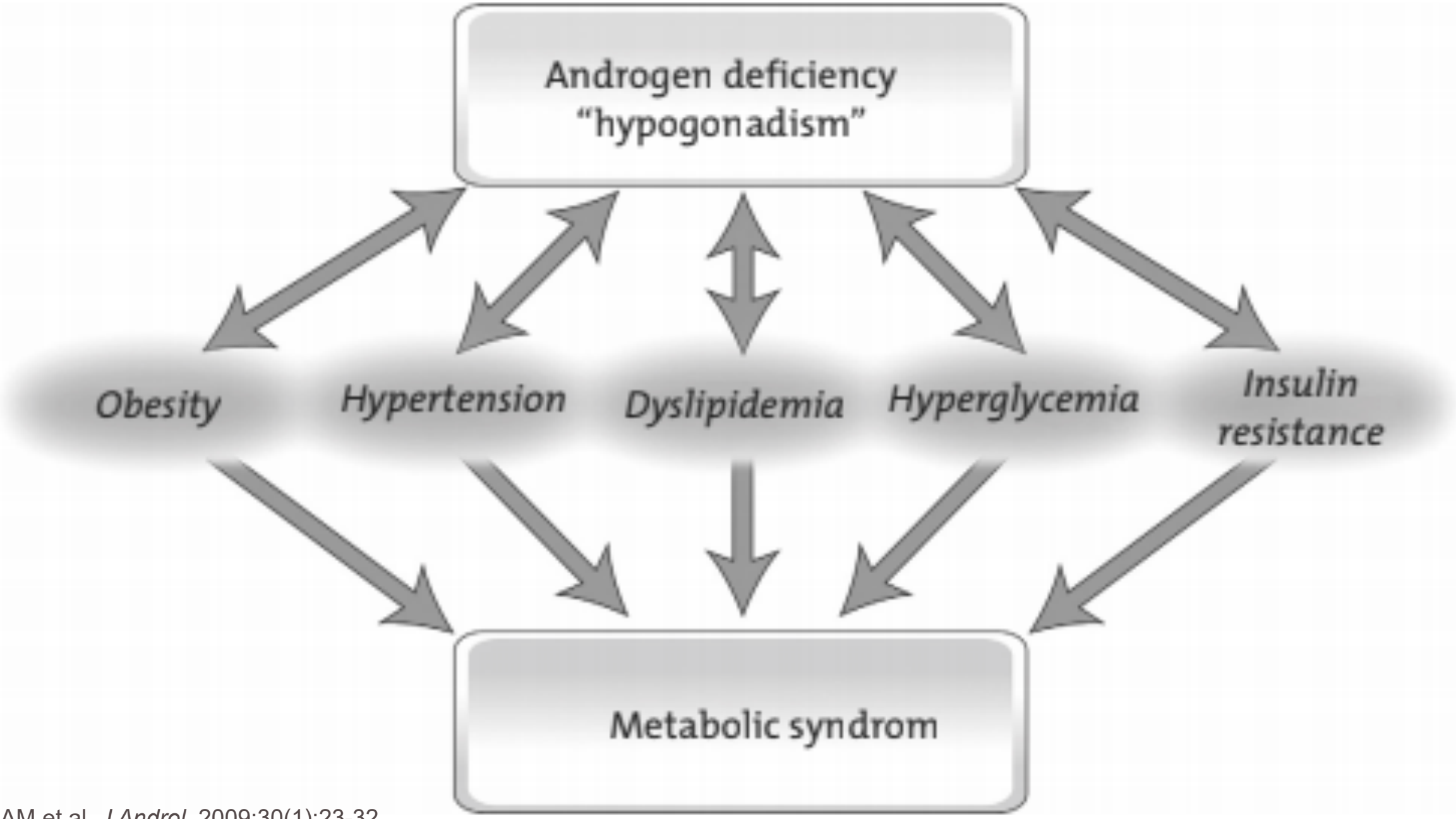
TD and Metabolic Syndrome

- Meta analysis of 20 observational studies looking at relationship between T and met syndrome found inverse rel between total T, free T and Met S (OR per quartile decrease in TT 1.69 (1.60-1.77) and for free T 1.46 (1.36-1.57) (*Brand, 2014)*

- T levels sig lower among men with one or more comorbid conditions (obesity, cancer, CHD, HTN, DM) Mass. Male Aging Study, n=1700 *(Feldman,2002; Kupelian,2006)*

- Lowest quartile of T associated with double the risk of new-onset DM and met syn in the Rancho Bernardo Study (Oh, 2002)

- 40-50% of men with DM are TD in Finnish population-based cohort study of 702 men *(Laaksonen, 2004)*



Traish AM et al. *J Androl.* 2009;30(1):23-32.

Evidence for the bidirectional rel between TD and Met Syn

- The increased risk of insulin resistance and met syn is not due to changes in SHBG as the inverse relationship with low T persists when looking at free T
- Weight loss improves levels of both free and total T proportionate to the amount of weight loss
- TD is associated with weight gain; weight loss improves T levels
- ADT is associated with increased BMI and decreased lean body mass (compared to men who had surgery and no ADT for prostate ca)

Dimopoulou. Male Repro Endo. 01 Sept 2018;86:61-68.
Basaria et al. Cancer 2006;196)3):581-8.

Christ-Crain M. Swiss Med Wkly. 2016;146:w14283.

The hypogonadal-obesity-adipocytokine mechanism

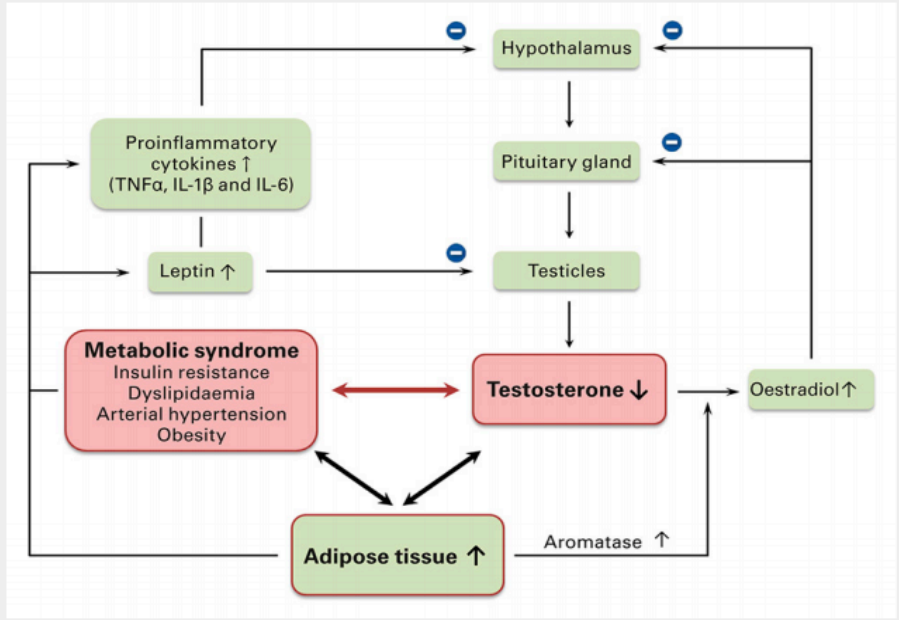


Figure 1

Pathophysiological interplay between adverse metabolic parameters, adipose tissue and testosterone deficiency. Adipose tissue as a pivotal component of the pathophysiological interplay leads to increased release of inflammatory mediators (TNF-α, IL-1β and IL-6) and leptin which cause dysfunctions of the hypothalamic-pituitary-testicular axis and result in decreased testosterone production. Increased activity of aromatase in adipose tissue enhances the conversion of testosterone to oestradiol which exerts negative feedback effects on both hypothalamus and pituitary gland. Consecutive testosterone deficiency promotes an increase in fat mass and worsening of metabolic surrogate parameters, demonstrating the bidirectional relationship.
TNF-α = tumour necrosis factor α;
IL-1β = interleukin 1β; IL-6 = interleukin 6

Things that increase insulin

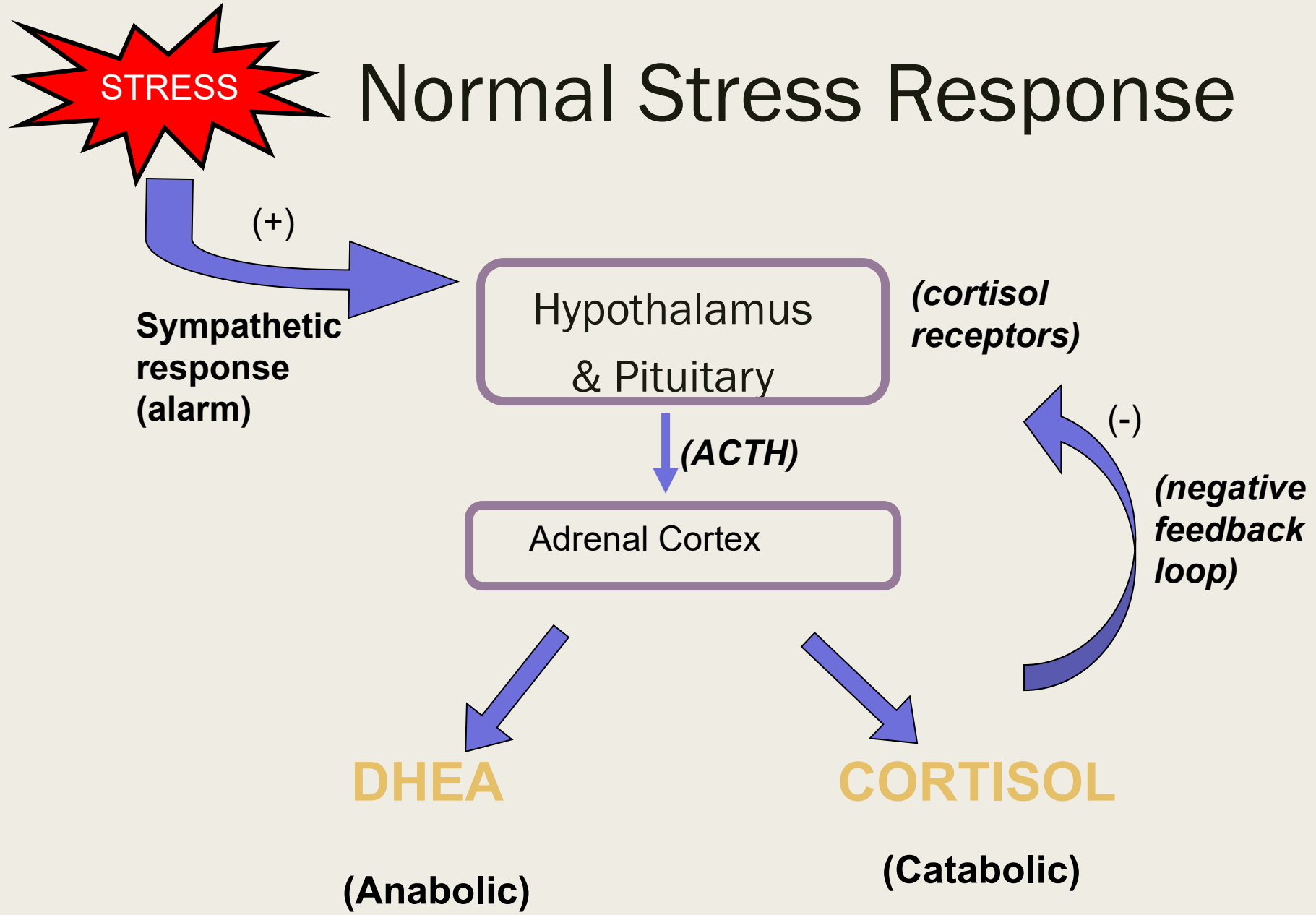
- High carbohydrate diet
- Increased stress
- Decreased estrogens
- Increased testosterone
- Insomnia
- Increased DHEA
- Decreased thyroid hormone
- Excessive progesterone
- Lack of exercise

Smith, HRT: The Answers, 2003

Impact of stress on T levels

- High chronic stress causes low DHEA and low T
- Cortisol acts as anti-T

Normal Stress Response



What Constitutes "Stress"?

- "Fight or flight" responses
  - *fear, anxiety, worry*
- Depression, feelings of defeat or helplessness
- Pain syndromes
- Infection, inflammation
- Hypoglycemia
- Inadequate sleep
- Disrupted light cycles
- Toxic exposure

Let’s Talk About Toxins…

- Pesticides
- Food additives and preservatives
- Electromagnetic radiation
- Heavy metals
- Phthalates
- Bisphenol A
- And many more….

Toxins - Phthalates

- Esters of phthalic acid and are mainly used as plasticizers
- As of 2004, 800 million pounds produced
- Introduced in the 1920's
  - *1856: castor oil*
  - *1870: camphor*
  - *Enteric coatings*
- Current uses:
  - *Enteric Coatings*
  - *Viscosity control agents*
  - *Binders*
  - *Lubricants*

Rudel R, Perovich L (January 2008). "Endocrine disrupting chemicals in indoor and outdoor air". **Atmospheric Environment** 43 (1): 170–81

Toxins - Phthalate Sources

- Personal care items
  - *Make-up, shampoo, moisturizer, liquid soap, hair spray, cologne*
- Detergents
- Cleaning materials
- Modeling clay
- Fishing lures
- Paints
- Children's toys
- Food packaging

Bisphenol A

- Primarily used to make plastics
- Used in commerce for the past 50 years
- Polycarbonate bottles (clear, flexible plastic)
  - *Baby bottles*
  - *Water bottles*
  - *Dental sealants*
  - *Sports equipment*
  - *Eye glasses*
  - *CD's and DVD's*

National Toxicology Program, U.S. Department of Health and Human Services (2007-11-26).

Increased risk from TD

- Obesity
- Metabolic syndrome
- Diabetes
- Dyslipidemia (low HDL and elevated TGs)
- Hypertension

Kupelian V et al. J Clin Endocrinol Metab. 2006 Mar;91(3):843-50. Epub 2006 Jan 4.
Brand et al. PLoS One. 2014 Jul 14;9(7):e100409. doi: 10.1371/journal.pone.0100409. eCollection 2014
Oh et al. Endogenous sex hormones and the development of type 2 diabetes in older men and women: the Rancho Bernardo study. Diabetes Care. 2002;25(1):55-60.
Laaksonen DE, et al. Testosterone and sex hormone-binding globulin predict the metabolic syndrome and diabetes in middle-aged men. Diabetes Care. 2004; 27(5):1036-1041.

Increased risk from TD on Cardiovascular events and mortality

The decrease in T that happens in men post age 40 has been associated with an increase in all-cause mortality and cardiovascular risk.

- A meta-analysis by which investigated 16,184 community-based participants with a mean follow-up of 9.7 years found that low T levels were associated with an increased risk of Overall and CV-related mortality with a HR for CV mortality of 1.35 (95% CI, 1.13-1.62; P<.001). (*Araujo, 2011)*
- Meta-analysis of 70 studies showed clear association between low T and CV disease Of those, 10 longitudinal studies demonstrated that overall mortality and CV mortality were highest in those with low T levels. Whether low T and increased mortality are simply covariates or a causal relationship remains to be proven" (*Corona, 2011)*

Araujo et al,. Clinical review: Endogenous testosterone and mortality in men: a systematic review and meta-analysis. J Clin Endocrinol Metab. 2011 Oct;96(10):3007-19.
Corona G, Rastrelli G, Monami M, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study.Eur J Endocrinol. 2011 Nov;165(5):687-701.

TD and Mortality in Male Veterans

- **N=858 men > age of 40**
- **Low T = total T < 250 ng/mL**
  - ***< 8.7 nmol/L***
- **Mortality over 5 years**
  - *20.1% with normal T*
    - 2 levels > 250
  - *24.6% with equivocal T*
    - Equal # N and low
    - Odds Ratio 1.38 (P=0.06)
  - *34.9% with low T*
    - 2 levels < 250
    - Odds Ration 1.88 (P<0.001)

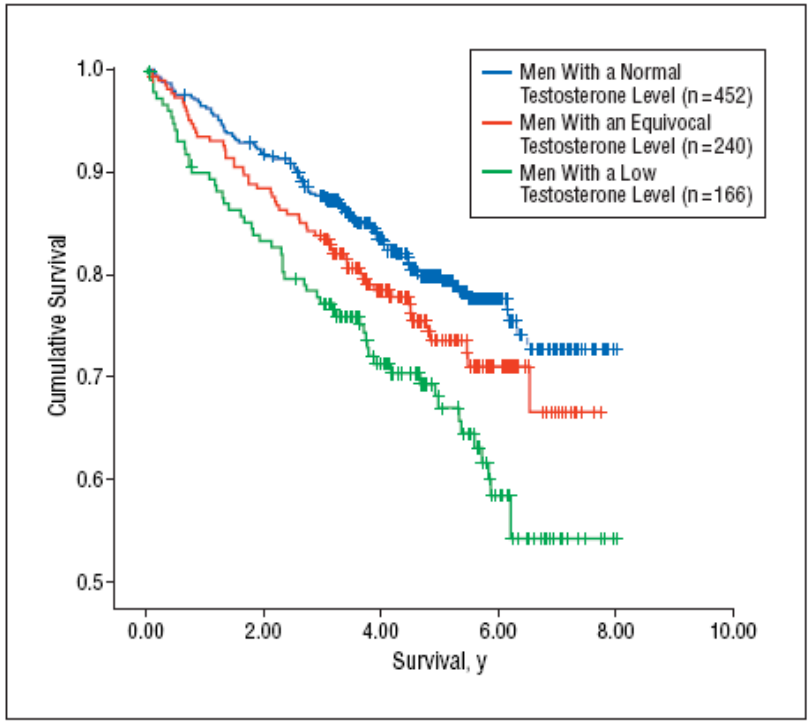


Figure. Unadjusted Kaplan-Meier survival curves for the 3 testosterone level groups. Men with low and equivocal testosterone levels had a significantly shorter survival than men with normal testosterone levels (log-rank test; χ^2_2=14.4, *P*=.001).

Shores et al (Seattle) Arch Int Med 2006; 166: 1660-1665

TD and CVD Risk and All-Cause Mortality

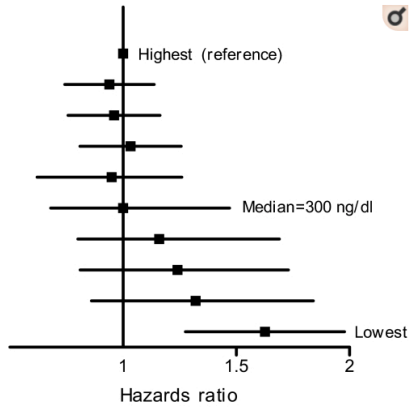
Khaw et al EPIC-Norfolk Sudy

- N = 11,606 men (no cancer or CVD)
  - *825 men died matched with 1489 living men in control group*
  - *Nested case-control looked at endogenous T at baseline*
- Mean follow-up 7 years
- "In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes"

Khaw KT, et al. *Circulation*. 2007;116:2694-2701.

PMC full text: J Clin Endocrinol Metab. 2008 Jan; 93(1): 68–75.
Published online 2007 Oct 2. doi: 10.1210/jc.2007-1792

Figure 1



All-cause mortality according to deciles of total testosterone adjusting for age, BMI, waist to hip ratio, current smoking, alcohol use, and exercise. The *squares* represent point estimates for HRs, the *lines* indicate 95% CIs. The median total testosterone values for deciles 1–10 were 171, 209, 241, 266, 288, 314, 338, 370, 422, and 507 ng/dl, respectively.

Laughlin Rancho Bernardo Study

- Prospective study of 794 men aged 50-91 with T at baseline and followed through mortality
- Average 11.8 years f/u (but up to 20)
- Total and Bioavail T inversely related to risk of death indep of DM, met syn, CVD but attenuated for adjustment by CRP ad IL-6
- Lowest vs highest quartiles of T conferred 40% increased risk of overall mortality and 38% higher risk of CV mort

Laughlin et al. J Clin Endo Metab 2008 Jan;93(1):68-75.

TD Cost

A wealth of modern data accumulated over the past 2 decades has generally revealed that a low serum T level is associated with increased risks of atherosclerosis, CV risk factors, and mortality and that T therapy has beneficial effects on multiple risk factors and risk biomarkers related to these clinical conditions. Notably, TD has been projected to be involved in the development of approximately 1.3 million new cases of CV disease, 1.1 million new cases of diabetes, and over 600,000 osteoporosis-related fractures

Moskovic et al.The 20-year public health impact and direct cost of testosterone deficiency in U.S. men. J Sex Med. 2013;10(2):562–569. doi:10.1111/j.1743-6109.2012.02944.x

Testosterone and Sarcopenia

- "Given the likelihood that age-related sarcopenia contributes importantly to frailty, and the importance of osteoporotic fractures as a cause of morbidity and mortality in elderly men, T replacement is a potentially useful strategy for reducing age-associated disabilities in some aged men."
  - *Three months of T enanthate injections increased lean body mass in men over 60 yr of age.*
  - *T treatment improved hamstring and quadriceps muscle strength after 4weeks in healthy older men*
  - *T replacement for2 yr produced a gain in bilateral grip strength in elderly hypogonadal men.*

Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. Baltimore Longitudinal Study of Aging. Longitudinal effects of aging on serum total and free testosterone levels in healthy men. **J Clin Endocrinol Metab**. *2001;86:724–731.*

Testosterone and Erectile Dysfunction

- "**Visceral obesity**, a component of metabolic syndrome, adversely **affects endothelial function and testosterone levels**, contributing to hypogonadism and erectile dysfunction."
- Clinical screening for the risk of erectile dysfunction in obese patients should include:
  - *Waist circumference*
  - *Testosterone levels*
  - *Body mass index*
  - *Physical inactivity*
- Study of Testosterone levels and ED in 802 men showed moderate and severe ED assoc w/ lower T levels
  - lower serum testosterone levels were strongly associated ($p < 0.001$) with severe (OR 0.78; 95% CI: 0.62-0.86), and moderate ED (OR 0.85; 95% CI: 0.72-0.97)

Traish et al, FEBS Journal, 2009 Oct;276(20):5755-67. Epub 2009 Sep 15

Novo S, Iacona R, Bonomo V, et al. Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the Framingham risk score. *Atherosclerosis*. 2015;238(2):415-419. doi:10.1016/j.atherosclerosis.2014.12.007

TRT BENEFITS

TRT and ED

- Review of studies done on TRT and ED. (Rizk et al, 2017)
- The recently published Testosterone Trials – a set of RCTs of 790 men with late onset hypogonadism randomly assigned to either testosterone gel or placebo – demonstrated that after 1 year of treatment that men who used testosterone gel had an IIEF-ED score 2.64 points [95% Confidence Interval (CI): 1.06 – 4.02] greater than men who had been assigned to the placebo arm
- "The available literature supports a role for TRT in men with low testosterone levels, ED, and low libido, with symptomatic improvement in these men."

Cunningham et al. Testosterone Treatment and Sexual Function in Older Men With Low Testosterone Levels. *PJ J Clin Endocrinol Metab. 2016 Aug; 101(8):3096-104.*

Rizk PJ, Kohn TP, Pastuszak AW, Khera M. Testosterone therapy improves erectile function and libido in hypogonadal men. Curr Opin Urol. 2017;27(6):511-515. doi:10.1097/MOU.0000000000000442

TRT and Cognitive Function

- Testosterone correlated with cognitive function and TRT improves it
  - *High free testosterone was associated with better performance on tests fro memory, executive function and spatial ability*
  - *Reduced risk for Alzheimer's*
  - *Improved cerebral bloodflow*

*Moffat SD, Resnick SM Long-term measures of free testosterone predict regional cerebral bloodflow pattern in elderly men. **Neurobiol Aging**. 2006 May11*

Testosterone and Cognitive Function

- Androgen supplementation in elderly hypogonadal men improves spatial cognition and verbal fluency
- In elderly men without dementia, it may reduce working memory errors
- Testosterone or DHT therapy in men aged 34 to 70 years improved verbal memory and spatial memory respectively

Bassil et al, "The benefits and risks of testosterone replacement therapy: a review," **Therapeutics and Clinical Risk Management** 2009: 5 427-448

Testosterone 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 USA 2000 Feb 1;97(3):1202-5***
- Alzheimer's male patients TRT treated 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*

Testosterone and Bone Mineral Density

- TRT improves bone mineral density in older men
  - *RCT; n=70*
  - T vs placebo vs T+finasteride
  - Treated 36 mos
  - Statistically significant increases in BMD in lumbar spine and hip in T groups but not in placebo groups

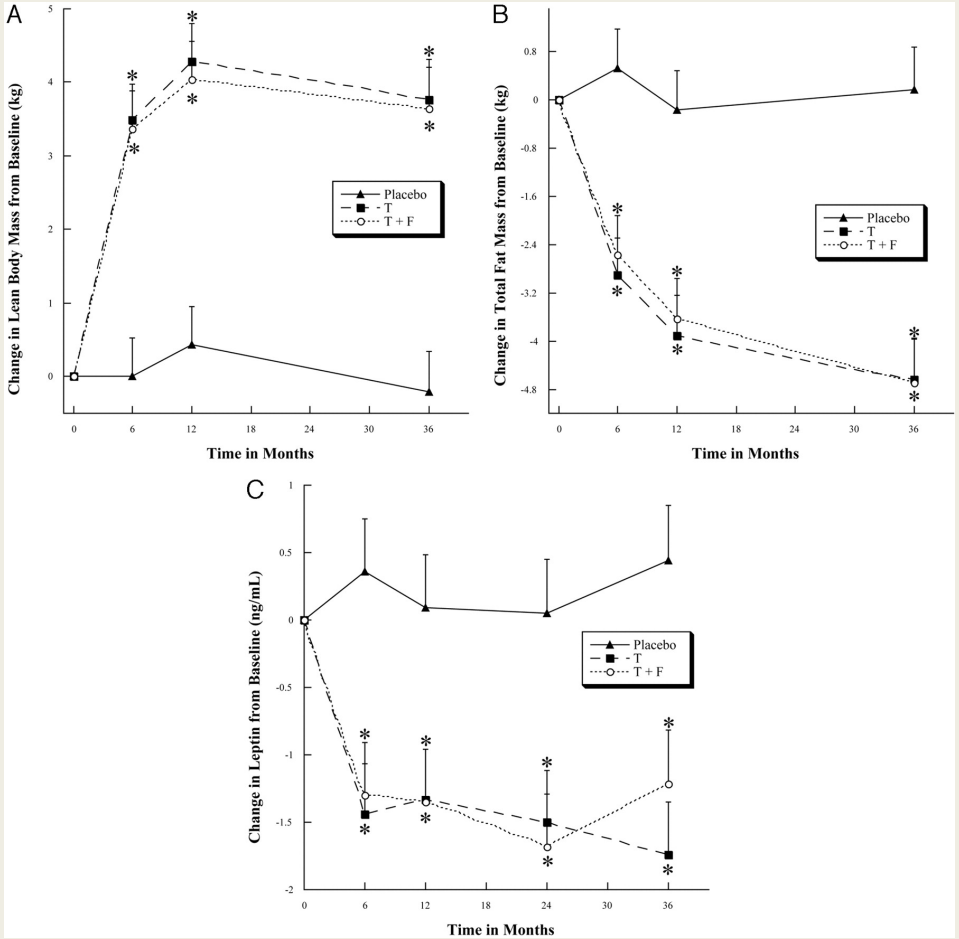
Amory et al Exogenous testosterone or testosterone with finasteride increases bone mineral density in older men with low serum testosterone. J Clin Endocrinol Metab. 2004 Feb;89(2):503-10. doi: 10.1210/jc.2003-031110. PMID: 14764753.

Testosterone and Body Composition

- 4 kg increase in lean mass in 3 years in older men with T use
- Loss of 4.8 kg of fat mass in 3 years

Page ST et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. J Clin Endocrinol Metab. 2005 Mar;90(3):1502-10. doi: 10.1210/jc.2004-1933. Epub 2004 Nov 30. PMID: 15572415.

Fig. 2. Change in body composition and leptin in older men with low T treated with T, T + F, or placebo for 36 ...



J Clin Endocrinol Metab, Volume 90, Issue 3, 1 March 2005, Pages 1502–1510, https://doi.org/10.1210/jc.2004-1933

TRT and Blood Sugar

- Cai et al. 2014 Meta analysis and systematic review of 3-4 studies looking at fasting glc, insuiin and A1C
  - *Statistically significant decrease in fasting glc*
  - *HA1C decrease on average 0.9%*

- Wittert et al.2021 TRT in men with IUGT or newly diagnosed T2DM
  - *40% reduction in number of people progressing to DM*
    - Metformin reduced incidence of DM by 31% in older studies showing its usefulness

Cai et al. Metabolic effects of testosterone replacement therapy on hypogonadal men with type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials; Asian Jnl Andrology 2014 | Volume: 16 | Issue Number: 1 | Page: 146-152
Wittert et al Testosterone treatment to prevent or revert type 2 diabetes in men enrolled in a lifestyle programme (T4DM): a randomised, double-blind, placebo-controlled, 2-year, phase 3b trial. Lancet Diabetes Endocrinol. 2021 Jan;9(1):32-45. doi: 10.1016/S2213-8587(20)30367-3. PMID: 33338415.

Testosterone and Bone Mineral Density and metabolic parameters

- *Shows increased BMD in observational study of TRt*
  - *N=262*
  - *Mean 65 mos but some went off and on (115 were on continuously)*
  - *Observational study*
- *Significant reduction in HA1C (6.4 % to 5.6%) over 9 years*
- *Reduction in SBP*
- *Reduction in waist circumference*

Yassin A et al L. Effects of intermission and resumption of long-term testosterone replacement therapy on body weight and metabolic parameters in hypogonadal in middle-aged and elderly men. Clin Endocrinol (Oxf). 2016 Jan;84(1):107-14. doi: 10.1111/cen.12936. Epub 2015 Oct 2. PMID: 26331709..

SO…TRT (in hypogonadal men) likely has beneficial impact on

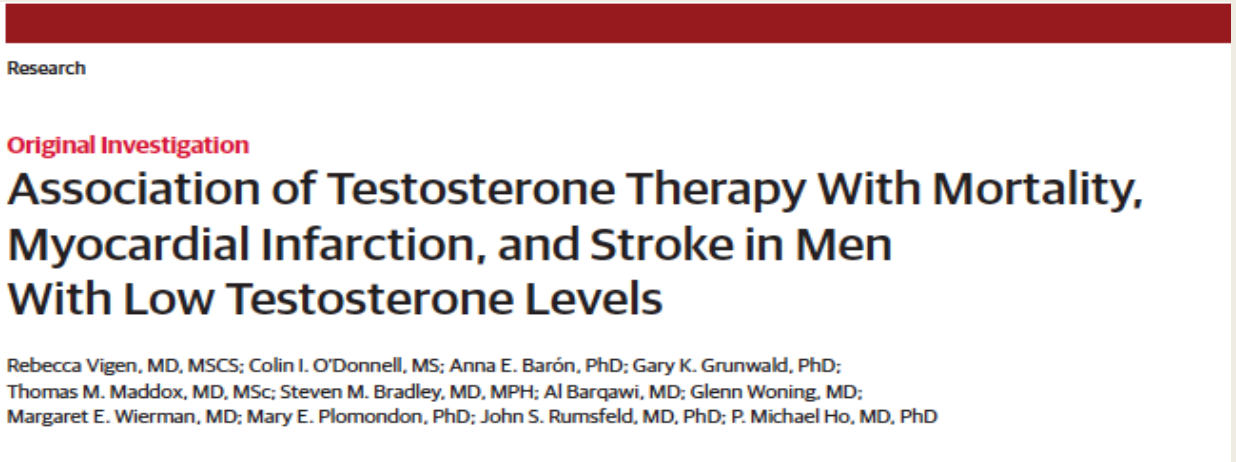
- ED
- Cognitive function in Alzheimers
- BMD
- Body composition
- Metabolic parameters
- Maybe blood pressure

TRT and CV Events

- Srinivas-Shankar et al, 2010
  - *Double-blind RCT of 274 frail elderly patients with low T*
  - *Treated for 6 months with T*
  - *No serious CV events with TRT*
  - *Physical function and strength improved; lean body mass improved*

Srinivas-Shankar et al. J Clin Endocrinol Metab. 2010;95(2):639–650.

Then these

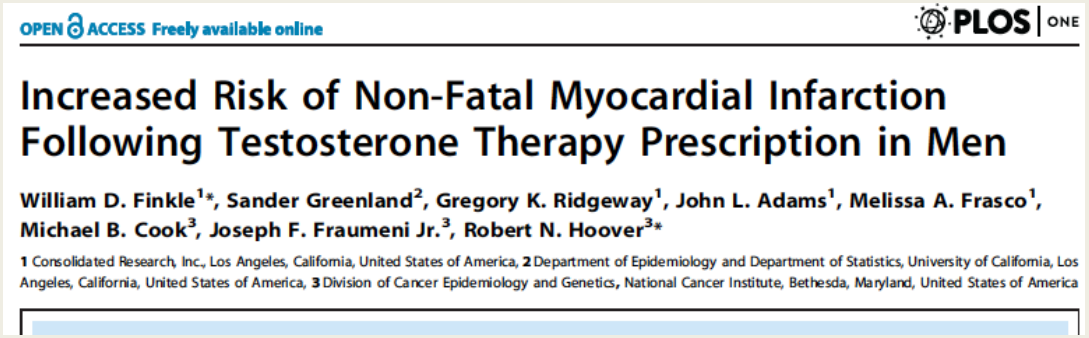


Research

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

Rebecca Vigen, MD, MSCS; Colin I. O'Donnell, MS; Anna E. Barón, PhD; Gary K. Grunwald, PhD; Thomas M. Maddox, MD, MSc; Steven M. Bradley, MD, MPH; Al Barqawi, MD; Glenn Woning, MD; Margaret E. Wierman, MD; Mary E. Plomondon, PhD; John S. Rumsfeld, MD, PhD; P. Michael Ho, MD, PhD



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PLOS | ONE

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle[1]*, Sander Greenland[2], Gregory K. Ridgeway[1], John L. Adams[1], Melissa A. Frasco[1], Michael B. Cook[3], Joseph F. Fraumeni Jr.[3], Robert N. Hoover[3]*

1 Consolidated Research, Inc., Los Angeles, California, United States of America, 2 Department of Epidemiology and Department of Statistics, University of California, Los Angeles, California, United States of America, 3 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

- Vigen R, O'Donnell CI, Barón AE, 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.

- Finkle WD, Greenland S, Ridgeway GK, et al, Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men. PLoS One. 2014 Jan 29;9(1):e85805.

The New York Times

Opinion

EDITORIAL

Overselling Testosterone, Dangerously

By The Editorial Board

Feb. 4, 2014

FDA Advisory Board Sept 2014

- Voted in favor of placing stricter limitations on T prescribing because of concern with “age-related” hypogonadism
- With regards to CV risk, panelists confirmed that “evidence linking T therapy to an increased risk of heart attack, stroke and death is inconclusive”
- Advised the FDA should require drug manufacturers to conduct comprehensive studies to better assess the potential cardiovascular risks with TRT

MARCH 2015: FDA CAUTIONS ABOUT USING TESTOSTERONE PRODUCTS FOR TD DUE TO AGING AND RELATED RISK OF MI AND CVA

Does TRT increase CVD Risk?

Vigen et al, 2013

- No randomization or placebo
- 2 major corrections published
  - *Absolute risk of MI (19.9 vs 25.7%) v (21 vs 10%)*
  - *Exclusion of 1132 men w/ prior MI*
  - *Inclusion of 1000 women*
- Retraction called for by 29 societies

Research

Original Investigation

Association of Testosterone Therapy With Mortality, Myocardial Infarction, and Stroke in Men With Low Testosterone Levels

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Margaret E. Wierman, MD; Mary E. P

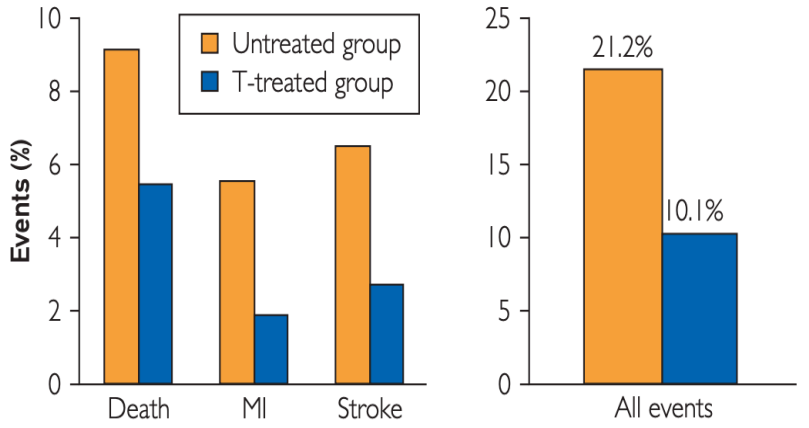
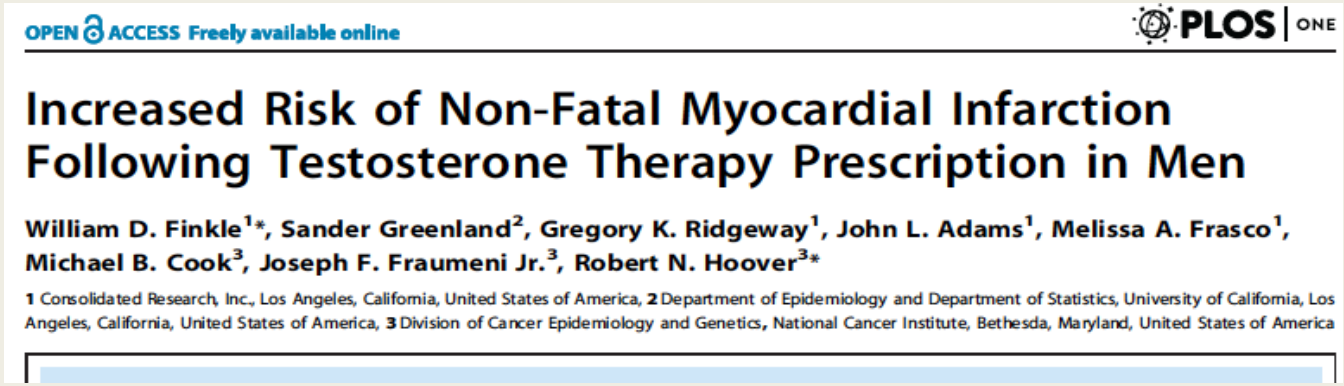


FIGURE. Actual percentage of individuals who experienced an adverse cardiovascular event in the testosterone (T)-treated and untreated groups in the study by Vigen et al.[1] The authors reported a higher rate of adverse events in the T-treated group using inverse stabilized propensity weighting in which an event was counted as more than 1 event in the T-treated group and less than 1 event in the untreated group. MI = myocardial infarction. From *J Sex Med*,[77] with permission. ©2014 International Society for Sexual Medicine.

Does TRT increase CVD Risk?

Finkle et al, 2014

- No randomization or placebo
- No control group or clinical info
- Health insurance database
- 90 days after start T
- PDE5i control group inherently healthier
- Pre-RX MI rate 3.48/1000
- Post-Rx MI Rate 4.75/1000



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PLOS ONE

Increased Risk of Non-Fatal Myocardial Infarction Following Testosterone Therapy Prescription in Men

William D. Finkle[1]*, Sander Greenland[2], Gregory K. Ridgeway[1], John L. Adams[1], Melissa A. Frasco[1], Michael B. Cook[3], Joseph F. Fraumeni Jr.[3], Robert N. Hoover[3]*

1 Consolidated Research, Inc., Los Angeles, California, United States of America, 2 Department of Epidemiology and Department of Statistics, University of California, Los Angeles, California, United States of America, 3 Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland, United States of America

Does TRT increase CVD Risk?

Basaria et al, 2010

Older sicker men with subclin vasc disease and T kept higher (TOM study: Testosterone on Mobility) raised questions of larger doses of T in older frail men

Pop older and sicker and small sample size so unclear how generalizable

- *High prev HTN, DM, hyperlipid, obesity*
- *Inadequate randomization*
- *Doses exceeded recs in guidelines*
- *Small number events*
- *Included high HCT and decrease HDL as event*

Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med*. 2010;363(2):109-122. doi:10.1056/NEJMoa1000485

From abstract conclusion:

In this population of older men with limitations in mobility and a high prevalence of chronic disease, the application of a testosterone gel was associated with an increased risk of cardiovascular adverse events. The small size of the trial and the unique population prevent broader inferences from being made about the safety of testosterone therapy.

The lack of a consistent pattern in these events and the small number of overall events suggest the possibility that the differences detected between the two trial groups may have been due to chance alone."

Does TRT increase CVD Risk?

Xu et al, 2014

Meta analysis of 27 studies

Excluded all studies with no CV events

Only 2 studies provided 1/3 of all CV events in T treatment arm (Basaria and a Danish study using an oral formulation of T at high dose leading to very high levels)

Excluding those 2 studies, CV events identical between T treated and untreated groups

Xu *et al. BMC Medicine* 2013, **11**:108
http://www.biomedcentral.com/1741-7015/11/108

BMC Medicine

RESEARCH ARTICLE Open Access

Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials

Lin Xu[1], Guy Freeman[1], Benjamin J Cowling[1] and C Mary Schooling[1,2*]

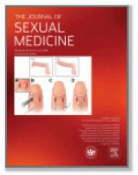
Xu Let al. BMC Med. 2013;11:108. Published 2013 Apr 18. doi:10.1186/1741-7015-11-108

Does TRT increase CVD Risk?

- Systematic review and meta-analysis of 75 placebo-controlled RCTs
- 3016 in T treated groups and 2448 in placebo groups
- Mean duration 34 weeks
- No evidence of increased risk with T therapy on composite or single adverse events
- Clear evidence of improved metabolic profiles from T use

ELSEVIER

The Journal of Sexual Medicine
Volume 15, Issue 6, June 2018, Pages 820-838



Review

Testosterone and Cardiovascular Risk: Meta-Analysis of Interventional Studies

Giovanni Corona MD, PhD [1], Giulia Rastrelli MD, PhD [2], Giuseppe Di Pasquale MD [3], Alessandra Sforza MD [1], Edoardo Mannucci MD, PhD [2, 4], Mario Maggi MD, PhD [2]

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EXPERT OPINION:

The present systematic review and meta-analysis does not support a causal role between TS and adverse CV events. Our results are in agreement with a large body of literature from the last 20 years supporting TS of hypogonadal men as a valuable strategy in improving a patient's metabolic profile, reducing body fat and increasing lean muscle mass, which would ultimately reduce the risk of heart disease.

Corona et al. Expert Opin Drug Saf. 2014; 13(10):1327-1351.

SPECIAL ARTICLE

MAYO CLINIC

Testosterone Therapy and Cardiovascular Risk: Advances and Controversies

Abraham Morgentaler, MD; Martin M. Miner, MD; Monica Caliber, MSc; Andre T. Guay, MD†; Mohit Khera, MD; and Abdulmaged M. Traish, PhD

Abstract

- Review of all articles from 1940-2014 relating to T and CVD
- Over 200 articles identified
- Only 4 articles suggesting increased CV risk with T
- Several dozen studies demonstrated beneficial effects of normalizing T on CV risk and mortality
- T therapy associated w/ reduced obesity, fat mass and waist circ and improves glycemic control
- Mortality was reduced with T in 2 retrospective studies
- Largest meta-analysis to date showed no increase in CV risks

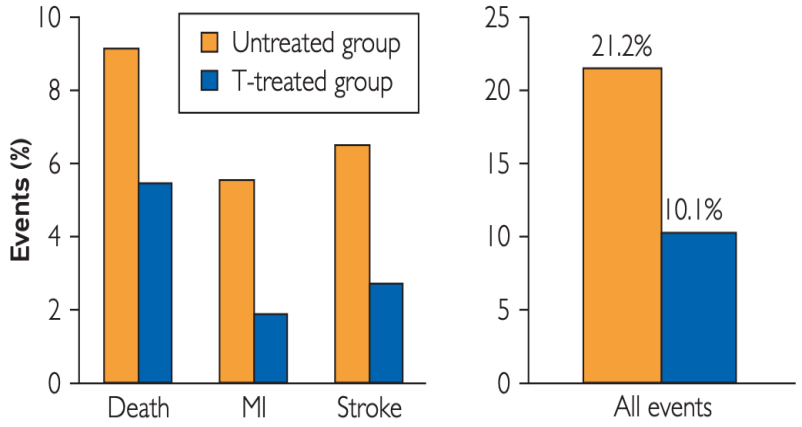


FIGURE. Actual percentage of individuals who experienced an adverse cardiovascular event in the testosterone (T)-treated and untreated groups in the study by Vigen et al.[1] The authors reported a higher rate of adverse events in the T-treated group using inverse stabilized propensity weighting in which an event was counted as more than 1 event in the T-treated group and less than 1 event in the untreated group. MI = myocardial infarction. From *J Sex Med*,[77] with permission. ©2014 International Society for Sexual Medicine.

Morgentaler et al. Mayo Clin Proc. 2015 Feb;90(2):224-51.

TRT and CV Mortality

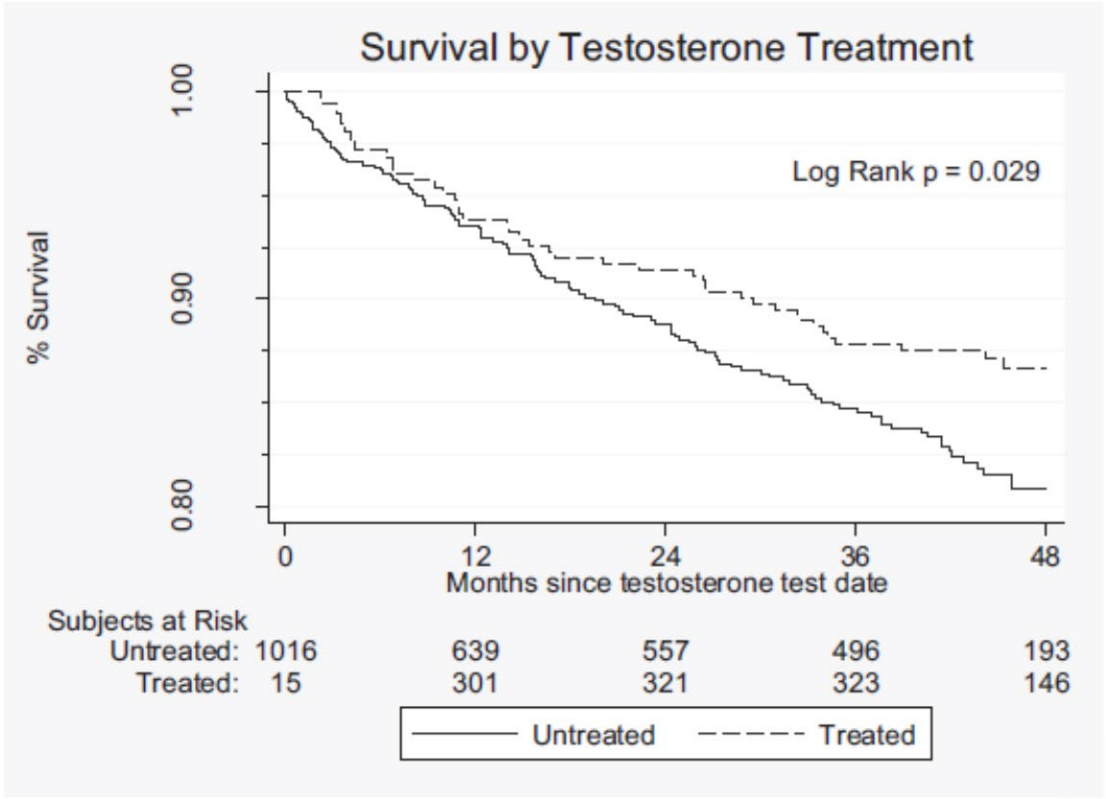
- Shores et al, 2012
  - *Observational study of 1031 male veterans with low T; treated with T in 398*
  - *T treatment was associated with decreased risk of death (hazard ratio 0.61 (0.42-0.88; P=0.008)) adjusted for age, DM, CHD, BMI, T level*
  - *3.4 vs 5.7 deaths per 100 pt years*

Shores et al. J Clin Endocrinol Metab. 2012;97(6):2050-2058.

- Muraleedharan, 2013
  - *Observational study of 581 men with Diabetes over a mean of 5.8 years with effect of TRT assessed retrospectively*
  - *TRT associated with reduced mortality of 8.4% compared with 19.2 % (p=0.002) in untreated group with HR of 2.3 in the untreated group vs the treated group (1.303.9, p=0.004)*

Muraleedharan V, et al. Eur J Endocrinol. 2013;169(6):725- 733)

Survival in T treated vs non T treated Men

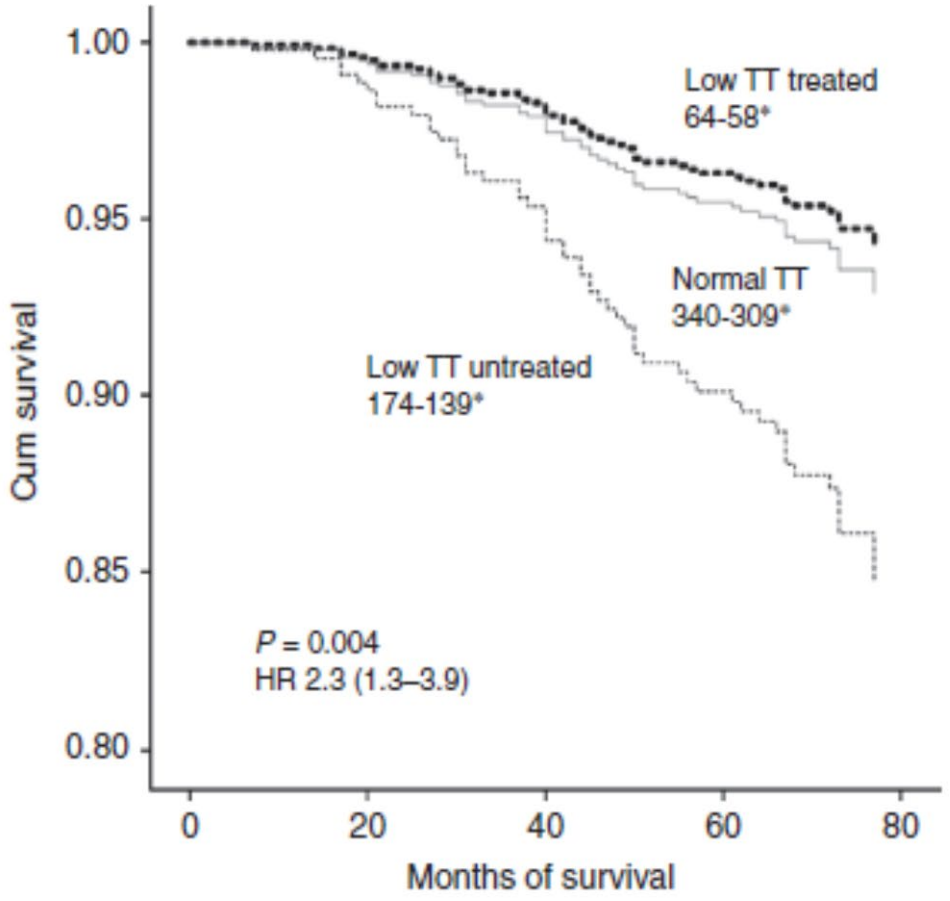


- N=1031
- Men>40y
- T<250 ng/dl
- Mortality:
  - 20.7% untreated
  - 10.3% T treated
  - P<0.0001

VA, US Department of Veterans Affairs

Shores MM et al. *J Clin Endocrinol Metab.* 2012 ;97(6):2050-8.

T deficiency in men with DM associated with lower survival; reversed with



- Muraleedharan V et al

  Eur J Endocrin 2013
- 581 men T2DM
- F/u 5.8y
- Low T defined <300ng/dl (10.4 nmol/L
- Men with low T untreated HR 2.3 (CI95% 1.3-3.5; p=0.004)
- T therapy- Reduced from 19.2% to 8.4%

The Testosterone Trials

7 placebo-controlled, double-blind trials

788 men mean age 72

- Sexual function trial – T increased sexual activity, sexual desire and erectile function
- Physical function – increased distance walked across all Ttrial participants, but not in those with slow walk speed
- Vitality trial – T improved mood but not energy
- Cognitive function – no change in cognitive function
- Anemia trial – T increased Hgb
- Bone trial – T increased BMD
- Coronary vascular trial – T increased noncalcified plaque volume by CT angio
- No increase in CV adverse events in T groups vs placebo


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 18, 2016 VOL. 374 NO. 7

Effects of Testosterone Treatment in Older Men

P.J. Snyder, S. Bhasin, G.R. Cunningham, A.M. Matsumoto, A.J. Stephens-Shields, J.A. Cauley, T.M. Gill, E. Barrett-Connor, R.S. Swerdloff, C. Wang, K.E. Ensrud, C.E. Lewis, J.T. Farrar, D. Cella, R.C. Rosen, M. Pahor, J.P. Crandall, M.E. Molitch, D. Cifelli, D. Dougar, L. Fluharty, S.M. Resnick, T.W. Storer, S. Anton, S. Basaria, S.J. Diem, X. Hou, E.R. Mohler III, J.K. Parsons, N.K. Wenger, B. Zeldow, J.R. Landis, and S.S. Ellenberg, for the Testosterone Trials Investigators*

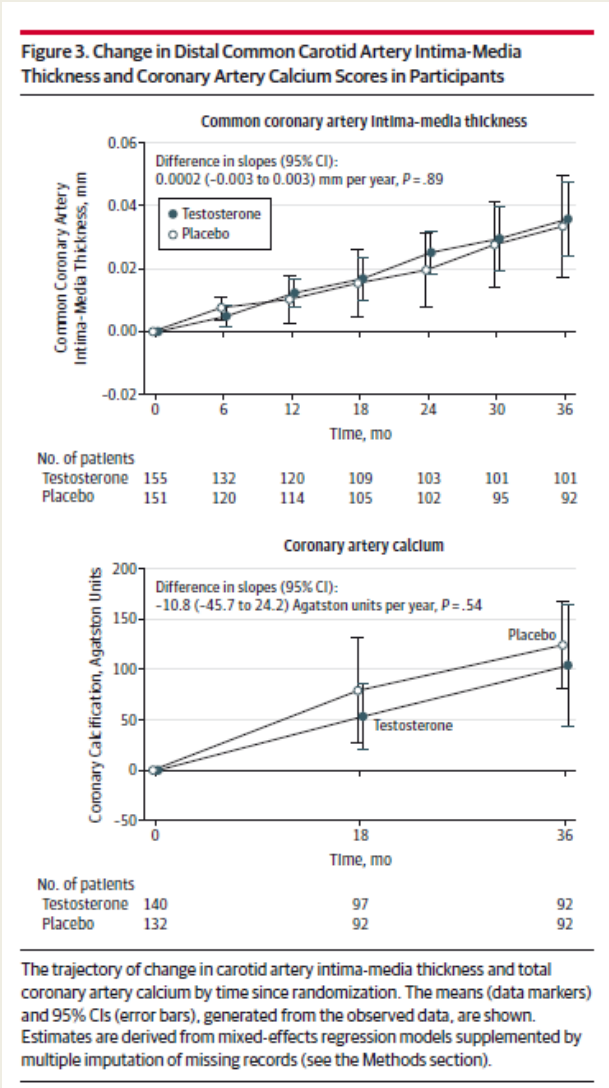
TRT and Atherosclerosis

- Randomized, placebo-controlled, parallel-group, double-blind trial
- Men > 60 yo with AM T 100-400 ng/dl or free T <50 pg/ml
  - *155 TRT versus 151 placebo*
- Primary: Measure change in distal right common carotid artery intima-media thickness
- Secondary: coronary artery calcium score change
- Men received 75 mg 1% T gel x 3 yrs. titrated between 500-900 ng/dL. Radiographic and lab measurements every 6 mo
- “No significant association between randomization to testosterone and the rates of intima-media thickness progression or change in coronary artery calcium scores”

Basaria S, JAMA. 2015 Aug 11;314(6):570-81..

Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels
A Randomized Clinical Trial

Shehzad Basaria, MBBS; S. Mitchell Harman, MD, PhD; Thomas G. Travison, PhD; Howard Hodis, MD; Panayiotis Tsitouras, MD; Matthew Budoff, MD; Karol M. Pencina, PhD; Joseph Vita, MD; Connie Dzekov, BS; Norman A. Mazer, MD, PhD; Andrea D. Coviello, MD, MS; Philip E. Knapp, MD; Kathleen Hally, BS; Emma Pinjic, MD, MPH; Mingzhu Yan, MD; Thomas W. Storer, PhD; Shalender Bhasin, MBBS



TRT and CAD

3 RCTs showing TRT improves myocardial ischemia in men with CAD

- English et al, 2000
  - n=46 with chronic stable angina used T patch and underwent ETT
  - Signif increase in time to 1-mm ST-segment depression from baseline vs non-intreated p=0.02
- Rosano et al, 1999
  - n=14 men with chronic stable angina underwent ETT within 30 minutes of IV T
  - Signif increase in time to 1-mm ST-segment depression from baseline vs non-intreated p<0.01
- Webb et al, 1999
  - n=14 men with CAD and low T; double blinded crossover underwent ETT
  - Signif increase in time to 1-mm ST-segment depression from baseline vs non-intreated p=0.016
    - Also published separate study in Circ showing infusion of T was followed by signif increase coronary blood flow using angio and intracoronary dopplers

- *English et al. 2000 Oct17;102(16):1906-11.*
- *Rosano et al. Circulation. 1999 Apr 6;99(13):1666-70.*
- *Webb et al. Am J Cardiol. 1999 Feb 1;83(3):437-9, A9.*
- *Webb et al. Circulation. 1999;100(16):1690-1696. doi:10.1161/01.cir.100.16.1690*

TRT and CAD

- Retrospective review
- 83,010 men in VA hospital system with low Testosterone
- Compared ~44,000 men on TRT who achieved normal follow up T levels (& 26,000 subtherapeutic T levels) to 13,378 untreated men
  - *Mean f/u 6.2 years*
- Men on TRT vs no treatment had decreased
  - *All-cause mortality*
  - *MI*
  - *Stroke*
- Treated men with normal f/u T levels versus treated men who failed to reach normal T levels had decreased
  - *All-cause mortality*
  - *MI*
  - *stroke*

Sharma R, Oni OA, Gupta K, et al. Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men. Eur Heart J 2015;36(40):2706–15.

European Heart Journal (2015) **36**, 2706–2715
doi:10.1093/eurheartj/ehv346

FASTTRACK CLINICAL RESEARCH
Coronary artery disease

Normalization of testosterone level is associated with reduced incidence of myocardial infarction and mortality in men

Rishi Sharma[1], Olurinde A. Oni[1], Kamal Gupta[2], Guoqing Chen[3], Mukut Sharma[1], Buddhadeb Dawn[2], Ram Sharma[1], Deepak Parashara[2,4], Virginia J. Savin[5], John A. Ambrose[6], and Rajat S. Barua[1,2,4]*

[1]Division of Cardiovascular Research, Kansas City VA Medical Center, Kansas City, MO, USA; [2]Division of Cardiovascular Diseases, University of Kansas Medical Center, Kansas City, KS, USA; [3]Division of Health Services Research, University of Kansas Medical Center, Kansas City, KS, USA; [4]Division of Cardiovascular Medicine, Kansas City VA Medical Center, 4801 E. Linwood Boulevard, Kansas City, MO 64128, USA; [5]Division of Nephrology, Kansas City VA Medical Center, Kansas City, MO, USA; and [6]Division of Cardiovascular Medicine, University of California San Francisco, Fresno, CA, USA

Received 2 June 2015; revised 1 July 2015; accepted 6 July 2015; online publish-ahead-of-print 6 August 2015

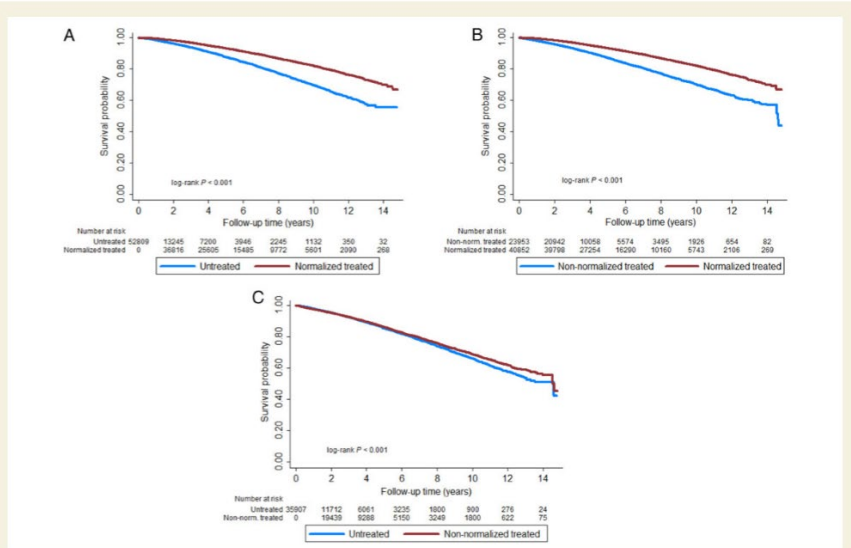


Figure 2 (*A*–*C*) Kaplan–Meier curve depicting the all-cause mortality among different propensity-matched study groups.

- T and CV studies from September 2014 to July 2017 [After the FDA Label Change]
- 23 studies (12 clinical trials, 11 observational studies)
- Results:
  - No study reported increased MACE with TRT
  - Men whose T normalized with TRT had reduced risk of MI and death compared with men whose T levels failed to normalize

Miner M et al Clin Endocrinol (Oxf). 2018;89(1):3-10. doi:10.1111/cen.13589

TRT and CVD Risk Factors: Met Syn / DM

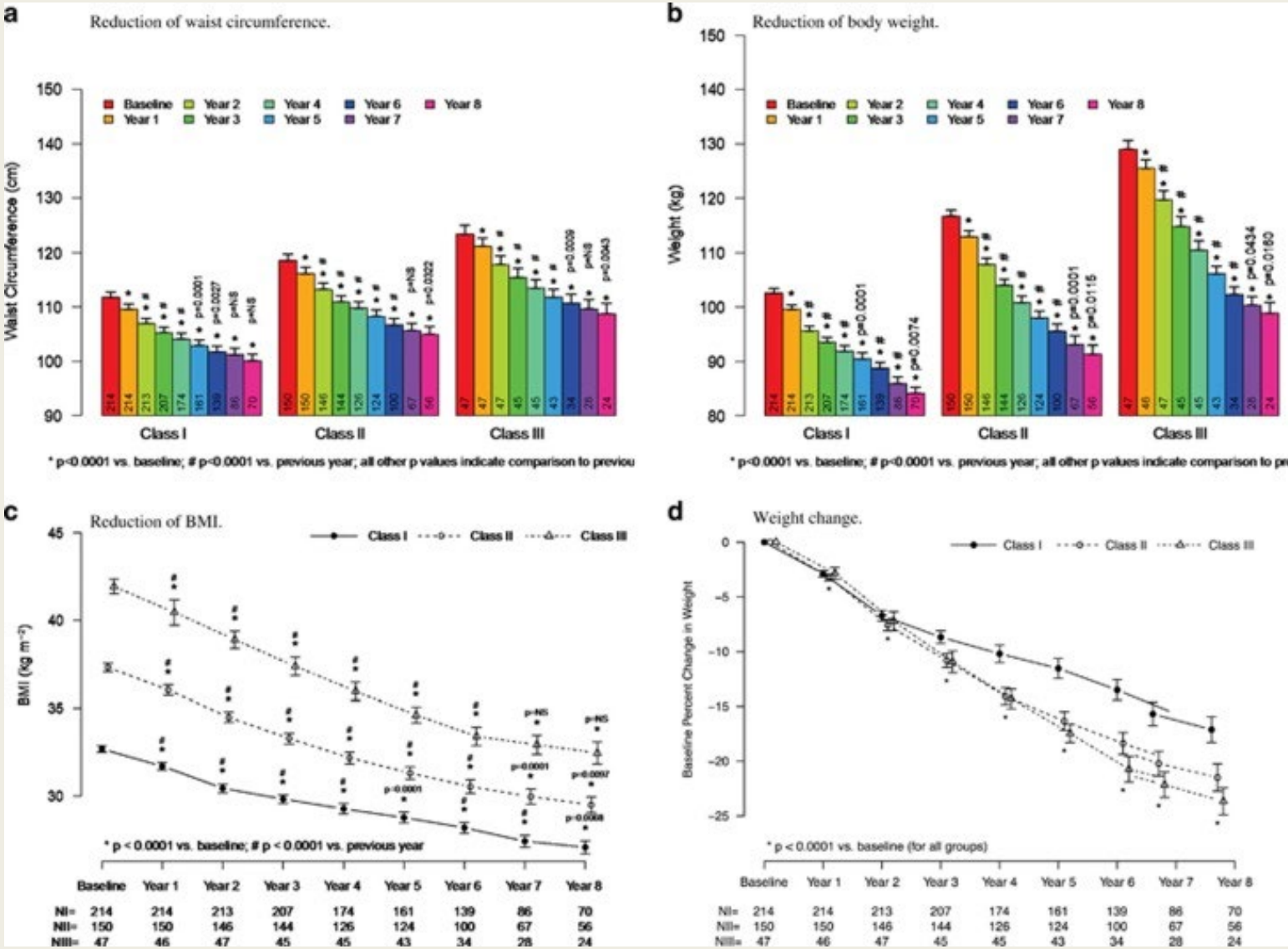
Good evidence TRT reduces fat mass in multiple studies

- 2 Registry studies of 411 men on T show significant decrease in body weight, BMI, waist circumference; mean f/u 6 years (Saad, 2016)

Many studies have sown that TRT improves insulin sensitivity and blood sugar control measured as HA1c or HOMA-IR.

- Meta analysis in 2016 looked at 32 published studies (cross-sectional, longitudinal and RCTs) showing that TRT was associated with weight loss and waist circumference reduction (3.5 kg (-1.8, -5.21)) and 6.23 cm (-4.7, -7.94)) at 2 mos and a significant reduction in fasting glucose and HOMA-IR (-0.80 (-0.45, -1.16))

- Improved HA1C has been shown from TRT in multiple studies in men with DM and pre-DM (Goodale, 2016)



Goodale et al. Methodist Debakey Cardiovasc J. 2017;13(2):68–72. doi:10.14797/mdcj-13-2-68

Corona et al. J Endocrinol Invest. 2016;39(9):967–981. doi:10.1007/s40618-016-0480-2

Saad F, et al. Int J Obes (Lond). 2016;40(1):162–170. doi:10.1038/ijo.2015.139

Testosterone and Inflammation

- Testosterone therapy created a more anti-inflammatory profile
- Fewer inflammatory cytokines
  - *TNF*
  - *IL-1 beta*
- 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 Endoclinol Metab.*** *2004 Jul;89(7):3313-8*

Testosterone and Inflammation

- Inflammation plays a central pathogenic role in the initiation and progression of coronary atheroma and its clinical consequences.
- Cytokines are the mediators of cellular inflammation and promote local inflammation of the arterial wall, which may lead to vascular smooth muscle apoptosis, degradation of the fibrin cap and placque rupture

Malkin et al. Testosterone as a protective factor against atherosclerosis ***J Endocrinol*** *2003 Sept;178(3):373-80*

Testosterone and BPH

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

Rhoden E et al. “Medical Progress: Risks of Testosterone Replacement Therapy and Recommendations for Monitoring.” **N Engl J Med** 2004; Jan 29; 350:482-492

Testosterone and BPH

- "Testosterone replacement therapy appears to have little effect on prostate tissue androgen levels and cellular function and causes no significant adverse effects on the prostate."
- "At the present time, there is no conclusive evidence that testosterone therapy increases the risk of prostate cancer or benign prostatic hyperplasia (BPH)"

Bassil et al, "The benefits and risks of testosterone replacement therapy: a review," **Therapeutics and Clinical Risk Management** 2009: 5 427-448

Testosterone and Prostate Cancer

Gould looked at the risk of testosterone therapy inducing prostate cancer:

- *Review of 16 studies – some placebo controlled*
- *No increased risk over background prevalence*
- *Up to 15 years following patients*

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):14-18*

Testosterone and Prostate Cancer

- Morgentaler A Testosterone and Prostate Cancer: An Historical Perspective on a Modern Myth. **Eur Urol.** 2006 Jul 26;
  - *1941: Huggins and Hodges reported that reductions in testosterone via castration or estrogen treatment caused metastatic prostate CA to regress*
  - *Administration of exogenous testosterone caused a PC to grow (one patient)*
  - *Multiple reports revealed no PC progression with testosterone administration*

Testosterone and Prostate Cancer

- No increased risk of prostate cancer in:
  - *Clinical trials of testosterone supplementation*
  - *Longitudinal or population-based studies*
  - *High-risk population of hypogonadal men receiving testosterone treatment*

Morgentaler A Testosterone therapy and prostate risks: where's the beef**? Can J Urol.** 2006 Feb;13 Suppl 1:40-43

Testosterone and Prostate Cancer

- "No compelling evidence at present to suggest that men with higher testosterone levels are at greater risk of prostate cancer or that treating men who have hypogonadism with exogenous androgens increases this risk. In fact, it should be recognized that prostate cancer becomes more prevalent exactly at the time in a man's life when testosterone levels decline."

Roden, E et al, "A medical progress: risks of testosterone-replacement therapy and recommendations for monitoring," **NEJM** 2004; 350:482-92

May 2016: TRT Does Not Inc Risk of Prostate Cancer

- Analysis of more than a quarter-million medical records of mostly white men in Sweden
- Men prescribed T for over a year had no overall increased risk of prostate cancer; had risk of aggressive disease **reduced** by 50%
- 38,570 men whose records were examined developed prostate cancer between 2009-2012
  - *284 of these men had prescriptions for TRT before diagnosis*
  - *192,838 men did not develop prostate cancer; 1,378 of them used TRT*
- Long-term reduction in aggressive disease observed only in men after over a year of TRT; risk of prostate cancer did not differ between dosage forms

Loeb, Stacy, Joseph Alukal, Yasin Folkvaljon, Jan-Erik Damber, Mats Lambe, and Pär Stattin. "Study Suggests Testosterone Therapy Does Not Raise Risk of Aggressive Prostate Cancer." NYU Langone Medical Center; Isaac Perlmutter Cancer Center; New York University School of Medicine, 7 May 2016.

TRT and Sexual Symptoms

Multiple reviews of studies on the topic confirmed treating with T in men who are T deficient help multiple aspects of sexual functioning including libido, erectile functioning and overall sexual satisfaction.

Generally they used 12 nmol/l (317 ng/dl) as the cut-off

Corona G, et al. Testosterone Therapy: What We Have Learned From Trials. J Sex Med. 2020;17(3):447-460. doi:10.1016/j.jsxm.2019.11.270

Rastrelli G,, et al. Testosterone Replacement Therapy for Sexual Symptoms. Sex Med Rev. 2019;7(3):464-475. doi:10.1016/j.sxmr.2018.11.005

TRT and mood

- TRT shown to help depressive symptoms and overall mood in men aged 65 and over (n= 790; Snyder et al, 2016)
- T trials: 7 double-blind placebo RCTs of 788 men 65 and older
  - *Compared to placebo, testosterone treatment moderately improved sexual function, hemoglobin concentration and corrected anemia, and slightly improved walking distance, vitality, mood and depressive symptoms and bone density and strength, but did not improve cognitive function.*

Snyder et al. N Engl J Med. 2016;374(7):611-624. doi:10.1056/NEJMoa1506119
Matsumoto et al. Curr Opin Endocr Metab Res. 2019;6:34-41. doi:10.1016/j.coemr.2019.04.004

Testosterone and symptoms overall

- Online self-reported survey of men 21 and over; n=105
- Results indicated that the most frequent reasons men gave for taking prescription testosterone were low testosterone (37.1%), well-being (35.2%), energy (28.7%), libido (21.9%), and social energy (19.4%); older men claimed libido as a motivation for testosterone initiation more frequently than younger men ($p < 0.001$). Men most frequently claimed testosterone improved their energy (52.3%), libido (41.9%), and muscle (28.5%).
- QOL: European stuy of 750 men on T
  - Patients on TRT reported rapid and sustained improvements in QOL, with fewer sexual, psychological, and somatic symptoms well maintained for up to 36 mos post initiation

Straftis A et al. . *Int J Environ Res Public Health*. 2019;16(18):3261. Published 2019 Sep 5. doi:10.3390/ijerph16183261

Rosen RC, Wu F, Behre HM, et al. Quality of Life and Sexual Function Benefits of Long-Term Testosterone Treatment: Longitudinal Results From the Registry of Hypogonadism in Men (RHYME). J Sex Med. 2017;14(9):1104-1115. doi:10.1016/j.jsxm.2017.07.004

Interim Conclusions

- Increased insulin resistance has led to an obesity epidemic
- Increased environmental toxins has created endocrine disruption leading to inflammation and imbalance
- Increased stress/cortisol demand has contributed to the obesity epidemic and enhanced hormonal imbalances
  - *Decreased availability of progesterone for testosterone production and estrogen balance*
  - *Decreased availability of DHEA*
  - *Increased aromatization of testosterone to estrogen resulting in a pro-inflammatory environment*

Interim Conclusions

- The environment for increased inflammation and its disease consequences has been created:
  - *Increased adiposity and testosterone conversion to estrogen*
  - *Decreased testosterone, progesterone and DHEA production*
- We must strive to limit toxin exposure.
- We must focus on hormone balance for all hormones; testosterone, estrogen, progesterone, DHEA, insulin, cortisol and thyroid.
- Treating T deficient men reduces risk of met syn, sexual symptoms and improves overall quality of life

General Treatment Plan

- Appropriate amount of sleep
- Reduce toxin exposure
  - *BPA*
  - *Phthalates*
  - *Organic foods to limit pesticide exposure*
- Reduce inflammation: Vitamin D and EPA/DHA supplementation; consider other anti-inflammatory herbs/nutrients
- Treat metabolic syndrome with meds, diet, exercise
- Stress management
- T Therapy if needed

HOW TO DO T THERAPY (TTH)

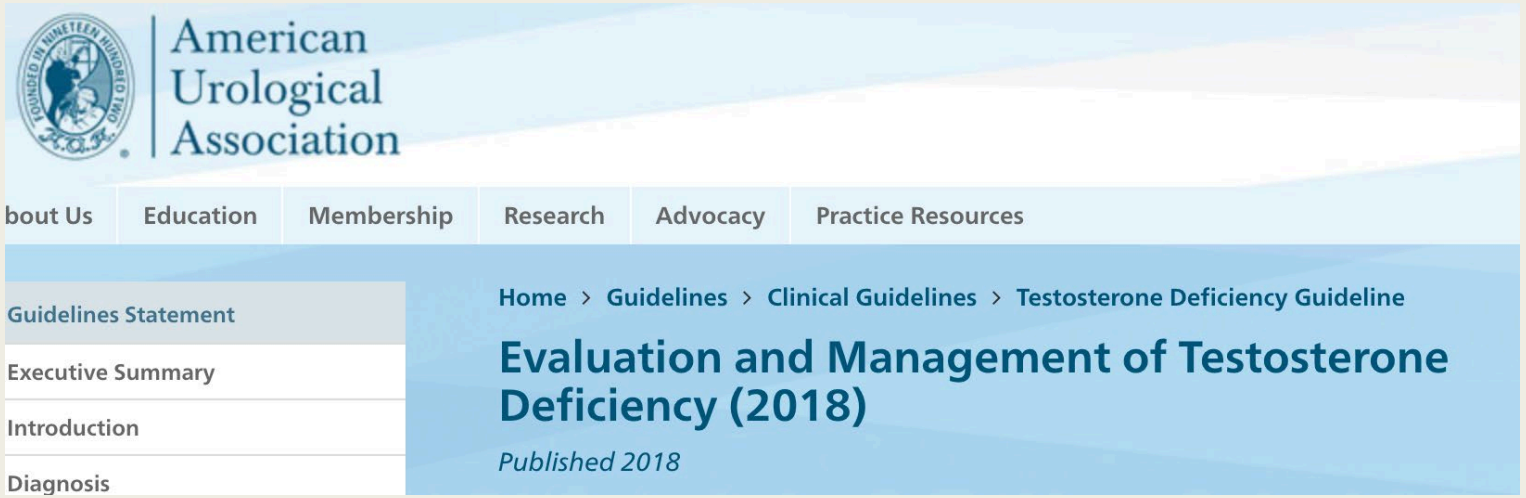
AUA and Endocrine Society Guidelines

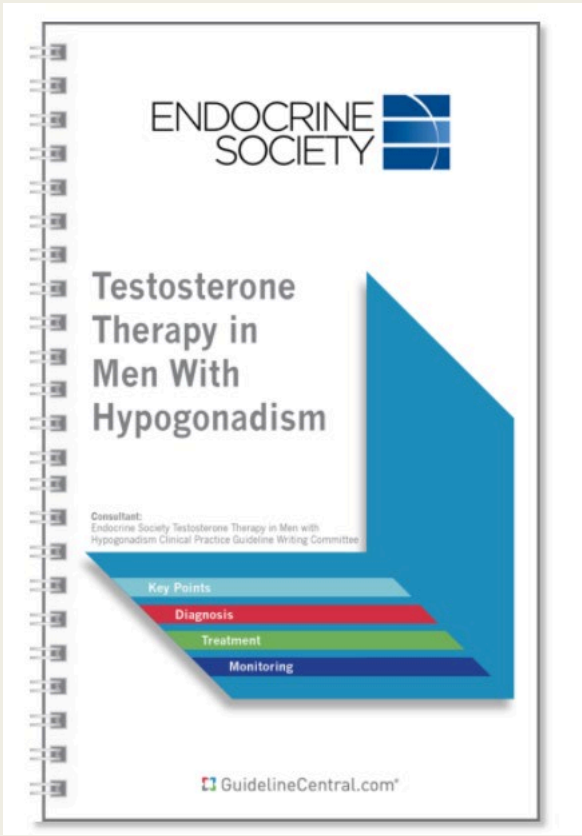
- AUA, 2018

https://www.auanet.org/guidelines/testosterone-deficiency-guideline

- Endocrine Society, 2018

https://www.endocrine.org/clinical-practice-guidelines/testosterone-therapy





Testosterone Treatment in Adult Men With Age-Related Low Testosterone

Background

There is a gradual decline in serum total testosterone levels in men associated with aging, referred to as age-related low testosterone. It is uncertain whether nonspecific signs and symptoms that are associated with age-related low testosterone, such as sexual dysfunction, decreases in energy and muscle mass, mood disturbances, and weakness, are a consequence of low testosterone levels or whether they are a result of other factors, such as chronic illnesses or concomitant medications.

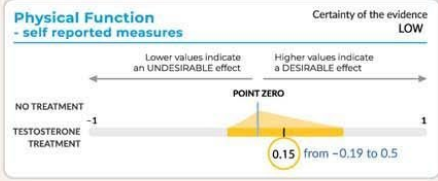
Patient Population
Adult men with age-related low testosterone

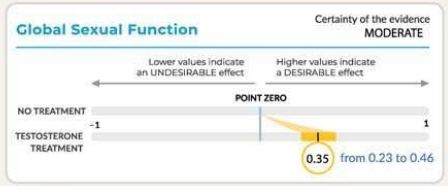
Interventions Compared
Testosterone treatment (transdermal or intramuscular) vs. no treatment

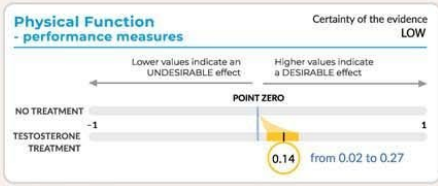
Outcomes Evaluated

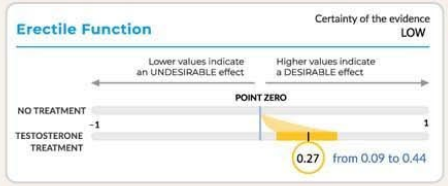
Standardized Mean Difference

With NO treatment, patient symptoms (measured with several different scales) will be "POINT ZERO." The effect of treatment is measured in standardized units and is shown with CIs.









Values and Preferences

Values and preferences vary according to individual patients. One study showed that more men preferred injectable testosterone compared with gel-based and pellet regimens due to the lower cost, whereas in another study, most men preferred a topical gel product over an injection or patch due to convenience, ease of use, and not staining clothes, among others.

Recommendations

RECOMMENDATION 1a: ACP suggests that clinicians discuss whether to initiate testosterone treatment in men with age-related low testosterone with sexual dysfunction who want to improve sexual function (conditional recommendation; low-certainty evidence). The discussion should include the potential benefits, harms, costs, and patient's preferences.

RATIONALE: *Current evidence shows that men with age-related low testosterone may show small improvements in sexual functioning with testosterone treatment, although there is little to no improvement on physical function, depressive symptoms, energy/vitality, or cognition. Evidence for harms was difficult to judge due to the low power of studies or limited available information.*

RECOMMENDATION 1b: ACP suggests that clinicians should re-evaluate symptoms within 12 months and periodically thereafter. Clinicians should discontinue testosterone treatment in men with age-related low testosterone with sexual dysfunction in whom there is no improvement in sexual function (conditional recommendation; low-certainty evidence).

RATIONALE: *Most studies included in the evidence review followed patients for 12 or fewer months, so the longer term benefits and harms of testosterone treatment are unknown.*

RECOMMENDATION 1c: ACP suggests that clinicians consider intramuscular rather than transdermal formulations when initiating testosterone treatment to improve sexual function in men with age-related low testosterone, as costs are considerably lower for the intramuscular formulation and clinical effectiveness and harms are similar.

RATIONALE: *Direct evidence was limited; however, there were no substantial differences in clinical effectiveness, benefits, or harms between intramuscular and transdermal testosterone applications. Intramuscular testosterone is substantially cheaper than transdermal testosterone ($156.32 vs. $2135.32 per person per year) and thus is the preferred option for testosterone treatment.*

RECOMMENDATION 2: ACP suggests that clinicians not initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition (conditional recommendation; low-certainty evidence).

RATIONALE: *Evidence showed very little or no benefits for common concerns of aging, including energy and vitality, physical function, and cognition, and evidence on long-term harms is lacking. Therefore, asymptomatic men with age-related low testosterone should not be prescribed testosterone treatment, except for treating sexual function issues.*

Clinical Considerations

- The testosterone level at which to start treatment is not clear. There were no clear differences in sexual function outcomes based on baseline testosterone level, although mean levels were below 10.4 nmol/L (300 ng/dL) in most of the trials.

  Use caution in applying these recommendations to persons with comorbid conditions.
- Safety monitoring varied across trials. Given the very low incidence of some adverse events, such as prostate cancer, in the trials, it is difficult to provide evidence-based monitoring recommendations. However, given the theoretical potential for an elevation of prostate cancer risk and polycythemia, some regular monitoring is reasonable.

Talking Points With Patients

- Testosterone treatment may improve sexual function in some men, but the amount of improvement varies.
- Testosterone is used to treat sexual symptoms, so if these symptoms do not improve, treatment should be stopped.
- Testosterone treatment does not seem to improve other common concerns of aging.
- Both injectable and topical forms of testosterone can improve sexual function, but the injectable form costs more than 10 times less.

Baseline Testing for Testosterone Deficiency

- Blood testing (serum)
  - *Total/free testosterone*
  - *SHBG*
  - *DHT*
  - *DHEA*
  - *Estradiol*
  - *LH/FSH*
- 24 hour urine testing
- Saliva testing
- Blood spot testing
- Dried urine test

Does time of collection matter?

- Guidelines recommend collecting an early-morning sample to compensate for the natural diurnal variation in testosterone levels. But for men 45 and older, this is unnecessary.
- 2569 men at Minneapolis VA looked at T levels based on age throughout the day
- Only youngest men (<45) had significant difference based on an age

Welliver RC Jr, Wiser HJ, Brannigan RE, et al. Validity of midday total testosterone levels in older men with erectile dysfunction. *J Urol.* 2014;192:165-169.

Morgentaler A. Commentary: Guideline for Male Testosterone Therapy: A Clinician's Perspective; The Journal of Clinical Endocrinology & Metabolism 92(2):416–417
Printed in U.S.A. Copyright © 2007 by The Endocrine Society
doi: 10.1210/jc.2006-2629

Methods of T Th

- Transdermal patch
- Topical T
- Injectable T
- Oral
- Pellets
- Clomiphene
- HGH

TRT: Transdermal Patches

- Testosterone Patch
  - *Available in 2-mg and 4 mg preparations*
    - Typical starting dose is 4-mg/day; can increase to 8-mg or decrease to 2 -mg as needed
  - *Applied at night to a clean, dry area of skin on the back, stomach, upper arms, or thighs.*
  - *Sites should be rotated daily, allowing 7 days before re-applying to the same site*
  - *Side effects:*
    - Skin irritation, vesicle formation, contact dermatitis, headache, and depression

TRT: Gel Formulations

- Testosterone Gels
  - *Applied in the morning to the shoulders, abdomen, or upper arm; preferably at the same location every day*
    - Use gloves or wash hands after application- They will have hormone on hands for 4-12 hours
    - Allow gel to dry (10-15 min) before covering with clothing
    - Wait 4 hours prior to showering or swimming
    - Wash with soap and water if skin-to-skin contact with another person anticipated
  - *Dosing: 1% or 1.62% generally available*
  - *5 grams (50 mg testosterone) daily, can be increased to 7.5 – 10 grams as needed or 40.5 mg of the 1.62%, can be increased in increments of 20.25mg*
  - *Side effects: acne, headaches, emotional lability, nervousness, gynecomastia, mastodynia, insomnia, hypertension, hot flashes, polycythemia, and increased PSA*
  - *Local skin irritation occurs much less frequently than with patches*
  - *Major issue is transference*
  - *Substantial variation in absorption*

Testosterone with Pentadecalactone

- Marbury T, et al.
  - *Randomized, complete crossover study to compare the pharmacokinetic profiles of Testosterone A and Testosterone B gel*
  - *Testosterone B provides higher serum levels and greater bioavailability than Testosterone A (at equal doses)*
  - *Difference was 30% for total and 38% for free T*
  - *Enhances absorption but has a unique odor and possible skin reaction*
- Grober E et al.
  - *Test of changing formulations found switching to pentadecalactone prep increased total T from an average of 311 to 484 ($p<0.001$)*

Marbury et al. Biopharm Drug Dispos. 2003;24(3):115–120
Grober E et al. *Int J Impot Res* **20,** 213–217 (2008). https://doi.org/10.1038/sj.ijir.3901618

Injectable Testosterone

- Testosterone esters in oil are slowly absorbed from the lipid phase
- Different esters absorb at various rates giving them different half lives:
  - *T cypionate 12 days*
  - *T enanthate 10.5 days*
  - *T propionate 4.5 days*
- The longer acting esters may convert more readily to estrogen
- Peak levels after IM use are greater than topical use but so is peak-tough fluctuation

Scott JD et al. *HIV Clin Trials. 2007 Nov-Dec; 8(6):412-20.*

Testosterone Propionate

- Contains three carbon atoms
- Shortest of the commonly available testosterone esters
- Most rapid onset and shortest half-life
- Use of the propionate ester is thought to result in less water retention then enanthate or cypionate (as discussed in the gyms – not great science here)
- Requires injections three times weekly to maintain constant levels
- Since this testosterone ester is one of the shortest and most water-soluble, the injection is said to be the most painful of the oil-based testosterone esters.
  - *Injection sites must be rotated, and frequently result in prolonged pain (weeks) at the injection site.*

Testosterone Enanthate and Cypionate

- Enanthate
  - *Composed of seven carbon atoms and is clinically indistinguishable from cypionate*
  - *Testosterone enanthate does reach its peak about six hours prior to testosterone cypionate*
- Cypionate
  - *Composed of eight carbon atoms*
  - *Most commonly used form of testosterone in the United States for replacement therapy*
  - *Clinically indistinguishable in all respects from enanthate*

Testosterone enanthate or cypionate Injections

- Commercially available or compounded
- **Q2 weeks 200mg IM** (Older method)
  - *Supraphysiologic levels followed by low levels*
  - *More aromatization to estradiol*
  - *Less DHT than transdermal*
- **Weekly dose 100mg IM**
  - *Better physiologic, stable levels*
  - *Less aromatization to estradiol*
- **Bi-weekly dose 25-50mg IM or SQ (more irritating)**
  - *SQ may have more consistent levels (Shippen)*
  - *SQ generally preferred by patients and achieves similar levels as IM*

Spratt et al. J Clin Endocrinol Metab. 2017;102(7):2349-2355. doi:10.1210/jc.2017-00359
McFarland J et al. *J Endocr Soc*. 2017;1(8):1095-1103. Published 2017 Jul 21. doi:10.1210/js.2017-00148

Testosterone undecanoate IM

- 750 mg every 10 weeks following a 4-week loading dose (3ml injection)
- Longer half life and duration of action than that of other testosterone esters
  - *Due to longer hydrophobic side chain & castor oil carrier*
  - *Maintains testosterone levels consistently within normal physiologic range*
  - *Minimizes side effects due to varying PK of shorter acting esters*

Testosterone Undecanoate IM

- Adverse effects:
  - *POME (Pulmonary Microembolism Reaction)*
  - *Anaphylaxis*
  - *Injection site reactions*
  - *Increase in hemoglobin and erythrocyte count*
  - *Gynecomastia and breast tenderness*
  - *Increased PSA and prostate size in the elderly*

Testosterone Undecanoate oral

- Adverse effects:
  - *Approved 3/2019*
  - *BID formulation taken with food*
  - *237 mg bid up to 396 mg bid (avail as 158, 198 and 237 mg softgels)*
  - *Can increase BP (Black box warning of risk of major cardiac events*
  - *Bypasses liver b/c absorbed through lymphatic circulation*
  - *Avoids skin irritation (patches), transference (Topicals), pain (injections)*

TRT: Compounded products

- Specifically designed to meet dosing needs of patient
- Utilizes bioidentical testosterone
  - *Chemically identical to testosterone made by the body*
  - *Available products include transdermal patches, creams/gels, implantable pellets, and sublingual tablets*

Testosterone Dosing

- 25-50mg per day topical
- I would recommend always adding Chrysin to cream unless E2 is low
- Chrysin is a natural aromatase inhibitor
- Male skin has higher concentration of aromatase enzyme on surface
- Add 2.5%-4% to start
- Has natural yellow color, does not stain skin

Testosterone Dosing

- Sample Rx
  - *Testosterone 25mg/Chrysin 25mg/mL cream to apply 1mL daily*
  - *Some data to suggest alcohol gel base will increase absorption of testosterone at higher doses*
    - Example of testosterone 50mg/mL in alcohol gel base
    - Cannot put chrysin in gel base

Optimal Transdermal Testosterone Application Pearls

- Rub at least 10 times back and forth over area for maximal skin absorption
- Always use a large skin area
- Apply to hairless areas of the skin
- Avoid putting creams, lotions or bath oils over the area where testosterone has been applied

Hertoghe; The Hormone Handbook, 2006, International Medical Publications, UK, pg 227

Testosterone Replacement: Transdermal Precautions

- Titrate follow up dose to:
  - *Clinical results*
  - *Salivary testosterone (cream)*
  - *Serum total and bioavailable testosterone for all others*
- Consider possible to transfer gel to others (women, children, pets)
  - *Avoid applying to skin with large potential for contact during intercourse*
- Can increase hair growth on area of application (except on the head)

Testosterone Replacement: Transdermal Precautions

- Avoid excessive levels of DHT
  - *Avoid putting testosterone on hairy skin*
  - *Avoid putting testosterone on testicles*
  - *Hair follicles have 5-alpha reductase (T - DHT)*
- Avoid excess estrogen conversion
  - *Avoid applying to areas of high fat that contain aromatase (T to E2)*
  - *Avoid other causes of high estradiol (alcohol, caffeine, varicocele)*

Testosterone Replacement: Pellets

- Offer the longest duration of action with prolonged zero-order, steady state characteristics
- Last 3 to 6 months depending on activity and stress level
- 75mg per pellet
- measures 3.2 mm (1/8 inch) in diameter and approximately 9 mm in length
- 150mg to 450mg SQ Q 3-6 months
- Insert 2 pellets for every 25 mg of testosterone propionate injection needed weekly
- Potential drawbacks:
  - *Minor office procedure*
  - *Risk of infection and pellet extrusion*
  - *Inability to remove pellet if contraindication to testosterone therapy develops*

Bassil et al, "The benefits and risks of testosterone replacement therapy: a review," **Therapeutics and Clinical Risk Management** 2009: 5 427-448

Testosterone Pellets

- Pellet implantation is much less flexible for dosage adjustment
- Can be compounded by pharmacy but technique is very critical and quality so choose pharmacies wisely
- contraindicated in men with carcinomas of the breast or prostate
- In patients with breast cancer, androgen therapy may cause hypercalcemia by stimulating osteolysis. DC
- high doses androgens has been associated with the development of peliosis hepatitis and hepatic neoplasms including hepatocellular carcinoma
- Edema with or without CHF may be a serious complication in patients with preexisting cardiac, renal, or hepatic disease.
- Gynecomastia may develop

Testosterone Options	Doses	Advantages	Disadvantages
transdermal patch	5-mg and 2.5-mg patches, replaced nightly	Recreation of normal circadian rhythm	Skin irritation
testosterone Gel or cream	5-10 g/day (40.5 mg, 50 mg or more/day)	Skin irritation less common than with patch	Concern of transfer to others
Injectable (IM or SC) Testosterone: **-cypionate** **-enanthate** **-propionate**	 50-100 mg qwk or BIWk 50-100 mg qwk or BIWk 10-25 mg 2-3x/wk	Inexpensive	Invasive, painful, injection site reactions
testosterone undecanoate IM	750 mg every 10 wks following a 4-wk loading dose	Consistent levels, 4-5 injections/yr	Must be done in office; POME and Anaphylaxis warnings
testosterone undecanoate oral	237-396 mg bid	Oral (no pain, transference or skin irritation)	BID dosing, BP impact, black box warning for MACE
testosterone pellets	600-900 mg	Leave it and forget it for 3-6 months; stable blood levels	Invasive in-office procedure; harder to titrate or remove if problems

Contraindications for Testosterone Therapy

- Active Prostatic carcinoma
- Breast cancer
- Prostate nodules or indurations
- Unexplained prostate-specific antigen (PSA) elevation
- Erythrocytosis (hematocrit >50)
- Unstable congestive heart failure
- Severe untreated sleep apnea

Bassil et al, "The benefits and risks of testosterone replacement therapy: a review," **Therapeutics and Clinical Risk Management** 2009: 5 427-448

Potential Adverse Effects

- Increased RBC's (Polycythemia)
  - *More likely with injections*
  - *Stop testosterone therapy or do phlebotomy at Hct 55+; evaluate patient for hypoxia and sleep apnea*
  - *Men with COPD, sleep apnea and smokers are at increased risk for polycythemia*
  - ***"It is reassuring that as far as we can determine, no testosterone-associated thromboembolic events have been reported to date."***

*Roden, E et al, "A medical progress: risks of testosterone-replacement therapy and recommendations for monitoring," **NEJM** 2004; 350:482-92.*

Potential Adverse Effects

Gynecomastia

- Monitor for elevated E2 and decrease testosterone dose or block aromatase

Fluid retention (rare)

Likely decrease in testicular size

Decreased sperm count

Elevated PSA

Stimulating growth of a prolactinoma

Testosterone

- Side Effects
  - ***Testosterone may lower your sperm count***
  - *Testicular atrophy*
  - ***Swelling of ankles, feet, or body***
  - ***Enlarged or painful breasts***
  - ***Problems breathing while you sleep (sleep apnea)***
  - ***Blood clots in the legs***

Testosterone Drug Interactions

- Androgens may decrease blood glucose and insulin requirement in diabetics
- Changes in anticoagulant activity may be seen with androgens
- Use of testosterone with Adrenocorticotropic Hormone (ACTH) or corticosteroids may result in increased fluid retention

TRT: Counseling Male Patients

- Three changes to labeling of testosterone products since 2009
- 2009: required box warning added to all gel products because of risk of transference to women and children
- 2014: Venous thromboembolism risk added to all testosterone products
- 2015: FDA released a Drug Safety Communication (DSC) directed to all manufacturers: label must include risk of heart attack and stroke

Douglas, Andrea G., Joylaina Speaks, Jennifer Elliot, and Deirdre B. Fanning. "Counseling Male Patients on Testosterone Replacement Therapy With Efficacy and Safety in Mind." *Medscape*. U.S. Pharmacist, 15 Aug. 2015.

TRT: Counseling Male Patients

- 2015: DSC also required this statement: “Testosterone is FDA-approved as replacement therapy only for men who have low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause a condition called hypogonadism.”

Douglas, Andrea G., Joylaina Speaks, Jennifer Elliot, and Deirdre B. Fanning. "Counseling Male Patients on Testosterone Replacement Therapy With Efficacy and Safety in Mind." *Medscape*. U.S. Pharmacist, 15 Aug. 2015.

Guidelines

AUA 2018

- Clinicians should inform testosterone deficient patients that low testosterone is a risk factor for cardiovascular disease. (Strong Recommendation; Evidence Level: Grade B)
- Prior to initiating treatment, clinicians should counsel patients that, at this time, it cannot be stated definitively whether testosterone therapy increases or decreases the risk of cardiovascular events (e.g., myocardial infarction, stroke, cardiovascular-related death, all-cause mortality). (Moderate Recommendation; Evidence Level: Grade B)
- *Testosterone therapy should not be commenced for a period of three to six months in patients with a history of cardiovascular events*. (Expert Opinion)

Endocrine Society 2018

- *We recommend against testosterone therapy in men with…. heart failure, myocardial infarction or stroke within the last 6 months*… (Low quality evidence)
- "…there is no conclusive evidence that T supplementation is associated with increased cardiovascular risk in hypogonadal men."
- "Thus, there are insufficient data to establish a causal link between T therapy and cardiovascular events."

ALTERNATIVES TO TESTOSTERONE FOR TD

Clomiphene

- Clomiphene citrate is used off-label to attempt to increase sperm density in men with oligospermia or azoospermia and normal to low serum testosterone concentrations.
- Clomiphene is also used for testosterone deficiency in men who wish to preserve or improve fertility.
- Clomiphene is a weak estrogen receptor antagonist that stimulates increased pulsatile GnRH secretion from the hypothalamus and subsequent pituitary gonadotropin (FSH, LH) release.
- There have been multiple studies that suggest clomiphene citrate can improve semen parameters in patients with oligo-, oligo astheno-, and azoospermia

Clomiphene dosing

- 25 – 50 mg every other day or 12.5 mg qd
- Clomiphene given by 2 different dosing regimens were compared in 89 oligospermic men. The group receiving clomiphene 25 mg every other day showed a greater overall sperm improvement response (80%) than the group receiving clomiphene 25 mg daily for 25 days (50%). Increases in sperm concentration and total sperm count were significantly greater with the lower dose regimen. Pregnancy rates in the study were not significantly different during the 6 month follow-up period (Homonnai et al, 1988).
- May raise T levels w/ less impact on libido than T

Dadhich P et al. *Indian J Urol*. 2017;33(3):236-240. doi:10.4103/iju.IJU_372_16

Clomiphene side effects

- Side effects: flushing, vasomotor, abdominal bloating, discomfort, distension, nausea, vomiting, headache, visual disturbance, breast pain
- Serious side effects: acute pancreatitis, functional visual loss, psychotic disorder, disorder of menstruation, hyperstimulation of ovaries, hypertrophy of ovary, ovarian cancer
- Watch out for pituitary apoplexy
- Contraindications: liver disease or dysfunction, endometrial carcinoma, ovarian cysts (not polycystic ovarian syndrome), undiagnosed uterine bleeding, pregnancy

HCG

- Does not negatively impact fertility / sperm count as testosterone often does
- Does not cause testicular atrophy
- Identical to LH with some FSH activity stimulating testosterone production by testicles

HCG Dosing

1000-3000 units intramuscularly 2-3 times weekly SC

Some use along with Testosterone for testicular preservation at doses from 500-1500 IU / week. No clear references for this

- Antibody production against the hCG is possible
  - *Most protocols recommend 2 months on and one month off hCG*

HCG Side effects and Precautions

- **Precautions**
  - *Anaphylaxis*
  - *Do not use in cancer or tumors*
  - *May cause water retention*
  - *VTE has been reported*
  - *Intracranial lesions*
  - *prostate cancer or other androgen-dependent neoplasm*
  - *Do not use orally, contains benzyl alcohol*
  - *Administration of chorionic gonadotropin can stimulate the production of antibodies.*
  - *In rare cases these antibodies may result in resistance to treatment by binding chorionic gonadotropin*

Natural ways to boost T

- Shilajit Ayurvedic natural substance has been shown to increase T in small studies at 250 mg bid (Pandit et al)
- Zinc – weak aromatase inhibitor at 20 mg/day
- Quercetin – found in apples, onions, tea, berries, red wine. Weak aromatase inhibitor at doses of 500-1000 mg/day
- Chrysin – found in plants and honey; natural aromatase inhibitor can be used topically

Pandit, S., et al. 2016 Andrologia, 48: 570-575. doi:10.1111/and.12482

Oxytocin

- The bonding hormone
- Released from posterior pituitary during labor, long hugs, following orgasms
- May increase intensity of orgasms
- Engenders trust and reduces anxiety
- Not for patients with psychotic disorders
- Used intranasally 24 iu / dose or sublingualy 10-20 iu per dose

Behnia et al.. *Horm Behav*. 2014;65(3):308-318. doi:10.1016/j.yhbeh.2014.01.009
Burri A, et al. *Psychoneuroendocrinology*. 2008;33(5):591-600. doi:10.1016/j.psyneuen.2008.01.014

Monitoring on T

- T with Free T (measured or calculated)
  - *Consider salivary T if on cream*
- PSA
- HCT
- PRL
- LH
- Estradiol
- DHEA-S if on DHEA
- DRE every 6 months x 1 year then yearly
- BP is on oral T Undecanoate
- BMD if evidence of osteopenia/osteoporosis after 1- years

After 6 weeks - 3 months starting or changing therapy and then every 6 months

Conclusions

- Low T associated with increased atherosclerosis & MACE
- Low T levels are associated with poor cardiovascular health and known risk factors for cardiovascular disease, such as obesity, diabetes, and the metabolic syndrome.
- There is no credible evidence at this time that testosterone therapy increases cardiovascular risk, but there is substantial evidence that it does not.
- Serious limitations of recent studies indicating increased CVD risk have been elucidated by many investigators and FDA and no causal basis is clear
- Increase in non-calcified plaque of unknown significance in the CVD T trial
- Meta-analyses show TRT has neutral (or possible beneficial) effect on CV risk factors and cardiac events
- **Studies have reported reduced mortality in testosterone-deficient men who underwent testosterone replacement therapy versus untreated men.**
- The body of evidence supports the need for long term placebo controlled randomized trials of T replacement in hypogonadal men with regard to morbidity and mortality
- Normalization of T levels may reduce incidence of Afib
- Testosterone replacement therapy has been shown to improve myocardial ischemia in men with CAD, improve exercise capacity in men with CHF. improve serum glucose levels, HbA1c, and insulin resistance in men with diabetes and prediabetes

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