

Hormone Replacement Therapy

What Role *Should* It Play With Our Patients?

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TESTOSTERONE FOR MEN: SALVATION
OR SNAKE OIL?

Definition

- Male hypogonadism means the testicles don't produce enough of the male sex hormone testosterone

Causes

- **Primary.** This type of hypogonadism — also known as primary testicular failure — originates from a problem in the testicles.
- **Secondary.** This type of hypogonadism indicates a problem in the hypothalamus or the pituitary gland — parts of the brain that signal the testicles to produce testosterone. The hypothalamus produces gonadotropin-releasing hormone, which signals the pituitary gland to make follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Luteinizing hormone then signals the testes to produce testosterone.

Diagnosis of hypogonadism

- Confusing diagnosis
- Many tests:
 - Total T, free T, bioavailable T, free androgen index (FAI)
- Thresholds
 - Total T < 200 ng/dl (Snyder),
 - < 300 ng/dl (FDA, Endo Society)
 - < 350 ng/dl (International societies)

Diagnosis of hypogonadism

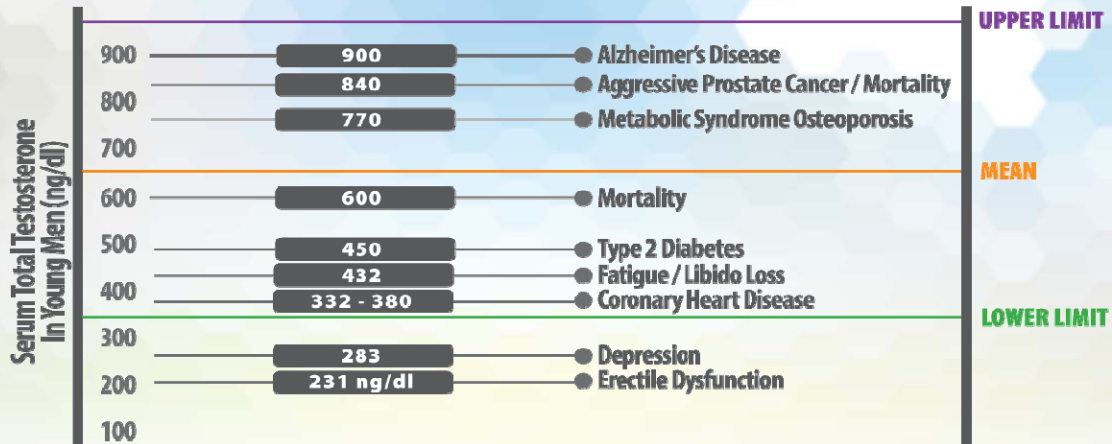
- **A clinical syndrome**
- Characteristic symptoms and signs
- Associated with reduced T levels

- ▶ How We Treat Hormone Replacement Today
 - ▶ Review current association guidelines & position statements
- ▶ What are Our Options as Physicians?
 - ▶ Synthetic vs. Bio-Identical
 - ▶ Compare formulations & efficacy
- ▶ Impact on Patients and Disease States
- ▶ Importance of Thyroid (T3)
- ▶ What Labs Should We Draw?
- ▶ Case Reviews

Endocrine Society Advises Against
Compounded Hormone Use April 01, 2016
*Journal of Clinical Endocrinology and
Metabolism.*

- ▶ "Custom-compounded hormones should be reserved for situations in which a patient is allergic to (or) does not tolerate any of the FDA-approved therapies (and) treatment is necessary for his or her health"
- ▶ Of all menopause therapy prescriptions, custom-compounded products garner about \$1 billion in annual sales. "This to us seems somewhat absurd when we have a variety of what are technically the same bio-identical hormones that are FDA-approved....It's kind of unfortunate that we live in an era where this has become so widespread it's a very big business."

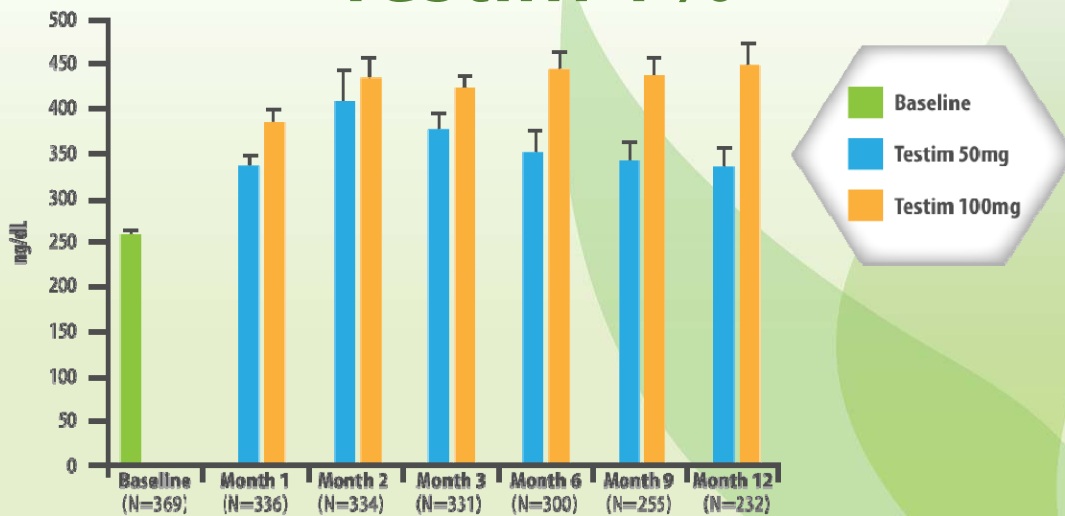
Testosterone Deficiency Thresholds Normal Levels vs. Optimal Levels



Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006 Nov; 91 (11): 4335-43 Institute of Reproductive Medicine of the University, Domagkstr. 11, D-48129 Munster, Germany

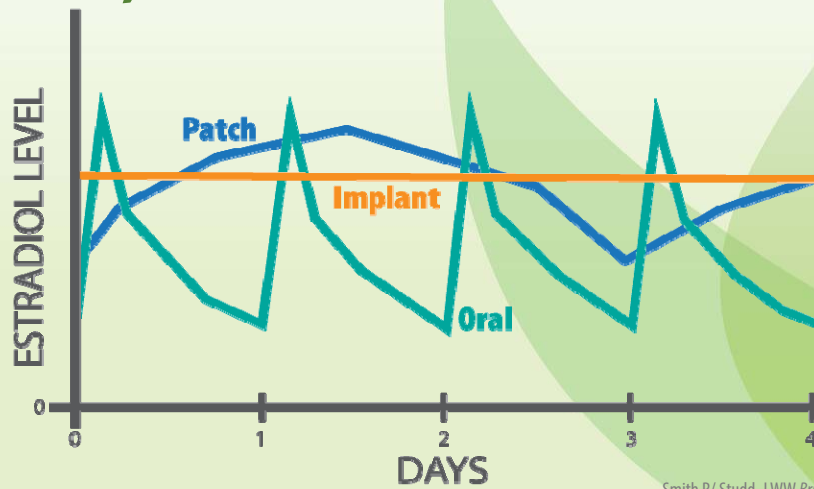
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Testim 1%



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Estradiol Levels- Pills, Patches vs. Pellets



Smith R/ Studd, J WW Brit Jour Hosp Med, 1993, Vol 49, No 11
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Hormone Replacement Method Options

▶ Synthetic

- ✓ Pills
- ✓ Patches
- ✓ Shots

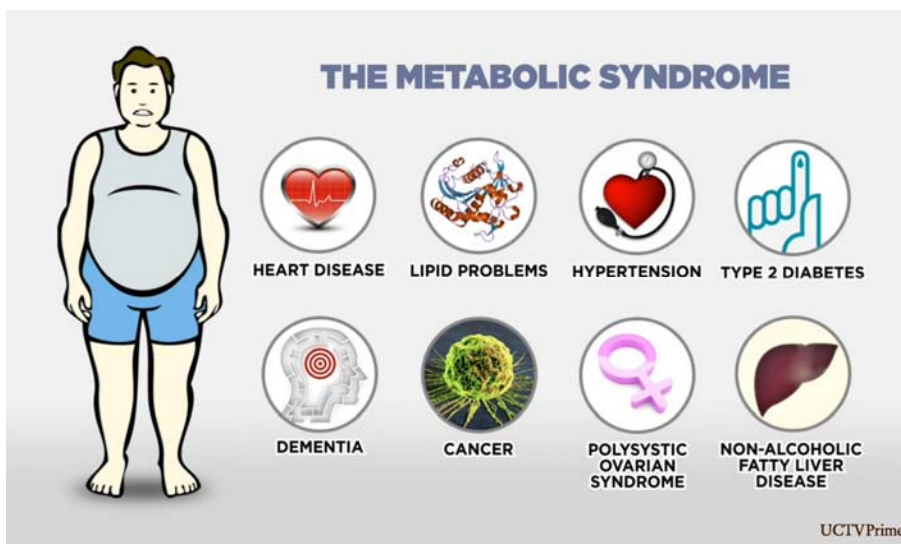
▶ Bio-Identical

- ✓ Pills
- ✓ Patches
- ✓ Creams/Gels
- ✓ Pellets

FACT: We Should Be Aiming for Best In Outcome Therapy Solutions

- ▶ Right Hormone (Bio-Identical)
- ▶ Right Dose (Multiple dosing strengths & individualized therapy)
- ▶ Right Route Of Administration (Consider Sub-Q)

Which Diseases Has HRT Been Shown to Be Protective Of?



Testosterone and C.A.D.

- **Men given aromatize-able testosterone**
- **Increase blood flow to the coronary arteries (even in patients with C.A.D.)**
- **Decrease plaque in the coronary arteries**
- **Decrease inflammation in the coronary arteries**

Zmuda J. ,*Amer. J. Card.* 1996; 77:1244-1247

Zmuda J., *Atherosclerosis.* 1997; 130:199-202

Collins P., *Circulation.* 1999; 100: 1690-1696

CV Benefits of Testosterone Therapy

- 83,000 Veterans GREATER 50 y.o. with Low T
- Tx with gels, patches and injections to normal levels (43000) vs controls untreated
- 35% DM, 20% HTN, 8% Heart Dz
- All Cause Mortality HR .40 (C.I. .39-.43)
- M.I. HR .70 (.59-.83)
- STROKE HR .57 (.40-.82)
- RETROSPECTIVE BUT LARGEST DATABASE AND LONGEST FOLLOW-UP 15 YEARS

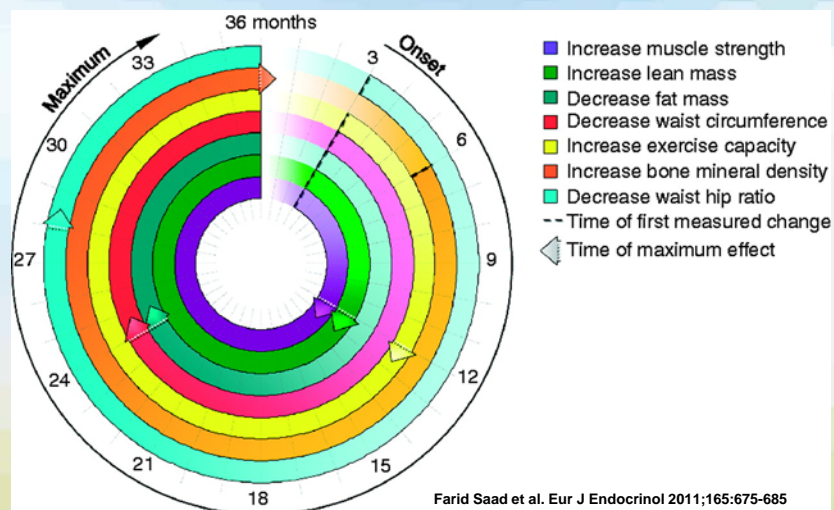
Sharma and
Barua.EUROPEAN HEART
JOURNAL 2015;August 6,
2015

Testosterone is an Insulin Sensitizer

- NIH double blind randomized controlled study
- Men with Type 2 DM benefit significantly from testosterone
- Men with low T had 36% reduction in glucose uptake in cells
- Obesity increases inflammation and inflammatory cytokines increase insulin resistance
- Testosterone decreases the inflammatory cytokines
- Obese patients with or without Type 2 Dm have dec T

Diabetic Care November 2015

Time-course on body composition and strength.



Testosterone and Coronary Artery Disease

- ▶ Testosterone reduces insulin resistance
- ▶ Testosterone reduces cholesterol
- ▶ Testosterone reduces visceral fat
- ▶ Testosterone reduces C.A.D.

Cardiovascular Disease

- ▶ Leading cause of morbidity and mortality in the United States
- ▶ Affects 12 million people
- ▶ 1 million deaths per year

JCEM 2005;90:6257-62

- Heart disease is the leading cause of death of American women, killing more than a third of them.
- 800,000 men die annually from heart attack.
- More than 200,000 women die each year from heart attacks, five times as many women as breast cancer.

www.cdc.gov/women/lcod/2010

Endogenous Testosterone and Mortality Due to All Causes, Cardiovascular Disease, and Cancer in Men-EPIC STUDY

- ▶ 11,606 men aged 40 to 79 years
- ▶ Endogenous testosterone concentrations at baseline were inversely related to mortality due to all causes, cardiovascular disease, and cancer
- ▶ 41% increase in all cause mortality
- ▶ Low T is predictive of CV disease

Khaw 2007. Circulation.; 116: 2694-2701

Hormones and the Heart

▶ Testosterone (Injectable)

- ▶ Increase Blood Flow
- ▶ Decrease Inflammation
- ▶ Increase Thromboxane A2 → increased platelet stickiness
- ▶ Increased clotting factors with shots

▶ Testosterone (pellets)

- ▶ Reduces insulin resistance
- ▶ Reduces cholesterol
- ▶ Reduces visceral fat
- ▶ Reduces Coronary Artery Disease
- ▶ Increase blood flow to the coronary arteries (even in patients with C.A.D.)
- ▶ Decrease plaque in the coronary arteries
- ▶ Decrease inflammation in the coronary arteries

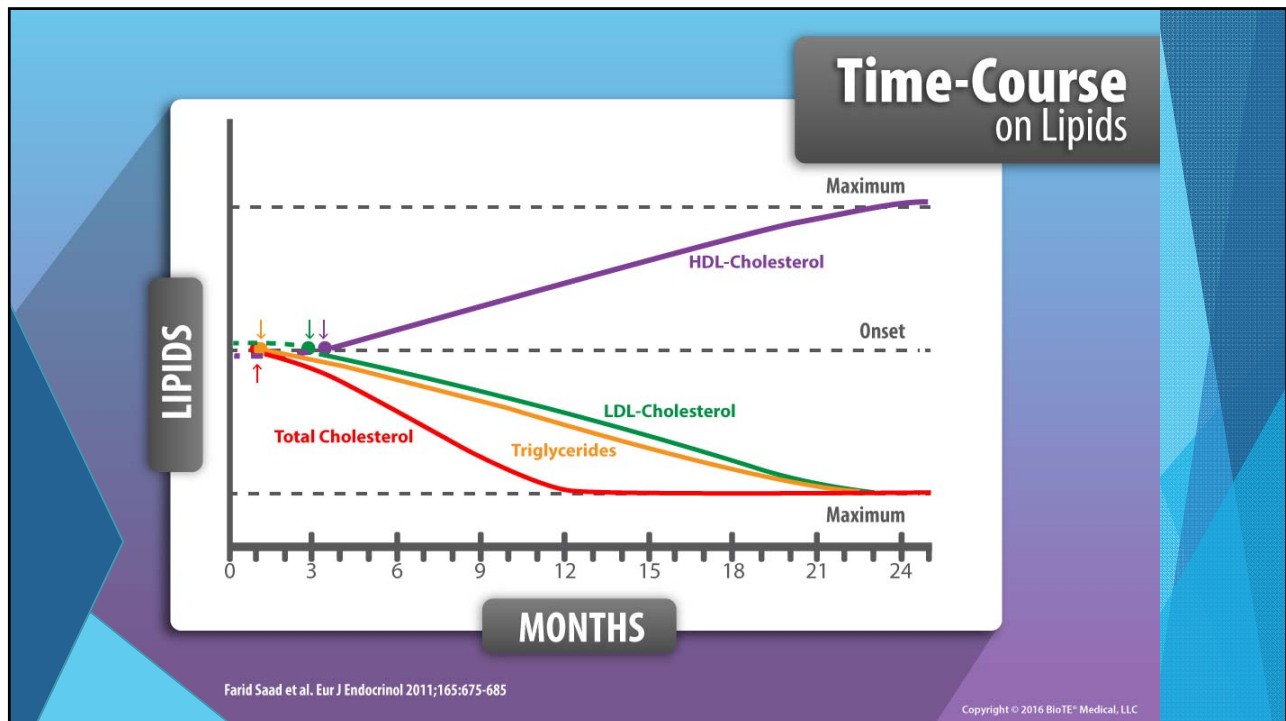
▶ Estradiol

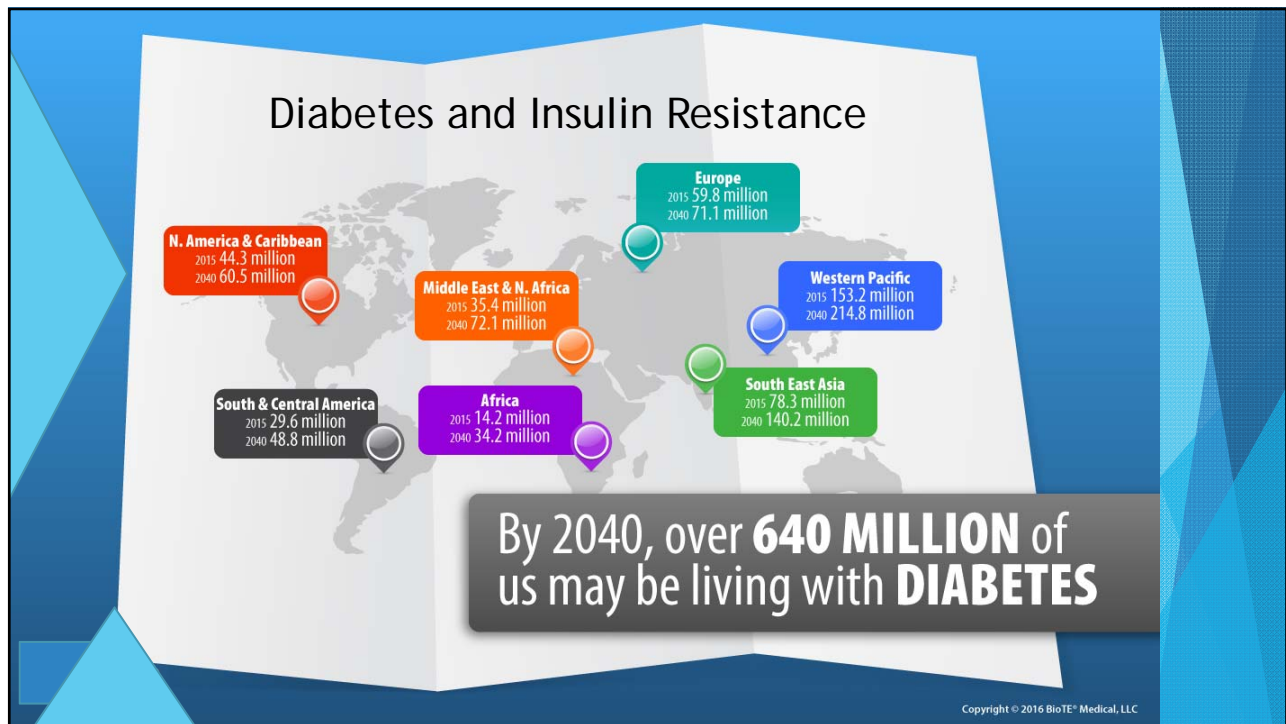
- ▶ Men with HF → more likely to die with estradiol levels that are too high or too low
- ▶ Healthy level E2 → increase in HDL
- ▶ Oral E2 increases MMP-9, non-oral lowers it
- ▶ Decreased progression of atherosclerosis
- ▶ Decrease Lp (a), associated with decreased risk for CHD events

JCEM 2005;90:6257-62
JAMA. 2009 May 13;301(18):1892-901
J Clin Endocrinol Metab. 2009 Jul;94(7):2482-8

Effect on Lipids & Body Composition

- ▶ Oral hormones increase triglycerides
- ▶ Injectables decrease total cholesterol and decrease triglycerides but have no effects on HDL
- ▶ Pellets have beneficial effects on all 3
 - ▶ Decrease TC
 - ▶ Decrease TG
 - ▶ Increase HDL

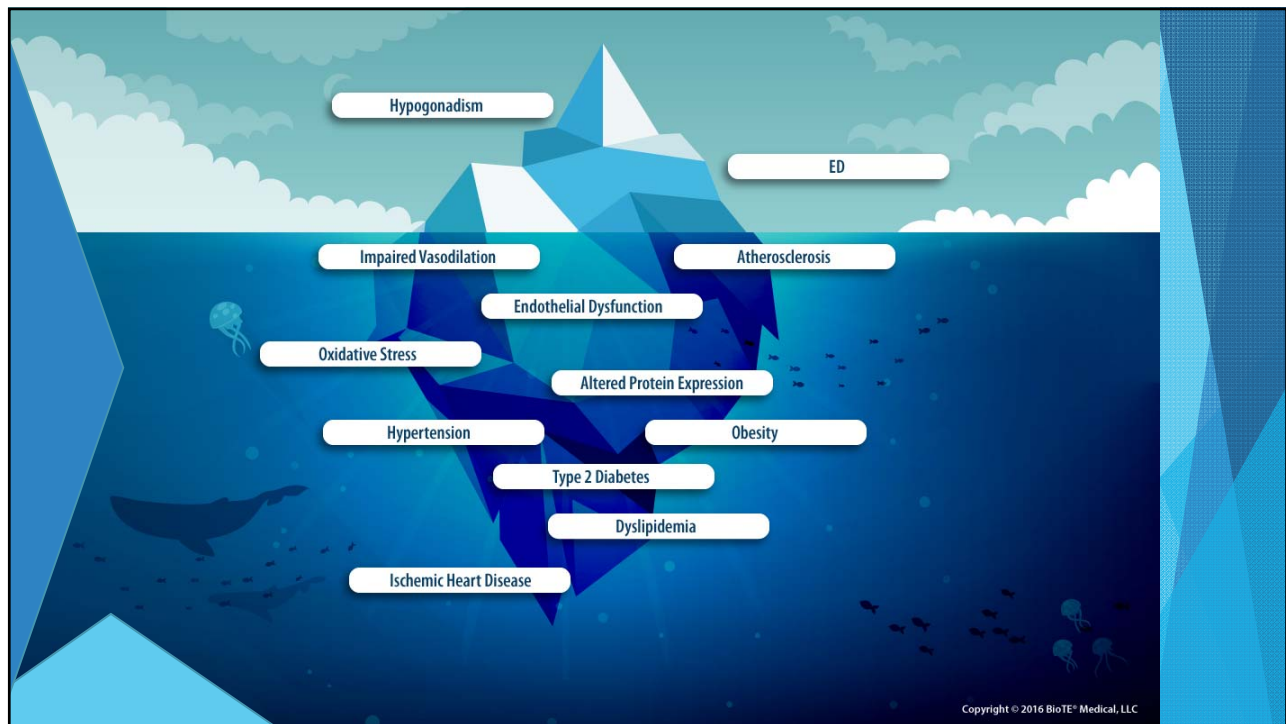




Testosterone is an Insulin Sensitizer

- ▶ NIH double blind randomized controlled study
 - ▶ Men with Type 2 DM benefit significantly from testosterone
 - ▶ Men with low T had 36% reduction in glucose uptake in cells
 - ▶ Obesity increases inflammation and inflammatory cytokines increase insulin resistance
 - ▶ Testosterone decreases the inflammatory cytokines
 - ▶ Type 2 DM have decreased T

Diabetic Care November 2015



Male HRT & the Prostate

The conclusion that “Cancer of the prostate is activated by testosterone injections” (Huggins and Hodges 1941) was based on...

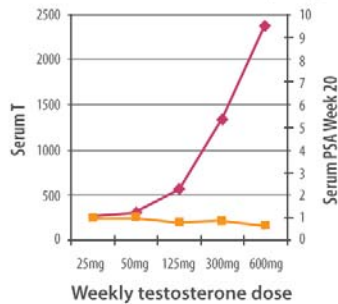
- ▶ Only 3 men received T injections (For 14 days): n = 3
- ▶ Results reported for only 2 men
- ▶ 1 previously castrated (androgen-deprived)

Males & Prostate Health

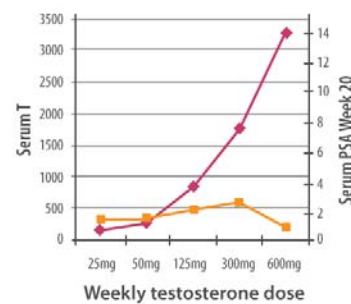
Does Testosterone Raise PSA?



(a) Serum testosterone & PSA in young men



(b) Serum T & PSA in older men



A New Era of Testosterone and Prostate Cancer: From Physiology to Clinical Implications Abraham Morgentaler M.D.

- ▶ MEN WITH HIGH T NOT AT INCREASED RISK FOR PROSTATE CANCER
- ▶ LOW T AFFORDS NO PROTECTION AGAINST DEVELOPMENT OF PCa
- ▶ MOST IMPORTANT THE ANDROGEN HYPOTHESIS (HUGGINS 1941 CANCER RESEARCH) PRIOR TO TESTOSTERONE ASSAYS
- ▶ 19 STUDIES NO INC RISK PCa IN MEN TX WITH T THERAPY
- ▶ MULTIPLE STUDIES LOW T ASSOC. W/ HIGH GRADE PCa AND HIGHER STAGE AT PRESENTATION

European Urology
Volume 65, Issue 1, January 2014, Pages 115-123

International Journal of Impotence Research 2009;21;9-23

- ▶ Meta analysis of 197 studies demonstrated that testosterone administration **DOES NOT**:
 - ▶ Increase the risk of prostate cancer or
 - ▶ Increase Gleason Score

Articles Showing T Therapy Causes Progression of PCa



PATUSZAK ET AL J Urology 2013;190:639-44

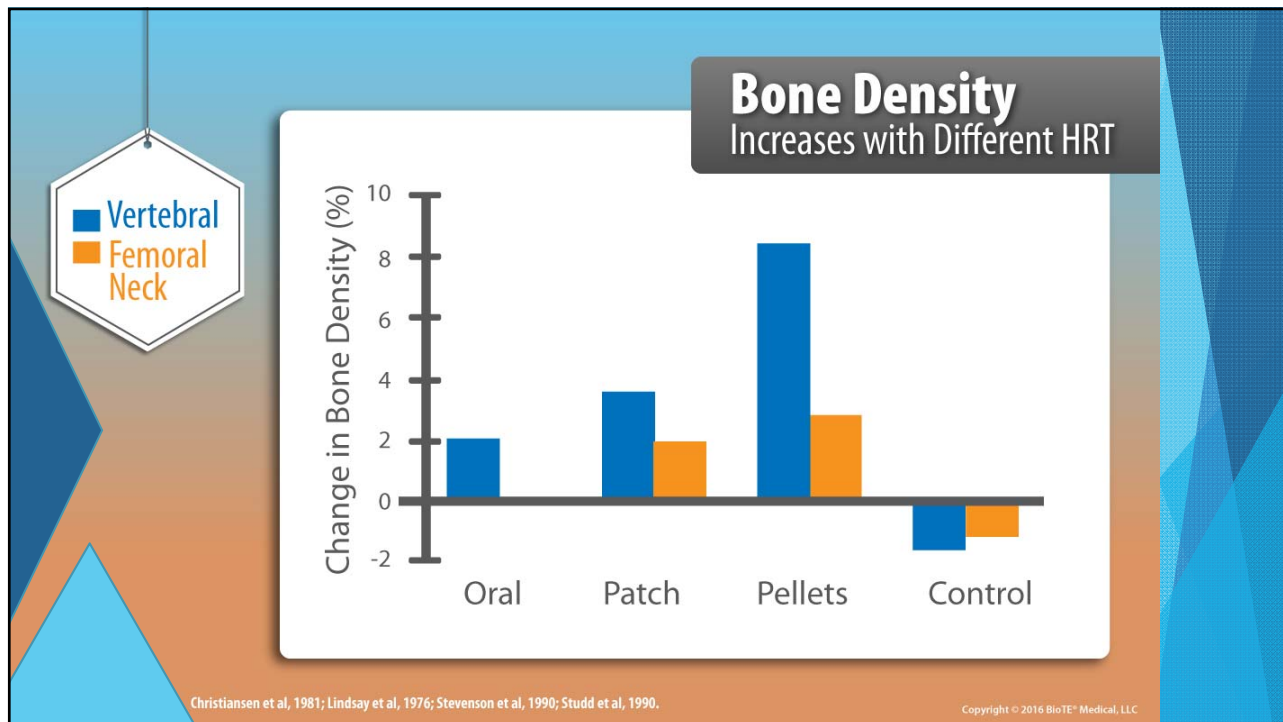
- **LARGEST POST TREATMENT STUDY 103 PATIENTS**
- **S/P RADICAL PROSTATECTOMY**
- **27 MONTH FOLLOW-UP**
- **INCLUDED 26 HIGH RISK MEN GLEASON SCORE > 8**
- **4% RECURRENCE IN TESTOSTERONE TREATED GROUP**
- **16% RECURRENCE IN UN-TREATED COMPARISON GROUP**

BHRT & Bone Support

1. Testosterone: “Bone Builder”
2. Demonstrated Four-fold Increase in Bone Density vs. Oral Estrogen and 2.5x Greater than Patches
 - **8.3% per/year for Pellet Therapy**
 - **3.5% per/year for Patches**
 - **1-2% per/year for Oral Estrogen**

Studd, J WW, et al (1990)
Am Journal OB/GYN 163, 1474-1479





Alzheimer's Disease

- ▶ Both Estrogen and Testosterone have Neuroprotective role
- ▶ Women have a higher incidence of AD 8:1 over men
- ▶ Women with lower E2 levels have even greater risk of AD
- ▶ There is overwhelming evidence that E and T helps decrease apoptosis
- ▶ This protective effect of both hormones decreases the beta amyloid deposition

Pike, CJ: Frontiers in Neuroendocrin 30(2009):239
Proc Natl Acad Sci USA. 2000 Feb 1;97(3):1202-5.

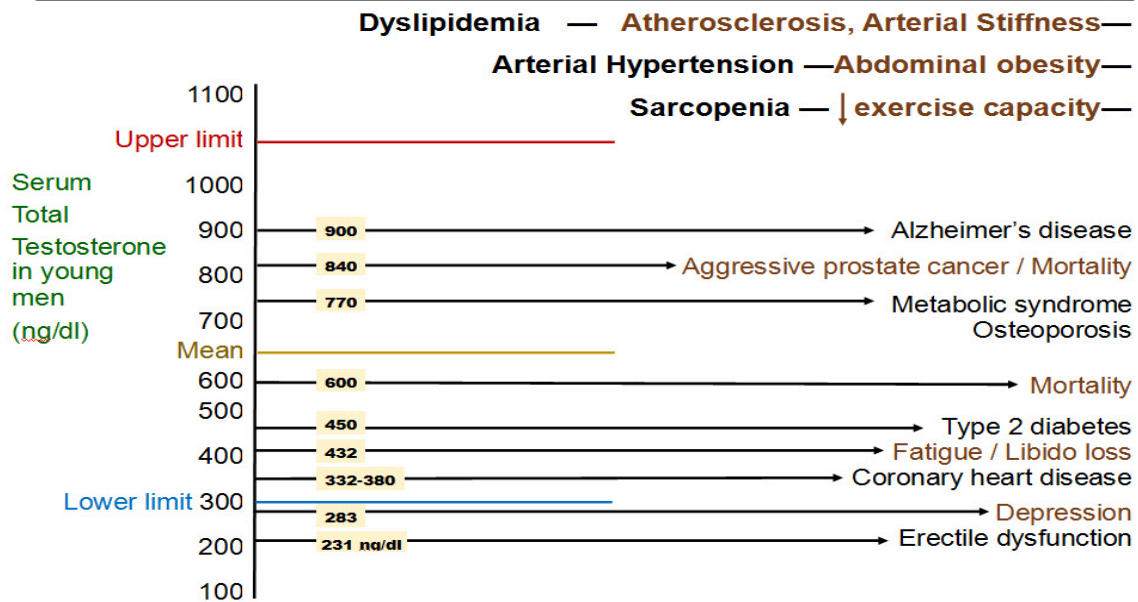
Testosterone Facts

- ▶ Men age 30-70 will lose 1- 3% of total testosterone production per year
- ▶ Women age 20-40 lose 50% of their testosterone production
- ▶ Only pellets give patients constant blood levels (24/7) without daily spikes
- ▶ Low testosterone is associated with excess abdominal fat, loss of insulin sensitivity, higher C-Reactive protein and atherosclerosis.

HYPOGONADISM

- ▶ SYMPTOMS
 - ▶ FATIGUE
 - ▶ WEIGHT GAIN
 - ▶ DEPRESSION
 - ▶ COGNITIVE CHANGES
 - ▶ DECREASED LIBIDO
 - ▶ ERECTILE DYSFUNCTION
 - ▶ MUSCLE PAIN
 - ▶ JOINT PAIN

Testosterone Thresholds below = > ↑ disease, mortality



Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. *J Clin Endocrinol Metab.* 2006 Nov;91(11):4335-43 Institute of Reproductive Medicine of the University, Domagkstr. 11, D-48129 Munster, Germany

Positive Effects of Bio-identical Testosterone

MEN

- Improved erectile ability
- Prostate protection
- Cardiovascular protection
- Lower cholesterol, Increase HDL
- Increased energy
- Feeling of overall well-being
- Reducing body fat
- Builds Muscle Mass
- Reduced anxiety and irritability
- Cognitive clarity

Minimal side effects for either men or women

Lab Workup for Men

Should include these minimum tests:

- ▶ CBC, CMP, FERRITIN
- ▶ PSA
- ▶ TSH, Total T4, Free T3, T.P.O.
- ▶ Testosterone - Total & Free
- ▶ Estradiol - to check for Aromatization
- ▶ Vitamin D
- ▶ Lipid Panel (Optional)
 - ▶ Follow up @ 4 weeks with modified panel

If on shots test on day 4 or 5, post injection

▶ **Today's truth is this:**

"There is no magic hormone or combination of hormones that can be indiscriminately used by all men and women. Each is an individual and hormone balance must be the ultimate goal for all."

▶ *Dr Joseph Collins*

- ▶ *Treat your patients...not their labs (and) consider "Optimizing" hormone levels*

Synthetic Testosterone Increases Platelet Thromboxane A2 Receptors and Platelet Aggregation

- ▶ Testosterone Cypionate vs Saline
- ▶ TXA2 is a metabolite of platelets
- ▶ Two significant activities
 - ▶ Increase platelet aggregation
 - ▶ Constricts vascular smooth muscle
- ▶ Inhibition of TXA2 by aspirin decreases thrombotic cardiovascular events

Synthetic Testosterone Increases Platelet Thromboxane A2 Receptors and Platelet Aggregation (cont.)

- ▶ Platelets implicated in occlusive intracoronary thrombi
- ▶ Patients with unstable angina and acute MI have increased TXA2
- ▶ **What about the receptors for TXA2?**
 - ▶ 4,468 sites per platelet in patients with acute events
 - ▶ 2,206 sites per platelet in controls
- ▶ **What happens after the Event?**
 - ▶ The receptors go back to normal levels

Dorn G. Circulation
1990;81:212

CASE 1

- ▶ 47 YR OLD WHITE MALE WITH FATIGUE, WEIGHT GAIN, MILD CHANGE IN ERECTILE FUNCTION, AND INCREASED ANXIETY.
- ▶ LAB
 - ▶ Total Testosterone 280, Free Testosterone 7.0
 - ▶ Other labs normal
- ▶ 3 MONTH FU AFTER TESTOSTERONE PELLETS
 - ▶ Symptoms resolved
 - ▶ Hematocrit elevated to 51% (erythrocytosis)

CASE 2

- ▶ 67 YR OLD WM 8 YRS S/P PROSTATE CA. TREATED WITH RADICAL PROSTATECTOMY. SYMPTOMS INCLUDE FATIGUE, JOINT PAIN, DECREASED LIBIDO AND ED.
- ▶ LAB
 - ▶ Total Testosterone 250, Free Testosterone 5.1, PSA 0
- ▶ 3 MONTH FU
 - ▶ Symptoms greatly improved except ED... Cialis added to treatment
- ▶ 1 YR FU
 - ▶ Stable with improved erectile function.



THANK YOU!