

Hormone Replacement/ Optimization Therapy

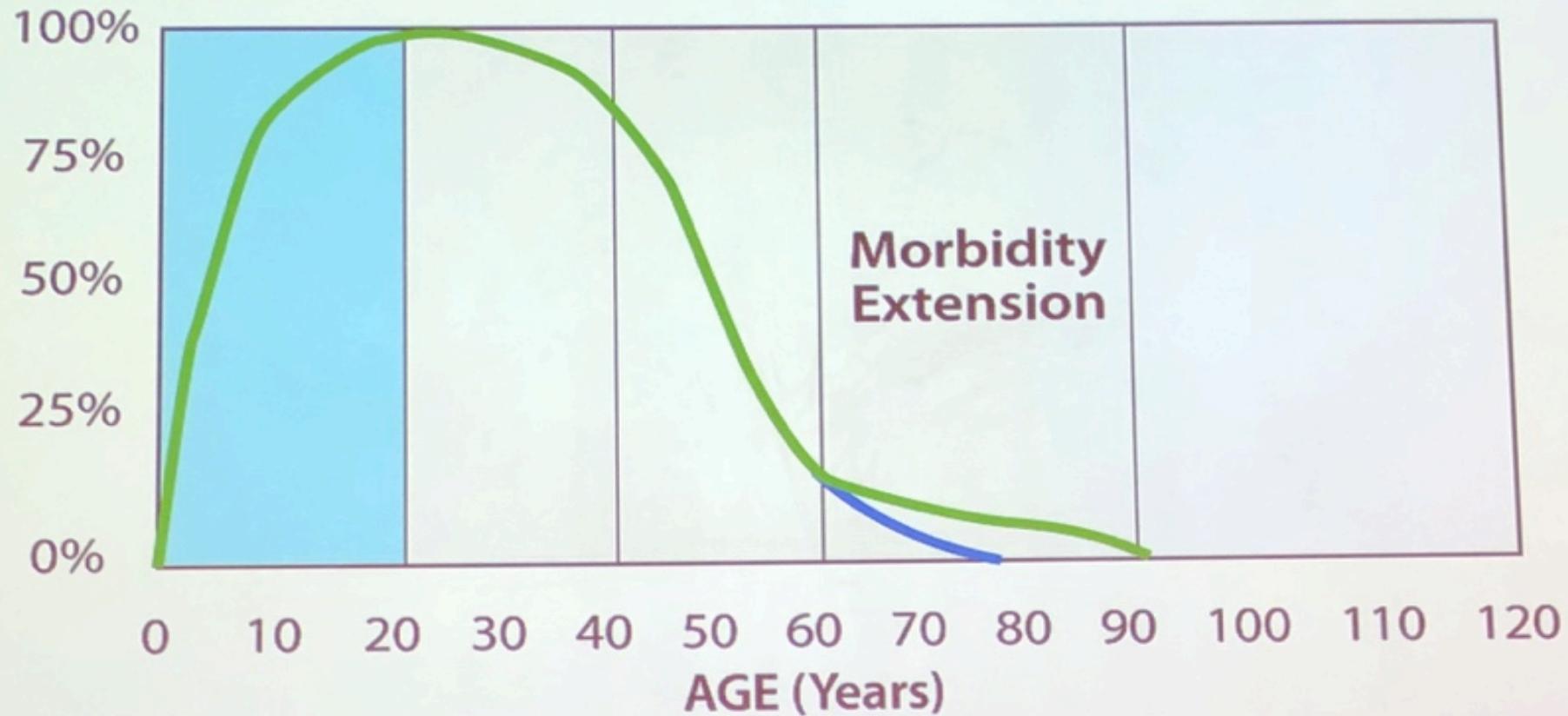
Is it alternative medicine?
Or is it an alternative to
BAD medicine?

What Role *Should* It Play With Our Patients?

NEAL SECRIST, DO
nealsecrist@gmail.com

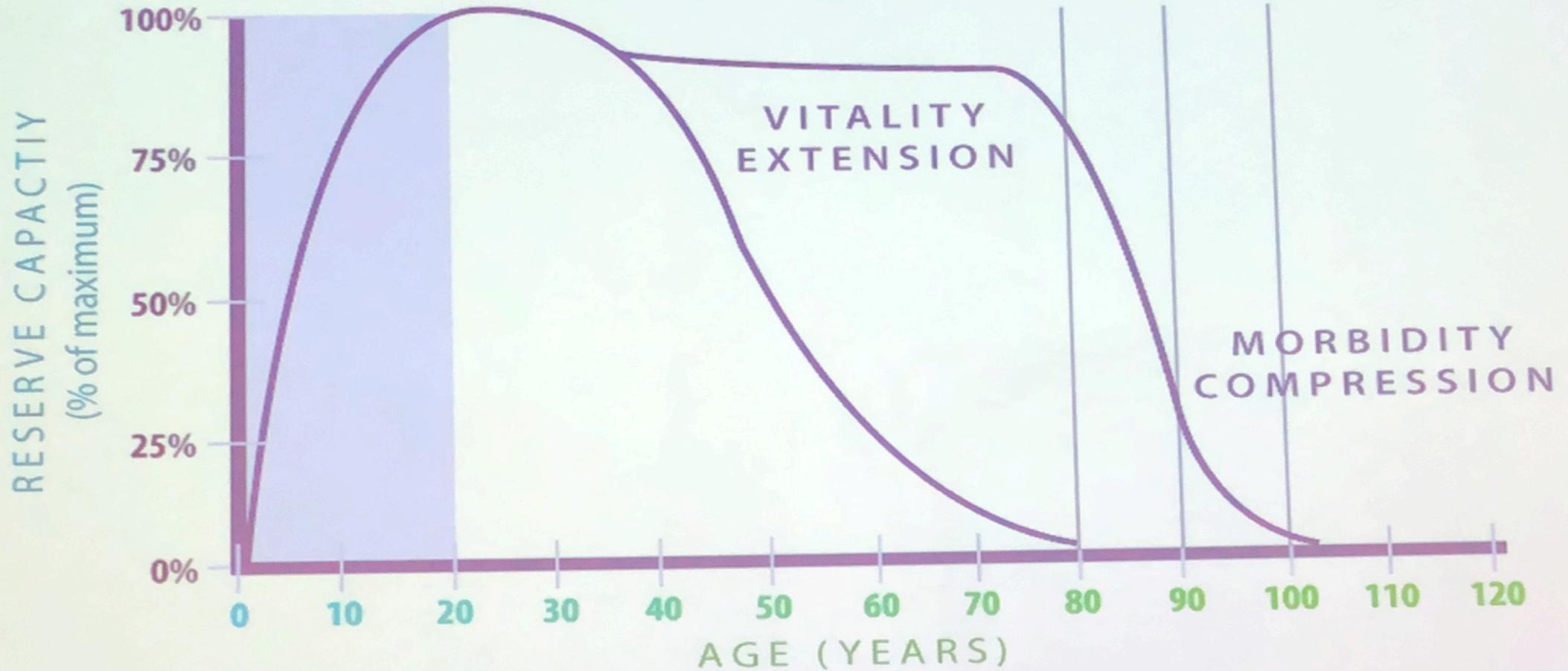
"CONVENTIONAL MEDICINE" Prolongation of Morbidity

Reserve Capacity (% of Maximum Function)

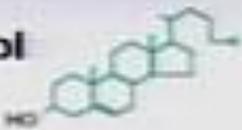


GOAL OF PREVENTIVE/REGENERATIVE MEDICINE

HealthSpan Extension, Morbidity Compression



Cholesterol



THE STEROIDOGENIC PATHWAYS

Pregnenolone

17-OH-Pregnenolone

DHEA

Androstenediol

Progesterone

17-OH-Progesterone

Androstenedione

Testosterone

DHT

Corticosterone

Cortisol

Cortisone

(Androgens)

Aldosterone

(Glucocorticoids)

Estrone (E1)

Estradiol (E2)

(Mineralocorticoids)

2-OHE1 → 2-MeOE1

16 α -OHE1 → Estriol (E3)

4-OHE1 → 4-MeOE1

(Estrogens)

- ▶ 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)
- ▶ Progesterone & Vitamin D3
- ▶ Case Reviews

What Do Our Peer Accredited Organizations (or) Older Clinical Studies Say About Menopause and Peri-Menopause Therapy?

- ▶ ACOG: American College of Obstetrics & Gynecology
- ▶ Endocrine Society
- ▶ NAMS: North American Menopause Society
- ▶ WHI: Women's Health Initiative Study (2002)

- ▶ For example...How do they feel about bio-identical hormones?

A.C.O.G. Position Statement

“In response to recent media attention being given to so-called bioidentical hormones, The American College of Obstetricians and Gynecologists (ACOG) reiterates its position that there is no scientific evidence supporting the safety or efficacy of compounded bioidentical hormones.”

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 bioidentical 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."

N.A.M.S. Position Statement 2012

“The risk of side effects (such as heart attack, stroke, blood clot, or breast cancer) with HT in healthy women ages 50 to 59 is low. In contrast, using HT for a long time or starting HT when you are a number of years beyond menopause is associated with a higher risk of these side effects.”

Conventional HRT Women's Health Initiative Trial (WHI)

- ▶ 41% Increase in stroke
- ▶ 29% Increase in heart attacks
- ▶ 26% increase in breast cancer
- ▶ 2x the rate of blood clots
- ▶ 76% increase in Alzheimer's dementia
- ▶ *Note: After this trial many women were left with NO alternative for hormone balance or symptom relief. Sadly, there have been safe, alternative methods available for years.*





If the shoe were on the other hoof

Hormone Replacement Method Options

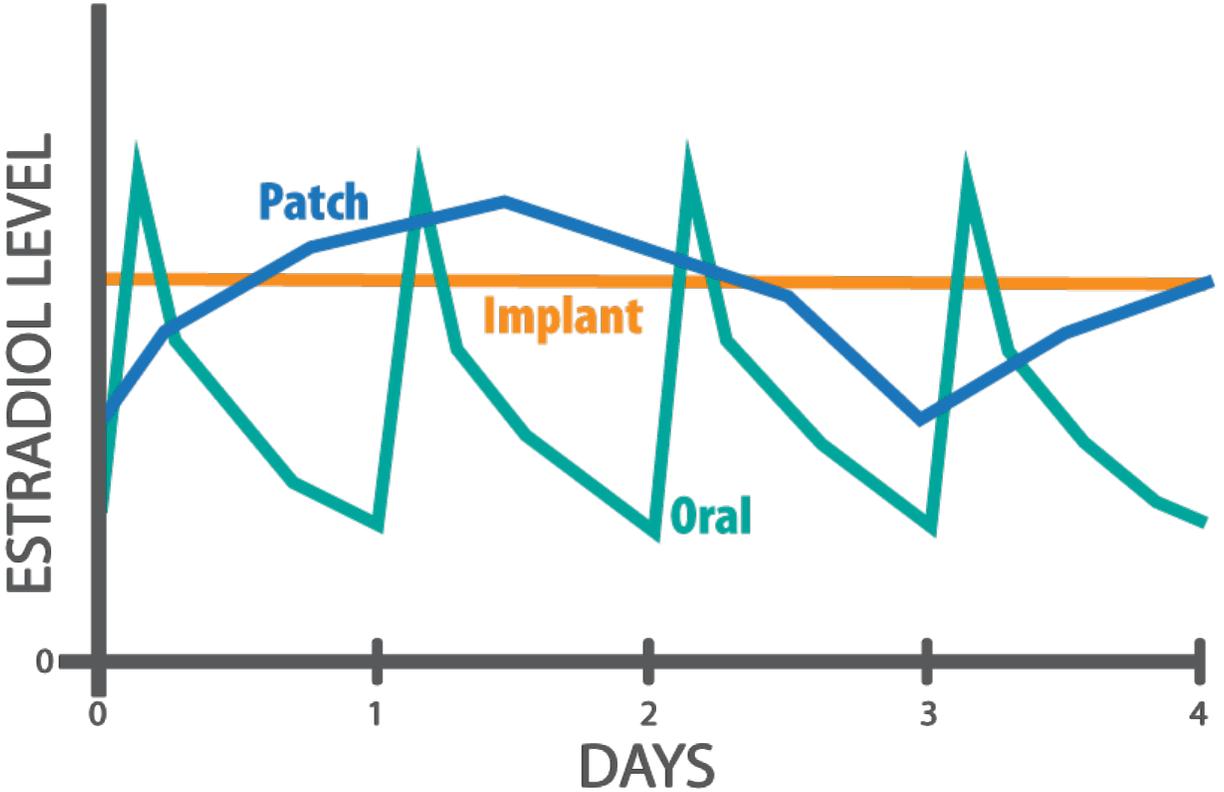
▶ Synthetic

- ✓ Pills
- ✓ Patches
- ✓ Shots

▶ Bio-Identical

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

Estradiol Levels - Pills, Patches vs. Pellets



Smith R/ Studd, J WW *Brit Jour Hosp Med*, 1993, Vol 49, No 11

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

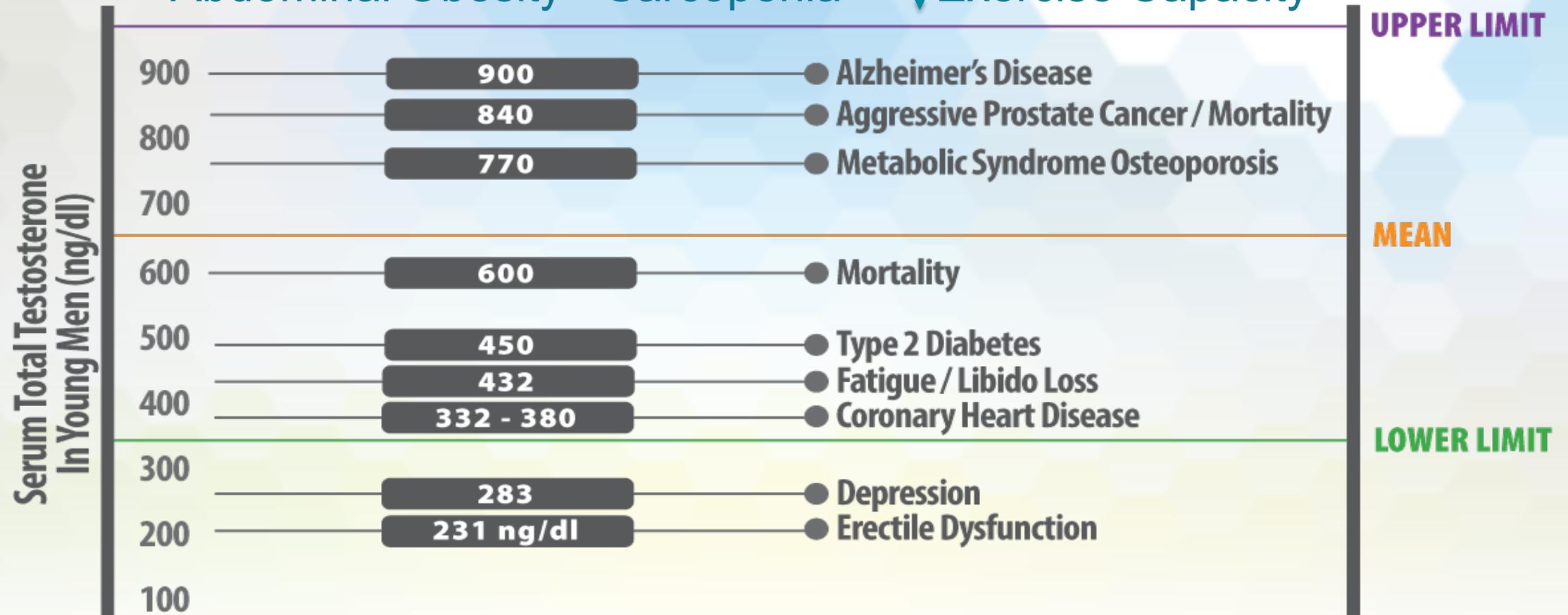
- ▶ Right Hormone (Bio-Identical)
- ▶ Right Dose (Multiple dosing strengths & individualized therapy)
- ▶ Right Route Of Administration (Consider Sub-Q)

Helps Body Return to Normal Hormonal Balance & Physiological State

Testosterone Thresholds

Below => ↑Disease & Mortality

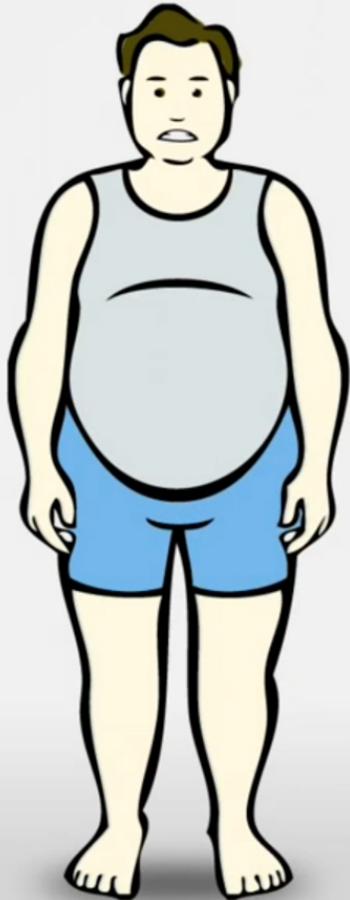
Dyslipidemia • Atherosclerosis, Arterial Stiffness • Arterial Hypertension
 Abdominal Obesity • Sarcopenia • ↓Exercise Capacity



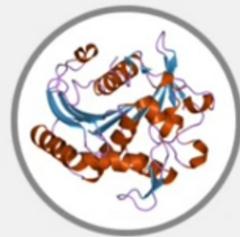
Zitzmann M, Faber S, Nieschlag E. Association of specific symptoms and metabolic risks with serum testosterone in older men. J Clin Endocrinol Metab. 2006 Nov; 91 (11) : 4335-43 Institute of Reproductive Medicine of the University, Domagkstr. 11, D-48129 Munster, Germany

Which Diseases Has HRT Been Shown to Be Protective Of?

THE METABOLIC SYNDROME



HEART DISEASE



LIPID PROBLEMS



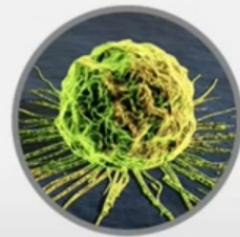
HYPERTENSION



TYPE 2 DIABETES



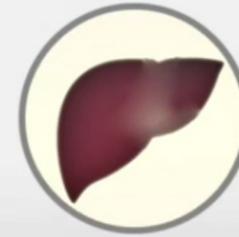
DEMENTIA



CANCER



POLYCYSTIC
OVARIAN
SYNDROME



NON-ALCOHOLIC
FATTY LIVER
DISEASE



1 in 7

Premenopausal Women Die from

**HEART
DISEASE**

For
POSTMENOPAUSAL WOMEN

That Number

RISES

to

1 in 3

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.**
- ▶ **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

Testosterone and Coronary Artery Disease

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

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

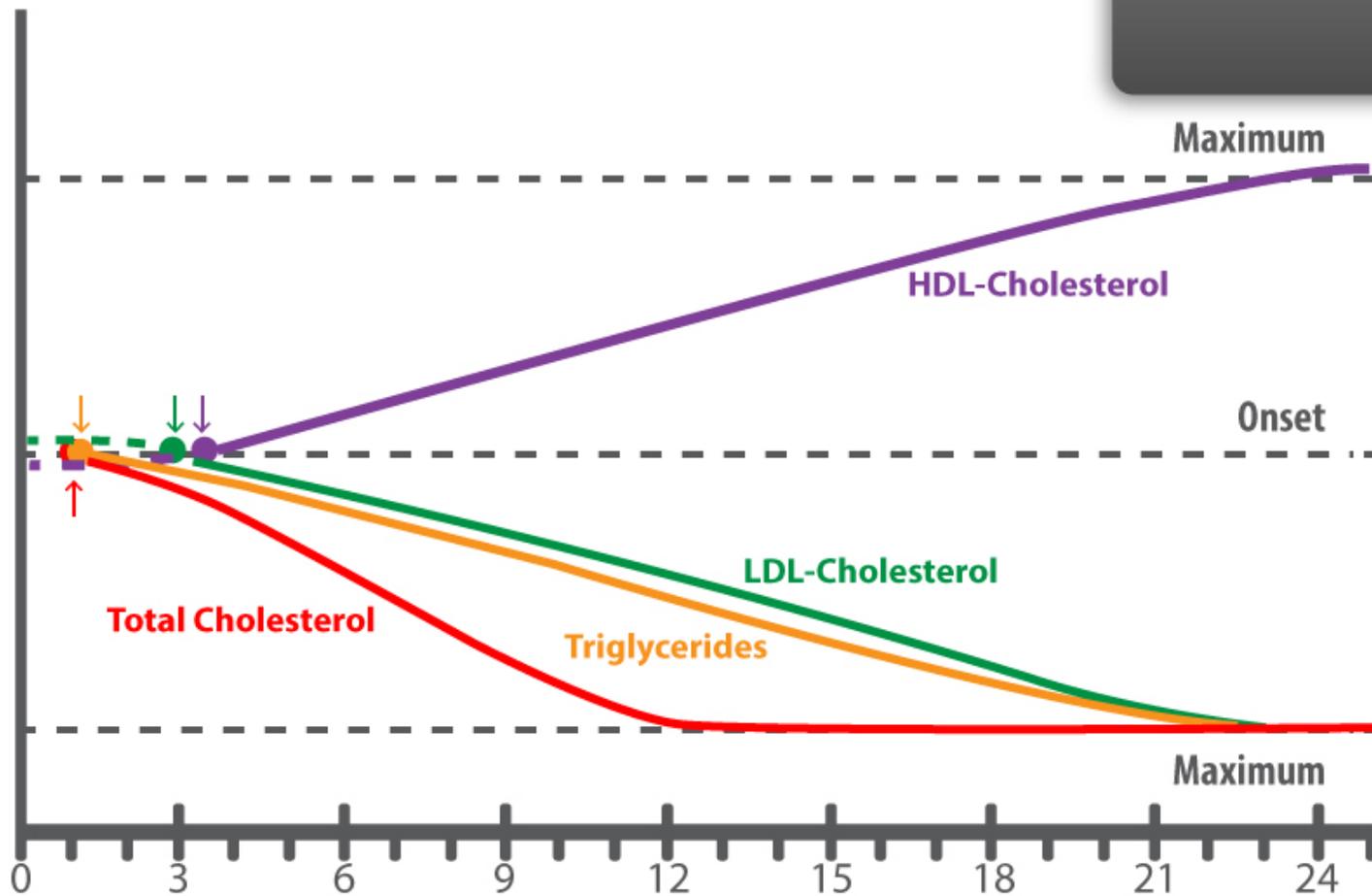
J Clin Endocrinol Metab. 2009 Jul;94(7):
2482-8

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

Time-Course on Lipids

LIPIDS



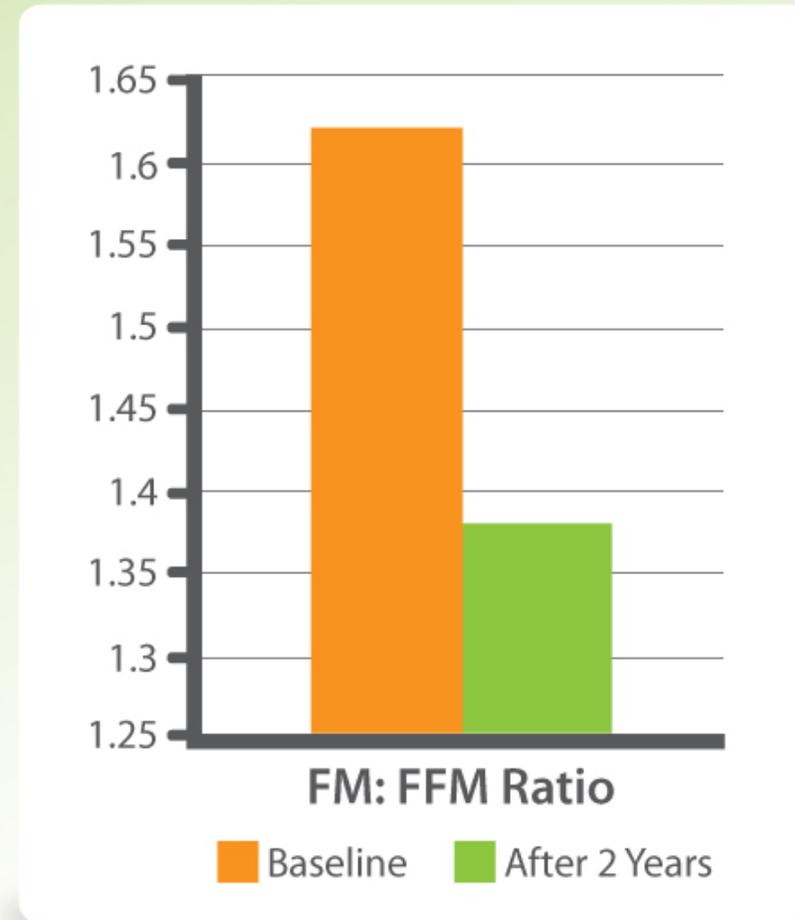
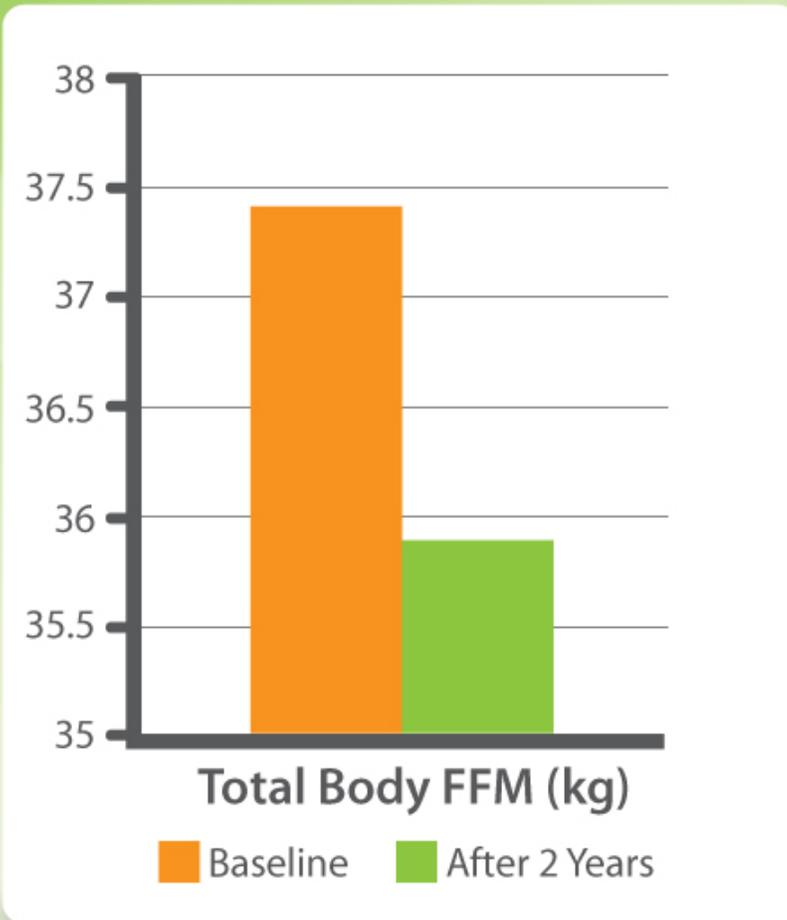
MONTHS

Frank Z. Stanczyk et al. American Journal of OB/GYN, Volume 159, No. 6 A Randomized Comparison of Non Oral Estradiol Delivery in Post Menopausal Women.

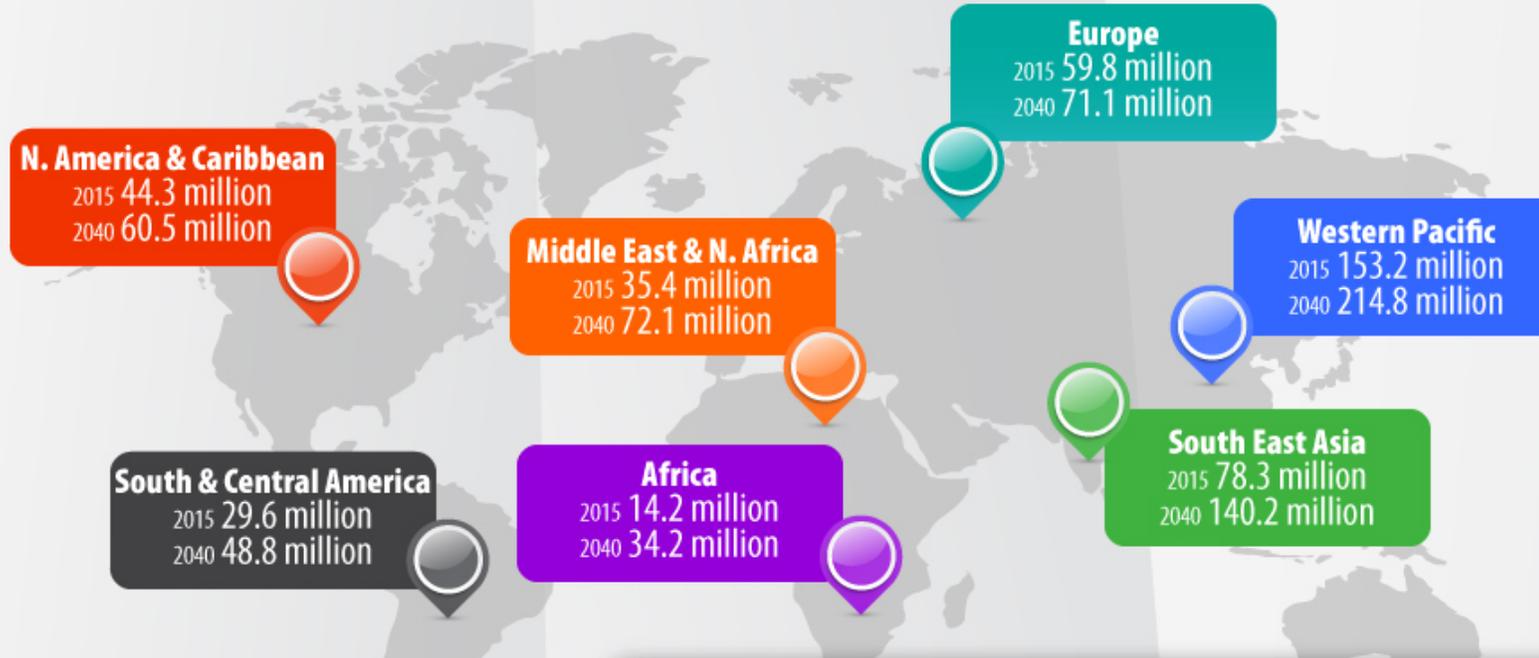
- ▶ Pellets produce more reproducible estrogen levels faster and remain steady longer than patches.
- ▶ Estradiol levels with patches were less than half of pellet patient levels and fluctuated widely
- ▶ **Significant increase in HDL at 12 weeks with pellets, but only at 24 weeks with patches.**

Change in body composition

in postmenopausal women who received hormonal replacement therapy with estradiol ($n=17$) or with estradiol plus testosterone ($n=15$) implants for a period of 2 years



Diabetes and Insulin Resistance



By 2040, over **640 MILLION** of us may be living with **DIABETES**

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

Testosterone and C.A.D.

- ▶ Low testosterone is associated with excess abdominal fat, loss of insulin sensitivity, higher C-Reactive protein and atherosclerosis.

J Clin Endocrinol Metab. 2002 Oct;87(10):4522-7

J Clin Endocrinol Metab. 2008 May;93(5):1834-40

Androl 2009 Jan-Feb;30(1):23-32

the Rotterdam study.

J Clin Endocrinol Metab. 2002 Aug;87(8):3632-9

Testosterone and Vitamin D3

- ▶ Deficiencies of either free testosterone or 25-OH vitamin D resulted in a 60% increased risk for non-cardiovascular mortality ($p=0.011$)
- ▶ Deficiencies of free testosterone and 25-OH vitamin D resulted in a 133% increased risk for non-cardiovascular mortality ($p<0.001$)
- ▶ Deficiency in 25-OH vitamin D increases the severity of prostate cancer

Combination of low free testosterone and low vitamin D predicts mortality in older men referred for coronary angiography, Lerchbaum E, et al, *Clinical Endocrinology (Oxf)*. 2012 Feb 22, vol 77(3)

Vitamin D3

- ▶ This fundamental micronutrient that affects 1 billion people worldwide
- ▶ Role in bone metabolism
- ▶ Deficiency in Vit D3 increases risk of DM, hypertension, coronary artery disease
- ▶ Implicated in many different kinds of cancer ranging from colon, breast, prostate, and colorectal, to lung, ovarian, esophageal, kidney and bladder cancer. (Women with vit D levels < 50 were SIX times more likely to develop breast cancer cf. levels > 50...Eur. J. Cancer 2005; 41:1164-9)
- ▶ Archives of Internal Medicine in 2008, low Vitamin D3 was found to be a predictor of all-cause-mortality
- ▶ Plays a role in moderating or preventing autoimmune conditions such as multiple sclerosis, type I diabetes, and rheumatoid arthritis.



The Breast

Updates in Hormone Replacement & Breast Cancer

- ▶ **Breast Cancer:**
 - ▶ Most common female cancer
 - ▶ Median age 61 y.o.
 - ▶ 400,000 deaths annually worldwide
 - ▶ 75% occur in postmenopausal women
 - ▶ 80% are hormone receptor positive

E.M. Davelaar et al Ned. Tijdschr Geneeskd 1991,
April 6: 13 (14): 613-15
No Increase in the Evidence of Breast Cancer

Conclusion:

- ▶ No increase in the incidence of breast cancer during the use of subcutaneous estradiol in 261 woman followed from 1972 to Mid 1990's.
- ▶ Less cancers overall than the control group who were on no estrogen replacement therapy.

NURSES HEALTH STUDY

▶ 121,700 Nurses

▶ **Conjugated Estrogens Increase Risk of Breast Cancer**

RR 1.32 (1.14-1.54)

▶ Estrogen PLUS Testosterone **No Increase Risk of Breast Cancer**

RR 1.64 (0.53-5.00)

Rapid response of breast cancer to neoadjuvant intramammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer

- ▶ 2.4-cm tumor in the left breast
- ▶ Three combination implants each containing 60 mg of testosterone and 4 mg of Anastrozole were placed anterior, superior, and inferior to tumor
- ▶ Three additional testosterone-anastrozole implants were again placed peritumorally 48 days later
- ▶ By day 46, there was a 7-fold reduction in tumor volume, as measured on ultrasound
- ▶ By week 13, they documented a 12-fold reduction in tumor volume
- ▶ Therapeutic systemic levels of testosterone were achieved without elevation of estradiol

Glaser R. Menopause: The Journal of The North American Menopause Society Vol. 21, No. 6

Hypogonadism

ED

Impaired Vasodilation

Atherosclerosis

Endothelial Dysfunction

Oxidative Stress

Altered Protein Expression

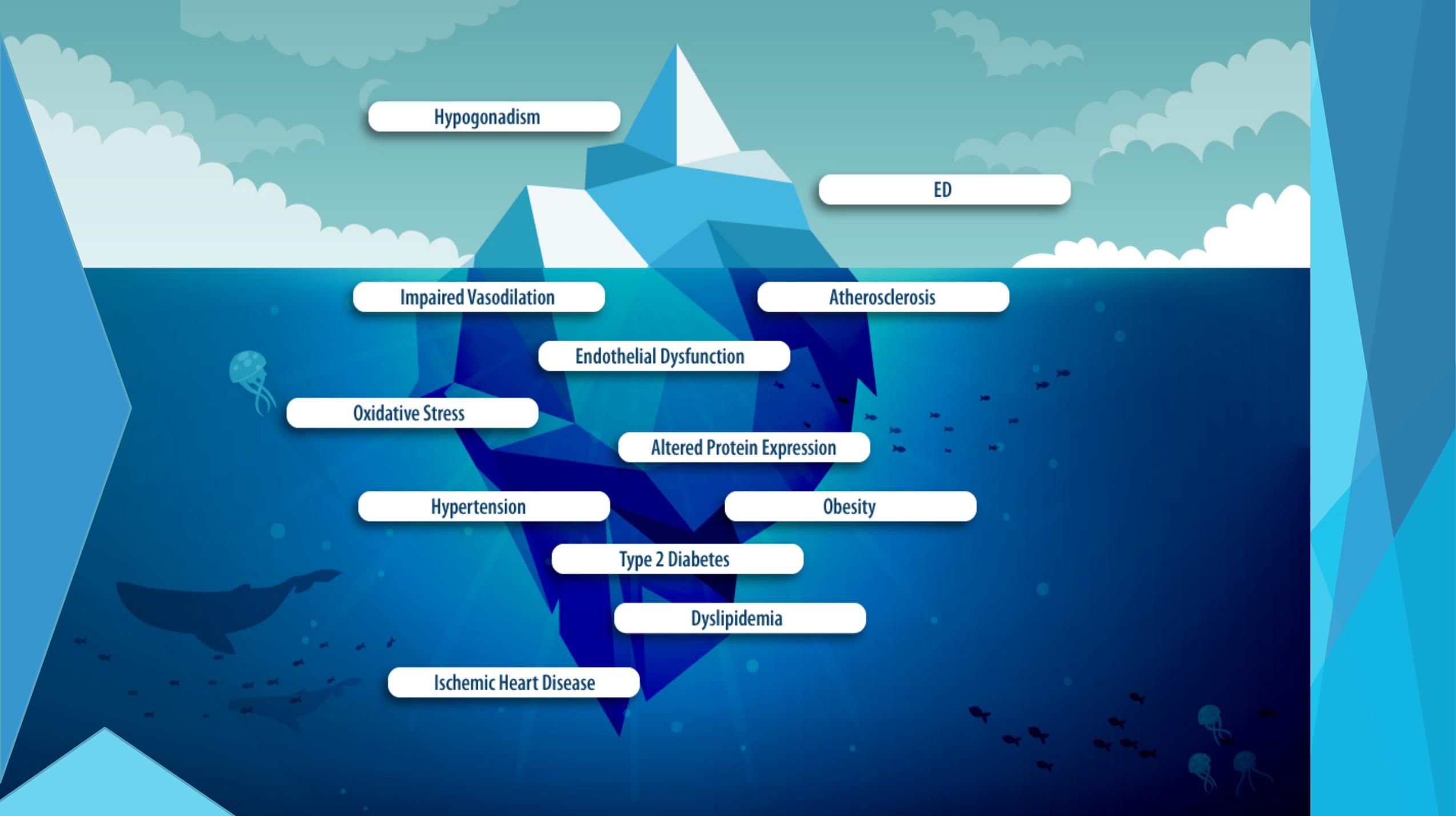
Hypertension

Obesity

Type 2 Diabetes

Dyslipidemia

Ischemic Heart Disease

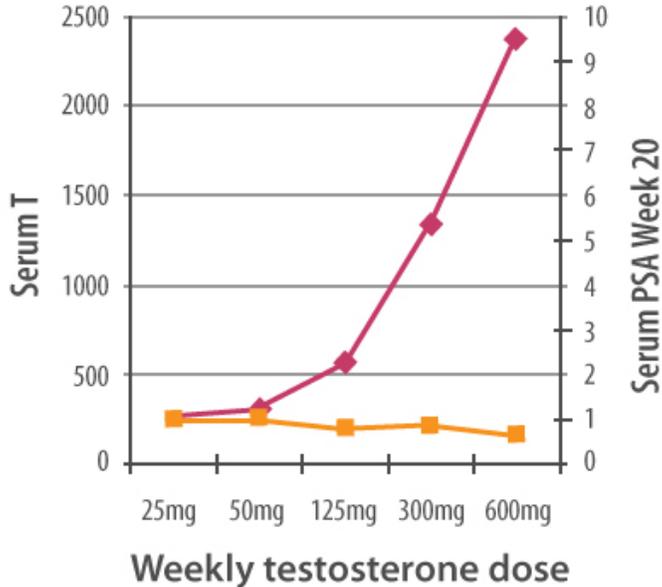


Males & Prostate Health

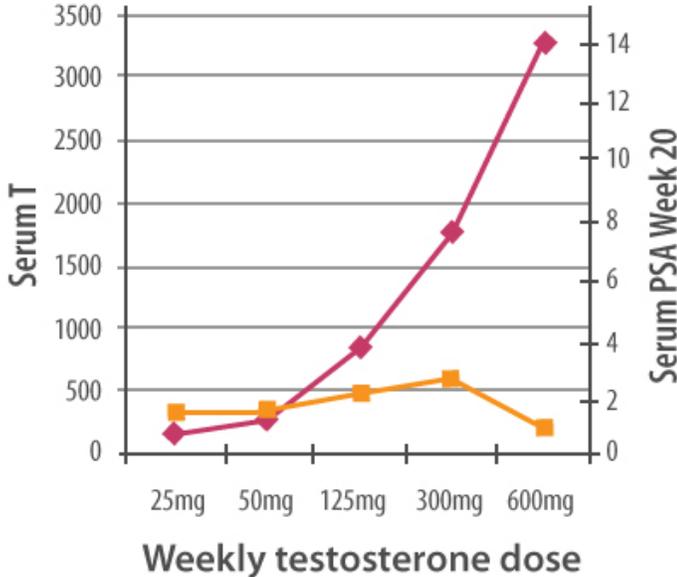
Does Testosterone Raise PSA?

◆ Testosterone
■ 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 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

Articles Showing T Therapy Causes Progression of PCa



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

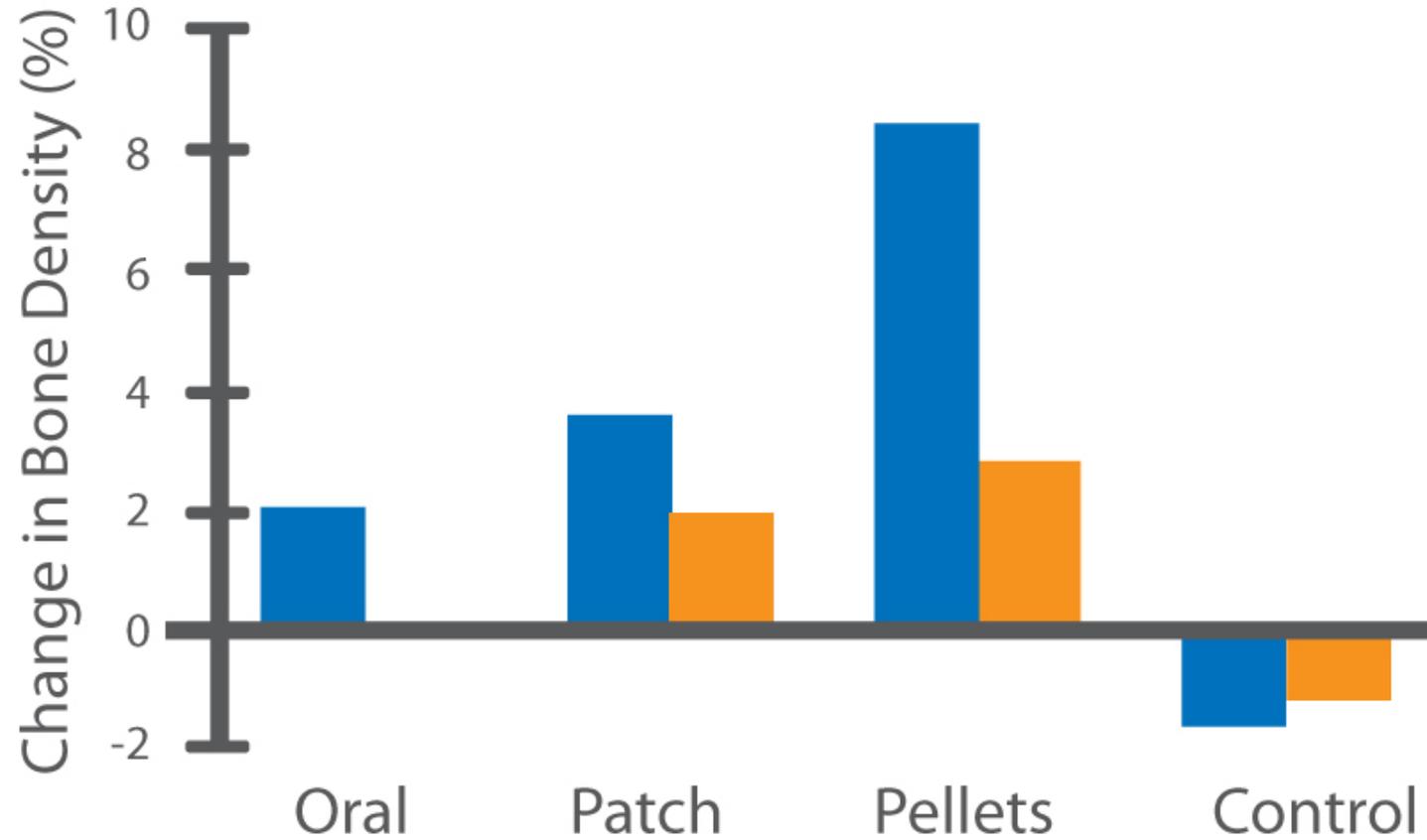
Studd, J WW, et al (1990)
Am Journal OB/GYN 163, 1474-1479



Bone Density

Increases with Different HRT

■ Vertebral
■ Femoral Neck



HRT and Neurodegenerative Conditions

- ▶ HRT and particularly ERT plays an efficacious role in preventing neurodegenerative conditions
- ▶ E2 (17 β Estradiol) can reduce the risk for Alzheimer's disease and minimize cognitive decline in otherwise healthy women
- ▶ E2 can protect against *B*-amyloid induced degeneration
- ▶ Progestins may actually dampen this affect
- ▶ Compared to non-users E2 used for avg. 15 years had increased cerebral blood flow

Intl. Journal. Alzheimer's Disease; 2012: 1-18

Alzheimer's Disease

- ▶ Both Estrogen and Testosterone have a 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.

Thyroid – What are we testing?

Thyroid hormone is a metabolic hormone secreted by the thyroid gland that regulates:

- ✓ Temperature
- ✓ Metabolism
- ✓ Cerebral Function
- ✓ Energy

New Thyroid Concepts

- ▶ T3 is needed for fat loss
- ▶ T3 protects against arrhythmias and heart disease
- ▶ T3 decreases with stress or dieting
- ▶ T4 does not necessarily convert to adequate T3
- ▶ Increased risk for anemia and other immunological changes in hypothyroidism
- ▶ Reverse T3 reverses T3

Thyroid (Cont.)

- It increases fat breakdown resulting in weight loss as well as lower cholesterol.
- It protects against:
 - ✓ Cardiovascular Disease
 - ✓ Cognitive Impairment
 - ✓ Fatigue & Weight Gain
 - ✓ Memory Loss

30-40% of Americans are hypothyroid = 52 MILLION PEOPLE

Thyroid Deficiency

- Thyroid deficiency causes symptoms of thin & sparse hair, dry skin, thin nails
- Has an adverse effect on mood
- Lowers energy
- Poor sense of well-being
- Causes changes in memory, cognition, mental slowness

Thyroid Deficiency: 3 Main Causes

- Over time the amount of thyroid hormone decreases secondary to a decreased production by the gland
- Decreased conversion of T4 to T3
- Less effectiveness at the receptor sites causing low thyroid symptoms in spite of “normal” blood levels
 - **It is the low T3 at the cellular level that is responsible for the symptoms**
 - Not TSH
 - Not T4

Optimal T3 Levels vs. Lab Levels

- FREE T3 2.3 – 4.3 (lab range)
- **OPTIMAL 4.0 – 4.3**

- TSH .3 – 5.0 (lab range)
- New proposed TSH levels .3 – 2.0
- OPTIMAL .3

- Treat the symptoms and patient
 - **NOT** the lab tests

Treat with T4 & T3

- Raising T3 levels to optimal will improve symptoms
- Raising T3 levels cannot be accomplished with just T4 alone
- A combination of T4 & T3 is required in order to optimize T3
- **Desiccated thyroid** is DOC

Side Effects

- Sweating
- Palpitations
- Tachycardia
- Tremor or nervousness
- **Rarely** seen with standard doses and normal Free T4 & Free T3
- Excess vs. Sensitivity
 - Treatment: lower dose

Progesterone is an important hormone

- Menopausal Women
- Perimenopausal Women
- Premenopausal Women
- Pregnant Women
- No Woman Should be without it – calming effects
- Perimenopause – 100 mg BID to QID
- Premenopause PMS:
 - ✓ 100 mg QD to QID until symptom relief
- Chronic vaginal bleeding post menopause:
 - ✓ 100-200 mg BID; titrate to prevent bleed
 - ✓ Endometrial hyperplasia 200mg BID

Tx the Patient, NOT the Lab

“Clinical manifestations of testosterone deficiency do not occur at a definitive threshold value”

Women with Low Testosterone

- ▶ Increased risk for Alzheimer's Disease
- ▶ Increased Risk for CVD
- ▶ Increased Risk for ORF
- ▶ Increased Risk for DM
- ▶ Possibly Breast Cancer

Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions

Abraham Morgentaler, MD (Chairman), et al

- ▶ Condition that negatively affects male sexuality, reproduction, general health, and quality of life
- ▶ Patients may benefit from treatment regardless of whether there is an identified underlying etiology
- ▶ It is a global health concern
- ▶ T therapy for men with TD is effective, rational, and evidence-based
- ▶ There is no T concentration threshold that reliably distinguishes those who will respond to treatment from those who will not

Mayo Clin Proc. 2016;91(7):881-896

Fundamental Concepts Regarding Testosterone Deficiency and Treatment: International Expert Consensus Resolutions

Abraham Morgentaler, MD (Chairman), et al

- ▶ There is no scientific basis for any age-specific recommendations against the use of T therapy in men
- ▶ The evidence does not support increased risk of CV events with T therapy
- ▶ The evidence does not support increased risk of PCa with T therapy
- ▶ The evidence supports a major research initiative to explore possible benefits of T therapy for cardiometabolic disease, including diabetes

Mayo Clin Proc. 2016;91(7):881-896

Unique Conditions That Respond Well to Pellet Therapy

- ▶ Chronic Pain Patients
- ▶ Chronic Opioid/Narcotic use
- ▶ Fibromyalgia
- ▶ PTSD/Soldiers
- ▶ Morbid Obesity
- ▶ Sleep Apnea
- ▶ Diabetes
- ▶ Night Shift Workers
- ▶ High Stress Jobs – doctors, lawyers, police officers, fireman, military
- ▶ Metabolic Syndrome
- ▶ Lipid Disorders
- ▶ PCOS patients
- ▶ Heart patients
- ▶ Breast Cancer Survivors
- ▶ Prostate Cancer Survivors
- ▶ Gym Goers/Athletes

Benefits to Patients

- ▶ Increased energy levels
 - ▶ Restored interest in life
 - ▶ Increased libido/performance
 - ▶ Consistency in moods
 - ▶ Relief from anxiety/depression/PTSD
 - ▶ Increased clarity and mental focus
 - ▶ Decreased body fat
 - ▶ Greater capacity for getting in shape
 - ▶ Prostate protection
 - ▶ Cardiovascular protection
- Safe: Hundreds of Studies, 75yrs Experience, Long-Term Safety Record, Used in 5 Continents
 - Clinically Effective: Steady State of Hormones – *“NO Roller Coaster Effect”*
 - 2-4 insertions per year = improved compliance
 - Improves lipids, insulin sensitivity, body composition
 - The *BEST* method to increase bone density
 - No increased prostate or breast cancer risk, does NOT Stimulate Breast Tissue
 - No increase in blood clots, heart attack or stroke
 - Protective to the *Breast, Bones, Brains, Heart, & Relationships*

Benefits to **Physicians/PAs** by Obtaining Training & Certification in HRT

- ▶ Learn advanced HRT in order to have an alternative to BAD MEDICINE while
 - ▶ Improving patient outcomes and
 - ▶ Limiting adverse effects and risks
- ▶ Learn proper interpretation of lab work
- ▶ Apply it to the proper use of bioidentical hormone implants
- ▶ Use a delivery system that is 80+ years old and proven safe
- ▶ Improves private-pay side of your practice and generates additional referrals and practice growth
- ▶ Overall improved patient and physician satisfaction

THANK YOU

The background features abstract, overlapping geometric shapes in various shades of blue, ranging from light sky blue to deep navy blue. These shapes are primarily located on the right side of the frame, creating a modern, layered effect against the white background.