Introduction to Bio-Identical Hormone Replacement Therapy and Preventive/Regenerative Medicine

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• Aging is a disease which can be prevented or reversed
• We are not prisoners of our genetic destiny
The HealthSpan Curve
“Conventional Medicine” Prolongation of Morbidity

Reserve Capacity (% of Maximum Function)

Morbidity Extension

AGE (years)
Goal of Preventive/Regenerative Medicine
HealthSpan Extension, Morbidity Compression
• Chronic Inflammation is a cause and the effect of the diseases of aging
“Unified Theory of Wellness”

- Chronic Inflammation is the cause and the effect of illness and the diseases of aging
- Anti-inflammation through the optimization of lifestyle, nutraceuticals, hormones, telomeres and stem cells
- Anti-inflammation = Wellness
- Anti-inflammation = Peak performance, health, happiness
- Anti-inflammation = optimal stem cell function
- Anti-inflammation = telomere optimization
Regenerative Medicine is:

• Optimal lifestyle
• Inflammation reduction
• Cutting edge technologies to detect, prevent and treat aging related disease
• Scientific and Evidence Based
• Documented in current Peer reviewed medical journals.
What do we do in Regenerative medicine?

• Design customized preventive/regenerative medicine programs
• Advanced lab testing
• Nutrition - personalized
• Exercise
• Stress Reduction
• Nutraceuticals
• Inflammation control
• Optimize Bio-identical hormones
• Stem cell banking and treatment
• Telomere testing and optimization
Bio-Identical hormones

- Defined as hormones atom for atom identical to endogenous hormones
- Treat a “deficiency disease”
- Improve Quality of Life
- Decrease Chronic Inflammation
- Do not increase cancer risk
- Do not increase heart disease risk
- Are a matter of personal choice
- Must be given by the correct route
- Are a “work in progress”
Balanced hormone optimization decreases chronic inflammation
Bio-identical hormones to consider for optimization

- Vitamin D
- DHEA, Pregnenolone, Melatonin
- Thyroid: T3, T4
- Cortisol
- Testosterone for men and women
- Estrogens: E1, E2, E3
- Progesterone for men and women
- Growth Hormone
- Optimal replacement considers levels and “How do you feel?”
Bio-identical hormone optimization

- Is a clinical specialty
- Optimal range not reference range
- When lab and clinical do not agree - clinical wins

Evolutionary Biology

- Hormone decline does not serve any positive biological function
- Evolution is blind to events after reproductive age
• Acute inflammation keeps us alive
• Chronic inflammation kills us slowly
• Why do we have all this inflammation anyway?
Aging causes inflammation
Youthful hormones protect

- IL-6 proinflammatory cytokine
- Stays low in youth except for trauma, infection, stress
- Testosterone and Estrogens down regulate IL-6 gene expression

Basics still apply

- Hormone optimization is the finishing touch on lifestyle: Nutrition, Exercise, Stress Reduction, Anti-oxidants and Nutraceuticals
- Use hormones when necessary to treat a deficiency disease
- Bio-identical
- Titrate to youthful levels and clinical response - control metabolites when needed
- Advanced treatments are backed up by current medical literature
New Thyroid Concepts

- Lab tests lack sensitivity
- TSH not most sensitive test
- “Normal” TSH getting lower all the time
- Free T3 best clue
- Clinical correlation required!
- When all else fails, look at the patient.
- The wide range of “euthyroid” is not “optimal thyroid”
• Patients feel better and lose weight on a T3/T4 combination
• Patients feel best on Porcine Desiccated Thyroid Extract
• Ask your patient if she thinks her thyroid replacement is optimal?
• Potential side effects of bone loss and atrial fib can be monitored and avoided with thyroid optimization
• Cardiovascular benefits of optimal T3
DTE = Desiccated Thyroid Extract = Porcine thyroid vs. Levothyroxine (T4)

- Double blind crossover study
- Conclusion:
  - DTE caused more weight loss
  - 50% felt better on DTE

Thyroid and Brain

- Linked to neurodegenerative process and cognitive impairment
- Modulates mood
- Can treat affective disorders
- Hypothyroidism linked to progressive cognitive impairment and slower thought process
- Within reference range TSH (inverse) and T3, T4 (direct) related to cognitive performance
Low T3 and Death

- Low T3 $< 3.1$ Free T3
- Low-T3 syndrome is a strong predictor of death in cardiac patients and might be directly implicated in the poor prognosis of cardiac patients.
- Strongest independent predictor of death $> \text{lipids or EF}$
- Iervasi, G et al. Low-T3 Syndrome, A Strong Prognostic Predictor of Death in Patients With Heart Disease *Circulation*. 2003;107:708
Mourouzis, I et al. Thyroid hormone and cardiac disease: from basic concepts to clinical application. *Journal of Thyroid Research*. Volume 2011
Cardiovascular benefits of optimal T3

• Lowers CRP - Christ-Crain, 2003
• Lowers Homocysteine – Nedrebo, 1998
• Dilates coronary arteries – Yoneda, 1998
• Anti-arrhythmic:
  • V Tach associated with low T3  low ratio of T3/T4 and high reverse T3 – Shimoyama, 1993
  • Low fT3 predicts post op AF  p=.001 – Cerillo, 2003
• RT3 strongest predictor of mortality in first year post Acute MI - Friberg, 2001
• Higher free T3, greater survival post MI – Pavlou 2003
TESTOSTERONE

Testosterone and diabetes later this afternoon
Testosterone Deficiency

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

Testosterone Deficiency is a lethal disease

- Diabetes, Metabolic syndrome
- Brain
- Heart
- Frailty syndrome
- Bone
- Inflammation
- Cancer
Testosterone Treatment – 56% less mortality

- 83,000 VA men > 50 y/o low testosterone
- Normalized-TRT – treated and test normalized
- Non-normalized-TRT – treated and test not normalized
- No TRT – not treated

Normalized-TRT vs. No TRT Hazard Ratios

- All cause mortality 0.44 CI 0.42-.46 p<.00001
- Risk of MI 0.76 CI 0.63-.93 p<.00001
- Risk of Stroke 0.64 CI 0.43-.96 p<.00001
- Significant but higher hazard ratios
  - Normalized-TRT vs. Non-normalized-TRT
- No difference
  - Non-normalized-TRT vs. No TRT

Testosterone

• Does not increase risk of prostate cancer
• Does not cause existing prostate cancer to grow
• Does not exacerbate lower urinary tract symptoms
• Does not increase cardiovascular risks
• Improves quality of life
2014 European Study

- 1023 patients up to 17 years with TRT
- Cohort 1 261 Pca 54.4/10000 pt years
- Cohort 2 340 Pca 30.7/10000 pt years
- Cohort 3 422 Pca 0/10000 pt years
- Background prevalence 96.6/10000 pt yrs
- Conclusion- Testosterone therapy in hypogonadal men does not increase the risk of prostate cancer.

Testosterone in Women

• Functional Androgen Receptors are located in almost all tissues
• Androgen deficiency symptoms
  – Anxiety, irritability, depression
  – Lack of well being, physical fatigue
  – Bone loss, muscle loss
  – Changes in cognition, memory loss
  – Urinary complaints, incontinence
  – Sexual dysfunction
Testosterone replacement decreases the risk of breast cancer.

- 1268 pre and post menopausal women
- 142/100,000 treatment groups
- 390/100,000 control groups
- $P < 0.001$
Estradiol
Estrogens

- **E1=Estrone**
  - May be more than she needs
  - Get some anyway through conversion of E2
- **E2=Estradiol**
  - Protective Estrogen via catechol and methoxy metabolites
- **E3=Estriol**
  - Cancer protective, weak
Bioidentical Estrogens and Progesterone

• Do not increase breast cancer risk

• Protect against
  – Cardiovascular disease
  – Cognitive dysfunction
  – Osteoporosis
  – Sexual dysfunction

• Women’s Heath Initiative studied Premarin (horse estrogen) and Provera (artificial progesterone)
Results from the E3N cohort study- Fournier 2007

- 80,377 postmenopausal women
- No increase or decrease in breast cancer in women on E2 and Progesterone. RR 1.0
- E2 plus MPA had RR of 1.69 or 69% increase in risk of breast cancer.
- Progestins are not Progesterone

Fournier A. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat. 2007 Feb 27
Estrogen Metabolism - Breast

- Testosterone
  - Aromatase
- Androstenedione
  - Aromatase
- Vitamin D
- E2, P4 sulfatase inhibitors
- E2, Vit D aromatase inhibitor
- Progestin (MPA) sulfatase stim

17Beta HSD

Sulfotransferase

Sulfatase
Advantages of Estriol (E3)

- E3 can bind preferentially to ER beta and inhibits ER alpha
- ER beta is protective of brain and cardiovascular function
- Low E3 levels associated with increased BC

Mortality from Estrogen Avoidance

- Hysterectomized women 50-59
- No Estrogen replacement
- 10 year period starting 2002
- 18,000-91,000 died prematurely - calculated
- Excess mortality from AMI, Breast cancer

CHOICE study: BHRT

- Cardiovascular biomarkers- CRP, Fibrinogen + other clotting factors, fasting glucose, triglycerides, BP and health outcomes were favorably impacted
- Transdermal Biest, Progesterone, Testosterone and DHEA

Stephensen, K et al. The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors, cardiovascular biomarkers, quality – of-life measures; and health outcomes in postmenopausal women. *Int J Pharm.Compd*. 2013 Jan-Feb 17(1) 74-85.
Bio-Identical Hormone Replacement in Women

- Balance Estrogens, Progesterone and Testosterone
- Every woman needs a unique balance
- Safe
- Improved Quality of Life
Growth Hormone Replacement Therapy

• Improves:
  – Body composition
  – Less abdo fat, more muscle
  – Osteoporosis
  – Cognitive function
  – Atherosclerosis
  – Cardiovascular function
  – Quality of Life
  – Traumatic Brain Injury
  – Immune function
Growth Hormone Replacement Therapy

- Does not increase cancer risks
- Minor side effects can be easily managed

• Logobardi, *J Endocrinol Invest*, May 1999. Bone density significantly improved with GH therapy


• Jenkins PJ et al. Does growth hormone cause cancer? *Clin Endocrinol (Oxf)*. 2006 Feb;64(2): 115-21
Melatonin

- Expressed by all life forms bacteria to mammals
- Declines with aging
- Sleep/wake cycle, Jet lag
- Buffers Immune system
- Prolongs lifespan/HealthSpan of animals
- Neuro protective
- Cardio-protective
- Anti-cancer
- Anti-inflammation
- Protects against ionizing radiation
Folate, B6

Melatonin

(N-acetyl-5-methoxytryptamine)

Inhibition

Stimulation


Suprachiasmatic nucleus
(the "biologic clock")

Retinohypothalamic tract

Superior cervical ganglion

Pineal gland
Protective effect of melatonin and/or growth hormone against myocardial infarct in rats

MARIA Study

• IV Melatonin used as an adjunct of treatment
• Patients with acute MI undergoing primary Angioplasty
• A unicenter, prospective, randomized, double-blind, parallel-group, placebo-controlled study
• End point- decreased infarct size at 0-72 hours or clinical events in first 90 days ie death
• No published results yet

Vitamin D

• Benefits from head to toe
• Most are deficient
• Prevention:
  – Cancer
  – Autoimmune disease
  – Cardiovascular disease
  – Viral Infections
Secosteroid hormone
Vitamin D3 = Cholecalciferol
“B” Ring is “Broken”
Vitamin D and inflammation

• Inversely associated with CRP and frailty
• Inhibits NFKB
• Boxer RS et al. The Association Between Vitamin D and Inflammation with the 6-Minute Walk and Frailty in Patients with Heart Failure. *J Am Geriatr Soc.* 2008 Jan 5

• Szeto, FL et al. Involvement of the vitamin D receptor in the regulation of NF-kappaB activity in fibroblasts. *J Steroid Biochem Mol Biol.* 2007, March
All percentages reference a common baseline of 25 ng/ml as shown on the chart. %’s reflect the disease prevention % at the beginning and ending of available data. Example: Breast cancer incidence is reduced by 30% when the serum level is 34 ng/ml vs the baseline of 25 ng/ml. There is an 83% reduction in incidence when the serum level is 50 ng/ml vs the baseline of 25 ng/ml. The x’s in the bars indicate ‘reasonable extrapolations’ from the data but are beyond existing data.

References:
Hormones Optimize stem cells

- Optimized hormones and nutraceuticals increase quality and quantity of endogenous adult stem cells
- Nutrients can act to promote healing via an interaction with stem cell populations.
Telomeres

- Region of repetitive nucleotide sequences (TTAGGG) at each end of the chromatid
- Protects the end of the chromosome from deterioration or from fusion with neighboring chromosomes
- Telomeres act as the cellular aging clock.
- Telomere loss is a Major Cause of Cellular Aging
Hormones and Telomerase Activity

- Androgen and Estrogen increase telomerase activity on TERT gene
- Optimized hormones protect
Optimized Hormones and Telomere length


What Can Be Done To Keep Telomeres Long?

• Lifestyle -
  – Nutrition, Exercise, stress reduction, meditation
  – Nutraceuticals
    • Omega 3’s, resveratrol, Vitamin D
    • Liu AJEpid, 2013, Liu HumaReprod 2013
  – Limit inflammation
  – Limit free radial damage
  – Limit toxic environmental exposure
• Restore Youthful hormone levels
• Activate Telomerase with TA-65
BHRT

- Safe
- Decreases cardiovascular risks
- No increase in breast or prostate cancer risk
- Improved Quality of Life
- Decrease Inflammation
- Improves telomere loss
- Anti-Aging available now
Know your Inflamm-aging numbers

- CRP <1
- Fasting Insulin <7
- Homocysteine <7
- AA/EPA Ratio <1.5
- 25-OH-D 65 -100 ng/dl
- Telomere length < 15 % short
- Cytokines
  - IL-6 <12 pg/l
  - TNF alpha <8 pg/l
  - IL-1 beta <15 pg/l
Hormones Inflam-aging numbers—youthful range

- Testosterone
- Estrogens
- Progesterone
- Thyroid
- DHEAS
- Cortisol
- Growth Hormone/IGF-1
Unified Theory of Wellness

- Control Inflam-Aging
- Optimize hormones with BHRT
- Optimize stem cells
- Optimize telomeres
- Increased **quality** of life
- We all have to die sometime
- What will the journey be like?
- Rectangularize
- And if we delay, intervene and reverse the diseases of aging....
- Increased **quantity** of life as well