"To Replace or Not to Replace, that is the Question"

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Disclosures

• **Research**: Abbott, Ascensia, BD, Boehringer Ingelheim, Companion Medical, Dexcom, Elcelyx, Glysens, Insulet, Janssen, Lexicon, Lilly, Medtronic, Novo Nordisk, Sanofi, Senseonics, Versartis, Yofimeter

• **Consulting**: Astra Zeneca, Bayer, Calibra, Lilly, Medtronic, Novo Nordisk, Sanofi

• **Speaking**: Abbott, Insulet, Medtronic, Novo Nordisk, Sanofi

• This slide deck: Dr. Herb Rettinger, MD, FACE
FEMALE HORMONE THERAPY
Estrogen Deficiency

- Menopause = 1 year without menses
- Can be gradual - begin in the late 30s with complete loss of production in the mid-50s
- Oophorectomy / Hysterectomy
- Presents with symptoms of hot flashes, sweating, insomnia, vaginal dryness/discomfort
  - Affects 85% menopausal women; (nearly 100% of women with surgical menopause)
  - Symptoms cease within 5 years for most individuals

Endocr Pract. 2011; 17 (supp 6)
Hormone Therapy (HRT)

- Most effective means to minimize symptoms
  - Estrogen therapy or Estrogen and a progesterone agent (E+P)

- To replace or not to replace?
  - Risk-benefit ratio must be determined individually

- Menopause is NOT a disease
2002 – The WHI was TWO trials!
Women’s Health Initiative (WHI)

- NIH sponsored multi-outcome study
- Most women were **largely asymptomatic**
  - Women up to the age of 79 were treated
  - Average age 63 (12 years postmenopausal)
  - Oral CEE used ( +/- Progesterone)

- In 2002, E+P trial was terminated after 5.6 years as rate of breast cancer crossed preset boundaries

JCEM, May 2013, 98(5): 1771-1780
JCEM, July 2010, 95 (S1)s1-66
WHI Update (Hysterectomized Group)

Breast Cancer Risk in WHI After Mean Follow-Up Time of 10.7 Years as a Function of Age Group When Therapy was Initiated

Estrogen alone (CEE) vs Placebo

There were fewer invasive breast cancers in the estrogen alone group compared with the placebo group in all 3 age groups (P<.01).

- Ages 50-59
- Ages 60-69
- Ages 70-79

Median estrogen use: 5.9 years

Myocardial Infarction Event Risk in WHI After Mean Follow-Up Time of 10.7 Years as a Function of Age Group When Therapy was Initiated

Estrogen alone (CEE) vs Placebo

(P = .007)

Ages 50-59
Ages 60-69
Ages 70-79

Absolute Risk of Myocardial Infarction
(Number of events in CEE group vs. placebo per 10,000 women per year)

Median estrogen use: 5.9 years

Risks: Coronary Heart Disease

- Evidence for early harm among the older women in the E+P trial in WHI
- No increase in younger women; instead a trend to benefit
- Older women who are distant from menopause, who have established atherosclerosis and who receive standard doses of oral hormone therapy are at increased risk of coronary plaque instability, mural rupture and thrombosis
Benefits of Hormone Therapy

- Improves hot flashes
- Relieves symptoms and normalizes vaginal atrophy, reduces incidence of UTI
- Prevents early postmenopausal bone loss and augments bone mass in late postmenopause
- Decreases colon cancer risk
- Associated with a decrease in diabetes risk
- Exerts a protective effect on osteoarthritis
- Improves quality of life

JCEM, July 2010, 95 (S1)s1-66
**Absolute Contraindications to Hormone Therapy**

- Current, past, or suspected breast cancer
- Known or suspected estrogen sensitive malignant conditions
- Undiagnosed genital bleeding
- Untreated endometrial hyperplasia
- Previous idiopathic or current venous thromboembolism
- Active or recent arterial thromboembolic disease (angina, MI)
- Untreated hypertension
- Active liver disease
- Known hypersensitivity to the active substances of HT
- Porphyria cutanea tarda

Endocr Pract. 2011; 17 (supp 6)
Risks of Hormone Therapy

- Cholecystitis
- Endometrial cancer (4.5-9x without P - Use if Uterus)
- Venous thromboembolic disease (smokers, clotting disorders, age, obesity) – Use Transdermal
- Stroke (1-2 more cases/10,000 women-years)
- Breast cancer (NOT if @ menopause) - ? lower P agent
- Coronary Heart Disease – timing & vascular state

Endocr Pract. 2011; 17 (supp 6)
JCEM, May 2013, 98(5): 1771-1780
JCEM, July 2010, 95 (S1)s1-66
Special Populations: Status Post Hysterectomy

- Hysterectomy is the 2nd most common major surgery in women (after cesarean)
- More than 6 million hysterectomies in the last 10 years
  - Ovaries removed in 54% → “surgical menopause”
  - In these patients, HT can decrease mortality and may be overwhelmingly beneficial

Special Populations: Status Post Hysterectomy

 Decreased Mortality in Hysterectomized Women Under Age 60 Using Hormone Therapy
Conclusions. ET in younger postmenopausal women is associated with a decisive reduction in all-cause mortality, but estrogen use in this population is low and continuing to fall. Our data indicate an associated annual mortality toll in the thousands of women aged 50 to 59 years. Informed discussion between these women and their health care providers about the effects of ET is a matter of considerable urgency. (Am J Public Health. 2013;103:1583–1588. doi:10.2105/AJPH.2013.301295)
Clinical Considerations

- Transdermal route of estrogen may theoretically decrease the risk of thromboembolic disease as it avoids the hepatic first pass effect
  - History of VTE is not a complete contraindication to HT. Consider transdermal in symptomatic patients with history of VTE
  - Also consider transdermal in patients with gallstones, hypertriglyceridemia and hypertension

- Transvaginal estrogen may be considered to have less systemic absorption
  - Best for localized symptoms of vaginal atrophy, urinary incontinence

Endocr Pract. 2011; 17 (supp 6)
Clinical Considerations

• Progestational agents for minimum of 10-14 days per month
  – Can consider 14 days every 3 months to decrease breast exposure to progesterone
  – Some women may experience premenstrual like symptoms of progesterone i.e. mood swings, bloating, fluid retention → switch to a different progesterone agent.
Clinical Considerations

- Hormone replacement therapy not recommended for prevention of dementia
- Not recommended for primary and secondary prevention of cardiovascular disease
- Not recommended as a 1st line agent for osteoporosis treatment
- “Bio-identical” = buzzword - Beneficial?
- “Compounded” = unregulated
Bioidentical Hormones

• Compounding of plant derived hormones that are marketed as identical in structure to human endogenous hormones
• Not subjected to FDA regulations for safety and effectiveness
• Different mixtures of estrogens
  – Estradiol (predominant estrogen before menopause)
  – Estrone (predominant estrogen after menopause)
  – Estriol (from placenta)
    ▪ Triest – has all 3.

Endocr Pract. 2011; 17 (supp 6)
Bioidentical Hormones

• Variable potency leading to over and under dosing
• Cross contamination and concerns over sterility of preparations
• Compounded HTs have the same risks as FDA-approved therapies
• Recommendations *against* bioidentical hormones

Endocr Pract. 2011; 17 (supp 6)
Approach to a Patient

• Identify if a patient is an appropriate candidate for HT
  – Symptoms?
  – Past medical history?

• Discuss treatment options with patient
  – Hormone therapies
  – Nonhormonal therapies (i.e. SSRi, SSNRs, gabapentin, clonidine)

• Review risks and adverse events

• If pt would like to try HT, use the lowest effective dose for symptom control
  – Relief of clinical symptoms is used to determine dosing decisions; RARELY need lab tests!
Conclusions

- Menopause and aging are associated with many chronic illnesses including CAD, stroke, osteoporosis, dementia, and cancer.
- Timing of therapy initiation may be critical.
- Disease prevention may be possible in early menopause; may be detrimental in later periods.
Conclusions

• Treatment should be absolutely considered in appropriate women <60 years of age
  – Would not consider starting HT in patients >70 years of age and >10 years post menopause
• All appropriate patients with surgical menopause should be considered for HT
• Duration of course should be based on a discussion between provider and patient, including risk factors, comorbidities, symptom relief.
MALE HORMONE THERAPY
The Massachusetts Male Aging Study

- The largest review of the effect of T levels on overall mortality
- 3,518 men were followed for 17 years
- Total testosterone levels were measured and divided into five categories at 200 ng/dL increments
- Multivariate analysis depicting the association with overall mortality, CVD, and prostate cancer specific mortalities was conducted

Estimates of the Cumulative Probability of Mortality, CVD Death, and Cancer Death

• Findings from follow up of 17 years:
  - Age adjusted HR’s* for men with Total T < 200 ng/dL vs. men with Total T of 410-509 ng/dL
    - 1.93 or two fold for all mortalities (p=.03)
    - 3.30 or three fold for Cancer death (p=.03)
    - 1.93 or two fold for CVD death (p=.28)

* Hazard Ratio

Production and Regulation of Testosterone

- CNS Stimulation
- Hypothalamus
- Hypothalamic-Pituitary Portal System
- Posterior Pituitary
- Anterior Pituitary
- Testis
- Sertoli Cells
- Leydig Cells
- Sperm Inhibin
- FSH
- LH
- GnRH
- Testosterone
Pathophysiology of Testosterone Deficiency: Testicular Dysfunction (Primary Hypogonadism)

Hormone Levels: \( \downarrow T, \uparrow LH/FSH, \uparrow GnRH \)

Causes: Klinefelter’s syndrome (47 XXY), undescended testes, orchiectomy, trauma, testicular cancer, radiation, chemotherapy, virus, hemochromatosis, EtOH, other drugs.
Pathophysiology of Testosterone Deficiency: Pituitary Dysfunction (Secondary Hypogonadism)

Hormone Levels: ↓T, ↓ or inapprop. normal LH, FSH
Causes: Pituitary tumors (eg, prolactinoma, acromegaly), radiation, craniopharyngioma, sarcoidosis, β-thalassemia major, Trauma.
Hypothalamic Dysfunction (Secondary/Tertiary)

Hormone Levels: ↓T, ↓GnRH or inapprop. normal LH, ↓GnRH

Causes: Kallman’s syndrome (with anosmia), idiopathic hypogonadotropin hypogonadism, head trauma, nutritional, chronic disease states, drugs.
<table>
<thead>
<tr>
<th>Certain Substances May Cause Low Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcohol</td>
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<tr>
<td>Amiodarone</td>
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<tr>
<td>Antivirals</td>
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<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Estrogens/progestins</td>
</tr>
<tr>
<td>Anabolic Steroids</td>
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<tr>
<td>Ganciclovir</td>
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<tr>
<td>Glucocorticoids</td>
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<tr>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Marijuana</td>
</tr>
<tr>
<td>Megestrol acetate</td>
</tr>
<tr>
<td>Opiates</td>
</tr>
<tr>
<td>Spironolactone</td>
</tr>
</tbody>
</table>

Adapted from Bhasin, S.in *Harrison's Principles of Internal Medicine*, 16th edit. 2005; 2185-2197
**The Influence of Testosterone**

**Skin**
Hair growth, balding, sebum production

**Liver**
Synthesis of serum proteins

**Bone**
Accelerated linear growth, closure of epiphyses

**Male sexual organs**
Penile growth, spermatogenesis, prostate growth and function

**Brain**
Libido, Mood

**Muscle**
Increase in strength and volume

**Kidney**
Stimulation of erythropoietin production

**Bone marrow**
Stimulation of stem cells

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AACE Hypogonadism Task Force
*Endocrinol Pract.* 2002;8:439-456
**Low Testosterone is Frequently Seen in Patients with the Following Conditions**

<table>
<thead>
<tr>
<th>Aging (↓1-2%/yr after age 30)</th>
<th>Obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erectile Dysfunction (ED)</td>
<td>Metabolic Syndrome</td>
</tr>
<tr>
<td>Type II Diabetes</td>
<td>Chronic renal failure</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>COPD, OSA</td>
</tr>
<tr>
<td>Cancer</td>
<td>Alcohol abuse</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Anabolic steroid abuse</td>
</tr>
<tr>
<td>Depression</td>
<td>Glucocorticosteroid use</td>
</tr>
<tr>
<td>Chronic pain treated with opioids</td>
<td>Chronic Infection</td>
</tr>
<tr>
<td>Head Trauma</td>
<td>Chronic Inflammatory Disease</td>
</tr>
</tbody>
</table>

Griffen JE. *Harrison’s Principles of Internal Medicine*. 1998
Winters SJ. *Arch Fam Med*. 1999;8:257-263
Shores M. *Arch Gen Psychiatry*, 2004;61:162-167
Signs and Symptoms of Low Testosterone (Hypogonadism)¹

- Loss of libido*
- Erectile dysfunction*
- Depression, irritability
- Lethargy, loss of motivation
- Osteoporosis
- Loss of muscle mass
- Regression of secondary sexual characteristics
- Oligospermia or azoospermia
- Insulin Resistance


* Hallmarks of hypogonadism
HIM Study*: Overall Conclusions

• Age-adjusted prevalence rate of low total testosterone levels was 38.4%; in Diabetics, 52% had low Testosterone!

• Odds of having total testosterone <300 ng/mL or currently being treated for low testosterone are:
  – 2.5 x higher if BMI $\geq$ 25 kg/m2
  – 2.0 x higher for diabetes
  – 1.8 x higher for hypertension
  – 1.4 x higher for asthma/COPD
  – 1.2 x higher for age $\geq$ 65
  • 1.2 x higher with each decade increase

How Do We Identify Patients?
Serum Testosterone Levels

- Total Testosterone < 300 ng/dL*
- Free Testosterone < 50 pg/mL (may be better test in older men)
- Bioavailable Testosterone < 70 ng/dL

*Total Testosterone is the most frequently used lab test for the diagnosis of hypogonadism

Brawer, M. Reviews in Urology Vol 6, Supp 6, 2004; pgs. S9-S15
Suspected or At Risk for Low Testosterone

Assess Symptoms

If Present

Testosterone Levels

Normal

Seek Other Causes

Abnormal

Evaluate Further by Urologist

If Low Testosterone
Total < 300 ng/dl; Bioavail < 70 ng/dl; Free <50 pg/dl

Repeat T with LH, FSH, Prolactin*

Digital Rectal Exam, PSA

Normal

TRT


*Pituitary MRI and/or refer to endocrinologist for further testing
Potential Risks of Testosterone Replacement Therapy

- Polycythemia (more common in IM injections and/or smokers)
- Increased PSA (BPH and prostate cancer- elderly pts)
- Edema in patients with or without pre-existing cardiac, renal, or hepatic disease
- Precipitation or worsening of sleep apnea
- Acne
- Decrease in testicular size
- Decrease in sperm count / Infertility
- Gynecomastia – (more common with IM injections)
- Hepatotoxicity only with oral therapy (increase in liver enzymes, cholestasis, and hepatic tumors)
- Hypertension

Brawer, M.  Reviews in Urology Vol 6, Supp 6, 2004; pgs. S9-S15
Package insert- Testim gel.
Testosterone Replacement Therapy (TRT): Prostate Issues

- Does TRT Cause Prostate Cancer?
  - To date, there is no conclusive evidence that TRT causes prostate cancer
  - Geriatric patients treated with androgens may be at an increased risk for development of prostatic hyperplasia and prostatic cancer (monitor PSA and DRE)
  - Before initiation of TRT, pre-existing prostate cancer should be ruled out
  - Testosterone should not be given to any man with suspected or current prostate cancer

Goals and Benefits of Testosterone Replacement Therapy

- Improve libido and improve erectile function
- Improve body mass and strength
- Improve bone mineral density
- Improve energy level
- Improve mood/sense of well-being

Testosterone Therapy Delivery Systems

- Intramuscular injections
- Pellet implants
- Transdermal patches
  - Applied to scrotal or non-scrotal areas
- Transdermal gel (most common)
- Chorionic gonadotropin or pulsatile GnRH for men interested in retaining fertility

Testosterone Levels after Replacement Therapy with Patch, Gel or Injection

Adapted from Bhasin and Bremner. J Clin Endocrinol Metab. 1997;82:3-8
Testosterone gel (AndroGel ®1%) Solvay Pharmaceuticals, 2002
Considerations for Referral to Endocrinologist

Signs and symptoms of pituitary tumor, including:

• Visual field abnormalities
• Headaches
• Hyperprolactinemia or hypopituitarism
• Testosterone <150 with normal LH, FSH
• Other pituitary abnormalities

Interest in fertility

Unclear etiology, signs/symptoms of estrogen excess.
Considerations for Referral to Urologist

- Abnormal DRE
- History of prostate cancer
- Rapid rise in PSA velocity ≥ 0.75ng/ml/year or ≥ 1.5ng/ml/2 years
- Interest in fertility (primary hypogonadism)
Summary

- Low testosterone is common with aging but rare in youth (where is is **always** a “disease”)
- It may be both:
  - Under (mis)-diagnosed
  - Over (mis)-treated
- Symptom improvement is seen if testosterone levels are raised to within normal range
- Requires patient monitoring and an understanding of underlying etiology. (Endocrine referral if etiology unclear).
HRT - BOTTOM LINE

• Make a correct diagnosis (not issue in menopause)
• Therapy safe and available
• Individualize therapy
  – don’t mis-, over-, or under- treat
  – duration
• Monitor therapy
  – Physiologic (safety with androgens)
  – Quality of life

• Your patients will thank you!