Effects of Hormone Therapy on the Metabolic Syndrome and Cardiovascular Disease

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Disclosures
None

Learning Objectives
• Understand the current guidelines for management of menopausal symptoms with hormone therapy.
• Be familiar with the data regarding the effects of the menopause and estrogen therapy on diabetes and cardiovascular disease
• Be comfortable with the work up and treatment of hypogonadism
• Recognize the controversies and unknowns surrounding testosterone treatment and cardiovascular disease
Case #1

- A 51 year old woman comes to see you complaining of night sweats and disordered sleep. Her last menstrual period was 4 months ago.
- She is wondering about hormone therapy but has concerns about weight gain and other side effects.
- She is healthy and takes no medications.
- Her family history is notable for a mother who fractured her hip at 75.
- Her father had Type 2 diabetes.
- On exam she has a BMI of 24, BP 124/80. Fasting glucose is 108 and A1C is 5.9%.
- What do you tell her about the risks and benefits of hormone therapy on metabolic parameters?

Questions

- Who should consider hormone therapy at menopause?
- What are the risk and benefits, particularly for metabolic parameters?

Review of hormone replacement trials

- Prior to WHI:
  - Many observational studies showed benefits of hormone therapy for symptoms
  - Potentially prevention of coronary disease and cognition benefits
- WHI:
  - randomized to look at both CVD prevention and benefit
  - 27,347 healthy postmenopausal women aged 50-79
Timing hypothesis

- Questions raised as to whether there may be a difference in terms of age of initiation
- Studies showed that early estrogen may prevent atherosclerosis while exposure when there is already atherosclerosis present may destabilize plaque.
Early versus Late Intervention Trial with Estradiol (ELITE)

6 year trial

643 healthy postmenopausal women
1mg oral estrogen + 10 days/month vaginal micronized progesterone

Slowed carotid atherosclerotic progression in women within 6 years of menopause onset (mean age, 55.4 years) but not in women more than 10 years past menopause onset (mean age, 65.4 years) (p, interaction = 0.007)

KEEPS trial

• Look at type of estrogen as well as timing.
• Women 42-58, 6-36 months from LMP
• CAC <50, No E, No lipid tx
• Measured CIMT at baseline and 48 months
**Guidelines for treatment**

- For women <60 or <10 years post menopause with bothersome symptoms
  - No contraindications
  - No excess breast cancer risk
  - No excess CVD risk
- If patient does not have uterus:
  - Estrogen alone
- If patient does have uterus
  - Estrogen and progesterone

**SWAN data on metabolic syndrome**

METS increased by 45% during perimenopause compared with 24% after
Lipids drove more than glucose
Arch. Int. Med. 2008
Does giving hormone therapy improve glucose?

• WHI CEE + P group
  – The cumulative incidence of treated diabetes was 3.5% in the hormone therapy group and 4.2% in the placebo group (hazard ratio 0.79, 95% CI 0.67-0.93, p=0.004). (Diabetologia 2004)
• Estrogen alone
  – The cumulative incidence of treated diabetes was 8.3% in the estrogen-alone group and 9.3% in the placebo group (hazard ratio 0.88, 95% CI 0.77-1.01, p=0.072). (Diabetologia 2006)
  • However lack of data and concerns for DM as CAD risk equivalent would argue NOT to use estrogen as a treatment for DM

Is there a timing hypothesis here as well?

• In a short term study with insulin clamp (1 week transdermal E vs placebo) glucose disposal improved in women closer to menopause (< 6 years LMP) but not further out (Pereira et al JCEM 2015)
• Further studies have suggested that there may be changes in estrogen receptor status that affect this.
  • Differences between oral/transdermal...
Back to the patient

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Risk and benefits in women 50-59

Back to the patient

- She is having symptomatic menopause.
- Any contraindications?
- Issues that may be helped by HT?

- Consider transdermal/oral estrogen with cyclic progesterone.
- This should be re-evaluated annually with consideration of stopping after 5 years.

Case #2

- A 66 year old man comes to see you for concerns about “Low T”
- He heard an ad on the radio for a center where they give testosterone injections and wants to know if he should try it or is this “just his age”
- He has also heard some TV commercials with warning about stroke and cardiovascular disease which concerns him.
- He notes some weight gain, a decline in libido and overall fatigue.
- BMI=28, BP=128/86
- His testosterone level was 275ng/dl (300-1000)
- Fasting glucose 108 and A1C 5.9.
Testosterone therapy in older men

- Is this hypogonadism? Should he be treated?
- What is the relationship between testosterone, obesity and the metabolic syndrome?
- What are the data on cardiovascular disease in older men?

"Low T? How's the rest of my alphabet?"

Hypogonadism: Definition

"Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal axis"

Testosterone products are FDA approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition.

Endocrine Society Clinical Practice Guideline
FDA drug safety communication 09/14
Hypogonadism, Obesity, Metabolic Syndrome

- Metabolic Syndrome
  - Visceral Obesity
  - Testosterone/SHBG

- Clinical relevance:
  - Insulin Resistance
  - Endothelial Dysfunction
  - Diabetes mellitus type 2
  - Cardiovascular disease
  - Erectile dysfunction

- Hypothalamic-pituitary


Weight Loss Improves Testosterone/SHBG

- T levels increase with weight loss
- Even free T levels increase when you lose 15% weight!
- SHBG levels increase


Testosterone therapy and CVD

- Historically testosterone has been correlated with improvements in mortality and metabolic syndrome.
- However, more recent data has raised some concerns about cardiovascular risk, particularly in older men.
Testosterone treatment and mortality

Unadjusted Kaplan-Meier survival curves illustrate that testosterone-treated men had a longer survival time than untreated men (P = 0.029).


Benefits of testosterone on MetS

Table 1: Randomized studies of testosterone replacement in hypogonadal men with metabolic syndrome or type 2 diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>Episcero et al. (14)</th>
<th>Handelsman et al. (16)</th>
<th>Wilhelmsen et al. (20)</th>
<th>Jorio et al. (27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>Type 2 diabetes</td>
<td>Metabolic syndrome</td>
<td>Type 2 diabetes</td>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Study design</td>
<td>102</td>
<td>152</td>
<td>105</td>
<td>101</td>
</tr>
<tr>
<td>Total testosterone (mg/day)</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>DHEA-S (mg/day)</td>
<td>12.5</td>
<td>10.5</td>
<td>11.5</td>
<td>11.5</td>
</tr>
<tr>
<td>Testosterone gel (mg/day)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Treatment effect change</td>
<td>DHEA-S</td>
<td>0.7</td>
<td>-0.3</td>
<td>1.3</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>4.6</td>
<td>4.4</td>
<td>4.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Total testosterone (mg/day)</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>LPA (molecules/mL)</td>
<td>500</td>
<td>500</td>
<td>500</td>
<td>500</td>
</tr>
<tr>
<td>HOMA-IR (mg/dL)</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Lp(a) (mg/dL)</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>20</td>
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<tr>
<td>Lipoprotein a (mg/dL)</td>
<td>60</td>
<td>60</td>
<td>60</td>
<td>60</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>120</td>
<td>120</td>
<td>120</td>
<td>120</td>
</tr>
<tr>
<td>Total testosterone (mg/day)</td>
<td>5</td>
<td>12</td>
<td>9</td>
<td>6</td>
</tr>
</tbody>
</table>

Relationship between T/E and developing MetS

Antonio et al JCEM 2015
TOM Trial

- Men >65, mean age 74
- Serum T 100-350 (ng/dL)
- Placebo vs T gel for 6 months
- 209 men were enrolled
- Plan was to look at strength outcomes, but the trial was terminated due to increased cardiovascular death.
- 23 subjects in the testosterone group, as compared with 5 in the placebo group, had cardiovascular-related adverse events.
- Cardiovascular-related adverse events were reported in 4 of 14 subjects with testosterone levels higher than 1000 ng per deciliter during the treatment period, by 5 of 21 with levels of 500 to 1000 ng per deciliter, and by 7 of 46 subjects with levels of less than 500 ng per deciliter.

Events happened early, within a month and persisted after a 3 mo follow up

Basaria et al NEJM 2010 363:109
Recent T and Cardiovascular Risk Epidemiology Studies: What to make of it all?

Yeap 2015

T trial on atherosclerosis (TEEAM)

- 156 men 60+ (mean 67.6) T with low or low normal T randomized to T gel or placebo for 3 years with goal T 500-900 ng/dL.

- Baseline
  - 15% DM
  - 42% HTN
  - 15% CVD
  - 27% obesity

- Looked at atherosclerosis progression and did not see difference
- Not powered for cardiovascular events

Basaria et al JAMA 2015
Recent T trials

- Group of recent trial of testosterone
- Double-blind placebo control
- Testosterone vs placebo gel for 1 year
  - CVD
  - Anemia
  - Sexual dysfunction
  - Cognition
  - Bone density
- CVD trial
  - 170 of 788 men
  - 65 years +
  - 2 serum testosterone levels lower than 275
Is there a happy medium?

Probability of dying from any cause according to plasma levels of T (A), calculated free T (B), DHT (C) and estradiol (D) in 3690 community-dwelling men age 70 to 89.
Yeap JCEM 2014

T Trial CVD

Table 2. Change from Baseline and Estimated Differences for Primary, Secondary, and Exploratory Outcomes in the Cardiovascular Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Treatment Group</th>
<th>Baseline</th>
<th>ΔԲ</th>
<th>Estimated Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Normotensive subjects, men</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>204 (46 to 429)</td>
<td>257 (50 to 393)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortal, Δ12 months</td>
<td>32 (16 to 479)</td>
<td>39 (17 to 30)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Change from baseline value, complete mean (SD)</td>
<td>46 (31 to 56)</td>
<td>81 (41 to 62)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>ΔΔ8 weeks (95% CI)</td>
<td>54 (41 to 67)</td>
<td>44 (14 to 67)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Total plasma volume, mL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>372 (191 to 665)</td>
<td>381 (362 to 642)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortal, Δ12 months</td>
<td>10 (8 to 44)</td>
<td>6 (1 to 10)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline value, complete mean (SD)</td>
<td>37 (19 to 59)</td>
<td>25 (16 to 42)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔΔ8 weeks (95% CI)</td>
<td>78 (39 to 126)</td>
<td>47 (29 to 65)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary</td>
<td>Age-related calcification, Atherosclerosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline, mean (SD)</td>
<td>218 (41 to 946)</td>
<td>304 (946 to 1083)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortal, Δ12 months</td>
<td>245 (41 to 133)</td>
<td>302 (136 to 140)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline value, complete mean (SD)</td>
<td>53 (25 to 62)</td>
<td>118 (75 to 164)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔΔ8 weeks (95% CI)</td>
<td>64 (19 to 246)</td>
<td>27 (10 to 24)</td>
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</tr>
</tbody>
</table>

Overall, the findings from subtrials of the T Trials do not materially change the unfavorable balance of safety and efficacy to initiate testosterone treatment for age-related hypogonadism. Rather, low testosterone levels due to obesity and other aging comorbidities are better addressed by lifestyle measures directed at those comorbidities. For physicians prescribing off-label testosterone, these cardiovascular findings make it incumbent to strengthen warnings of adverse cardiovascular risk. Moreover, similar warnings apply for androgen-anabolic steroid abuses. These findings also support the US Food and Drug Administration (FDA) decision in September 2015, based on warned safety signals, to tighten cardiovascular safety warnings about off-label testosterone prescribing.
Just right?

- "Abundant epidemiologic data suggest that both very low and high testosterone levels are associated with increased cardiovascular risk. Thus, as with Goldilocks and her porridge, too much is bad, too little is bad, and just right is needed when it comes to testosterone treatment strategies in men with hypogonadism"

Wierman ME. JAMA Int Med July 2015

Initiating and monitoring testosterone

- Forms of testosterone
  - Gel: 5-10g of testosterone gel
  - Patch 2mg, 4mg
  - Injection 75-100 IM testosterone enanthate or cypionate weekly or 150-200 every 2 weeks
- Reassess in 3-6 months
  - Mid normal range
  - Check Hct baseline, q3-6 months, then annually
  - If over 40 PSA at baseline, 3-6 months and then annually

Adapted from Endocrine Society Guidelines 2010 JCEM

Back to the patient

- Would not prescribe based on one lab value
- Recheck AM testosterone level, along with FSH/LH/prolactin.
- Look for other etiologies:
  - Untreated OSA
  - Narcotics
- Check CBC/CMP/PSA/Lipids and glucose
Conclusions

• Although there may be metabolic benefits, due to other risks/concerns hormone therapy should not be used for primary prevention of CVD or MetS.
• There may be different actions of hormones depending on physiologic vs pharmacologic levels.
• Underlying disease and differing stages of life require different treatments and discussions.
• Consider and discuss the risks and benefits in individual patients before prescribing.

Thank you for your attention